รายงานวิจัยฉบับสมบูรณ์

โครงการ เมธีวิจัยอาวุโส สกว. เพื่อพัฒนาศักยภาพการประเมินเทคโนโลยีด้านสุขภาพ

TRF Senior Research Scholar Program on the Development of Health Technology Assessment Capacity in Thailand

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ดร. นพ.ยศ ตีระวัฒนานนท์

โครงการประเมินเทคโนโลยีและนโยบายด้านสุขภาพ

สำนักนโยบายและยุทธศาสตร์ กระทรวงสาธารณสุข

สนับสนุนโดยสำนักงานกองทุนสนับสนุนการวิจัย

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การประเมินเทคโนโลยีด้านสุขภาพเป็นหนึ่งในกลไกที่สนับสนุนให้ผู้บริหารหรือผู้กำหนดนโยบายใช้ข้อมูลทางวิชาการในการตัดสินใจใช้ทรัพยากรด้านสุขภาพที่มีอยู่อย่างจำกัดให้เกิดประโยชน์และคุ้มค่า โดยปี 2557 องค์การอนามัยโลกได้สนับสนุนให้ทั่วโลกโดยเฉพาะประเทศที่มีระบบประกันสุขภาพถ้วนหน้าพัฒนาระบบการประเมินเทคโนโลยีด้านสุขภาพ ซึ่งประเทศไทยมีการใช้ข้อมูลด้านการประเมินเทคโนโลยีและนโยบายด้านสุขภาพในการตัดสินใจในเชิงนโยบายตั้งแต่ปี 2551 แต่การประเมินเทคโนโลยีด้านสุขภาพยังไม่เป็นที่แพร่หลาย เนื่องจากข้อจำกัดด้านบุคลากรด้านการประเมินเทคโนโลยีและไม่มีระบบการใช้ข้อมูลด้านการประเมินอย่างเป็นทางการ ซึ่งการให้การสนับสนุนของสำนักงานกองทุนสนับสนุนการวิจัยในโครงการเมธีวิจัยอาวุโส สกว. เพื่อพัฒนาศักยภาพการประเมินเทคโนโลยีด้านสุขภาพที่มีวัตถุประสงค์เพื่อ 1) พัฒนาศักยภาพนักวิจัยรุ่นเยาว์ และบุคลากรทางการแพทย์ด้านการประเมินเทคโนโลยีด้านสุขภาพ 2) ทำงานวิจัยด้านการประเมินเทคโนโลยีด้านสุขภาพสำหรับใช้ในการตัดสินใจเชิงนโยบายในระดับชาติและสถานพยาบาล 3) พัฒนาระเบียบวิธีวิจัยและคู่มือที่จำเป็นสำหรับการประเมินเทคโนโลยีด้านสุขภาพในประเทศ และ 4) วิจัยและพัฒนาระบบ กลไก การนำผลการประเมินเทคโนโลยีด้านสุขภาพไปใช้ในการตัดสินใจด้านสุขภาพ รวมถึงการจัดสรรงบประมาณ จากการดำเนินโครงการเมธีวิจัยอาวุโสฯ ตั้งแต่ 25 กันยายน 2555 ถึง 24 กันยายน 2558 มีการรับนักวิจัยรุ่นเยาว์จำนวน 15 คน และมีนักวิจัยศึกษาต่อทั้งในและต่างประเทศ 8 คน นักวิจัยภายใต้การดูแลของดร.นพ.ยศ ตีระวัฒนานนท์ผู้รับทุนเมธีวิจัยอาวุโส ดำเนินการศึกษาวิจัยด้านการประเมินเทคโนโลยีและนโยบายด้านสุขภาพเสร็จสิ้นจำนวน 46 เรื่อง ซึ่งงานวิจัยได้นำเสนอให้กับผู้กำหนดนโยบายทั้งในและต่างประเทศจำนวนทั้งสิ้น 17 หน่วยงาน ในจำนวนนี้อย่างน้อย 35 เรื่องมีการตัดสินใจเชิงนโยบายเป็นที่สิ้นสุดแล้ว ซึ่งนอกจากการศึกษาวิจัยเพื่อใช้ในเชิงนโยบาย โครงการประเมินประเมินเทคโนโลยีและนโยบายด้านสุขภาพได้ศึกษาการวัดคุณภาพชีวิตสำหรับประชากรไทยและจัดทำคู่มือด้านการประเมินเทคโนโลยีด้านสุขภาพสำหรับประเทศไทย ฉบับที่ 2 เพื่อใช้เป็นแนวทางการประเมินเทคโนโลยีด้านสุขภาพ นอกเหนือจากการพัฒนางานศักยภาพนักวิจัย โดยการทำวิจัยและพัฒนาเครื่องมือต่างๆ สำหรับการประเมินเทคโนโลยีด้านสุขภาพแล้ว การเผยแพร่ผลงานวิจัยไปสู่สาธารณะก็เป็นอีกกิจกรรมหนึ่งที่จะสร้างความสนใจและทำให้ผู้มีส่วนเกี่ยวข้องได้เห็นความสำคัญของการประเมินเทคโนโลยีและนโยบายด้านสุขภาพ โดยการจัดทำสื่อจะมีหลายกลุ่มเป้าหมาย ได้แก่ การทำ policy brief รายงานการวิจัย จุลสาร จดหมายข่าว การนำเสนอผลการศึกษาในการประชุมวิชาการ และการตีพิมพ์งานวิจัยในวารสารทั้งในประเทศและต่างประเทศ รวมแล้ว 22 ฉบับ ซึ่งมากกว่าที่ระบุในผลงานของโครงการเมธีวิจัยอาวุโส สกว. เพื่อพัฒนาศักยภาพการประเมินเทคโนโลยีด้านสุขภาพ ปี 2555-2558

จะเห็นได้ว่าการทำงานโครงการประเมินเทคโนโลยีและนโยบายด้านสุขภาพ โดยดร.นพ.ยศ ตีระวัฒนานนท์ สามารถดำเนินงานได้ตามวัตถุประสงค์ของโครงการ และดำเนินงานได้เกินเป้าหมายตามสัญญาที่ได้รับจากสำนักงานกองทุนสนับสนุนการวิจัย ยิ่งไปกว่านั้นการดำเนินงานของโครงการประเมินเทคโนโลยีและนโยบายด้านสุขภาพได้ตอบสนองต่อความต้องการในการประเมินเทคโนโลยีด้านสุขภาพในต่างประเทศ ทำให้ประเทศไทยได้รับการยกย่องจากองค์การอนามัยโลก และได้รับทุนเพิ่มเติมเพื่อพัฒนาศักยภาพด้านการประเมินเทคโนโลยีด้านสุขภาพในต่างประเทศอีกด้วย

คำสำคัญ: ประเมินเทคโนโลยีด้านสุขภาพ, พัฒนาขีดความสามารถ

Abstract

Health Technology Assessment (HTA) is one of the mechanism for High-level management or policy-maker to make use of academic data to support decision making process as to obtain efficiency in allocating of health-resources. Therefore, ultimately ensure benefit maximization and cost-effectiveness.

In year 2557, World Health Organization (WHO) gave global support to strengthen HTA, especially in countries where Universal Health Coverage Scheme have been employed. Since year 2551, HTA has been adopted in decision making process in the realms of policy-making in Thailand. However, the use of HTA is not yet rampant due to limitation in workforce specializing in HTA, and the fact that there was no standard operating procedure (SOP) to use academic data to conduct evaluation in an official manner. Under Thailand Research Fund (TRF) support, an aim to strengthen Health Intervention and Assessment Program under Health Policy and Strategy as followed:

1) Develop capacity building for young junior researcher, and HTA health professionals.
2) Conduct HTA research to be used in policy making decisions in hospital settings and at a National level.
3) Develop methods, tools, and guidelines necessary for HTA evidence generation locally.
4) Research and develop systems and mechanisms to promote the official integration of HTA information to be incorporated into policy decisions, including resource allocation under public health plans.

Under TRF support, from 25th of September 2555 to 24th of September 2558, Health Intervention and Technology Assessment Program (HITAP) recruited 15 young researchers and subsidized 8 researchers to further studies at both domestic and aboard institution. Fellow researchers under the supervision of Dr. Yot Teerawattananon, whom received funding under Senior Research Scholar Program (SRS), had completed 46 topics of HTA researches. The outcome of researches were presented to policy-maker of 17 for domestic and international organizations. Out of 46 topics, there were at least 35 were selected for policy-making decision. HITAP does not only conduct research to support the policy-making process, it also conducts studies to measure the quality of life for Thai citizens. In addition to this, 2nd edition of HTA manuals were produced as guideline to conduct HTA. Besides developing researchers' capacity by building research experiences, and making improvement on tools used to conduct HTA research, research dissemination was another activity to arouse people' interest, educate public, and draw in stakeholders as to acknowledge them on the importance of HTA. Communication methods were selected for various target group such as policy brief, researches reports, pamphlet, and presentation of studies in academic

conference. Additionally, 22 domestic and international peer review journal were published, which exceeded the target set by TRF.

In the light of HTA development from year 2555 to 2558 lead by Dr.Yot Teerawattananon demonstrated accomplishment in performance according to the objective of SRS, and exceed the target set by TRF. Moreover, the work of HITAP, and HTA in Thailand was recognized internationally by World Health Organization (WHO). Consequently, HITAP was able to obtain additional funding for development of HTA in other countries as well..

Keyword: HTA, Capacity building

สรุปผลการดำเนินงานโครงการเมธีวิจัยอาวุโส สกว. เพื่อพัฒนาศักยภาพการประเมินเทคโนโลยีด้านสุขภาพ ปี 2555-2558

โครงการเมธีวิจัยอาวุโส สกว. เพื่อพัฒนาศักยภาพการประเมินเทคโนโลยีด้านสุขภาพ โดยโครงการประเมินเทคโนโลยีและนโยบายด้านสุขภาพ กระทรวงสาธารณสุข ได้รับทุนสนับสนุนจากสำนักงานกองทุนสนับสนุนการวิจัย ตั้งแต่วันที่ 25 กันยายน 2555 – 24 กันยายน 2558 มี ดร. นพ.ยศ ตีระวัฒนานนท์ เป็นหัวหน้าโครงการเพื่อดำเนินการให้เป็นไปตามวัตถุประสงค์ของโครงการคือ

1. เพื่อพัฒนาศักยภาพนักวิจัยรุ่นเยาว์ และบุคลากรทางการแพทย์ด้านการประเมินเทคโนโลยีด้านสุขภาพ
2. เพื่อทำงานวิจัยด้านการประเมินเทคโนโลยีด้านสุขภาพสำหรับใช้ในการตัดสินใจเชิงนโยบายในระดับชาติและสถานพยาบาล
3. เพื่อพัฒนาระเบียบวิธีวิจัยและคู่มือที่จำเป็นสำหรับการประเมินเทคโนโลยีด้านสุขภาพในประเทศ
4. เพื่อวิจัยและพัฒนาระบบ กลไก การนำผลการประเมินเทคโนโลยีด้านสุขภาพไปใช้ในการตัดสินใจด้านสุขภาพ รวมถึงการจัดสรรงบประมาณ

โครงการเมธีวิจัยอาวุโส สกว. เพื่อพัฒนาศักยภาพการประเมินเทคโนโลยีด้านสุขภาพ ดำเนินงานวิจัยด้านการประเมินเทคโนโลยีและนโยบายด้านสุขภาพ ซึ่งครอบคลุมยา เครื่องมือแพทย์ หัตถการ มาตรการสร้างเสริมสุขภาพและป้องกันโรค รวมถึงนโยบายสาธารณะอื่นๆ ที่มีผลกระทบต่อสุขภาพ เพื่อสนับสนุนข้อมูลวิชาการที่ช่วยในการตัดสินใจเชิงนโยบายรวมถึงการจัดสรรทรัพยากรในระบบสุขภาพให้เป็นไปอย่างมีประสิทธิภาพตลอดจนมุ่งให้การใช้เทคโนโลยีด้านสุขภาพเป็นไปอย่างสม โครงการดำเนินกิจกรรมในระยะเวลา 3 ปี มีกิจกรรมด้านการพัฒนาศักยภาพนักวิจัยและบุคลากรทางการแพทย์ด้านการประเมินเทคโนโลยี จำนวน 587 คน และมีการดำเนินกิจกรรมต่างๆ ที่เกี่ยวข้องกับการประเมินเทคโนโลยีการเสร็จสิ้นจำนวน 46 โครงการ และมีโครงการดำเนินงานต่อเนื่อง 13 โครงการ ซึ่งโครงการเหล่านี้ได้ถูกนำไปใช้ในเชิงนโยบายในการพัฒนาระบบสุขภาพและสิทธิประโยชน์เพื่อให้ประชาชนมีคุณภาพชีวิตที่ดีขึ้น โดยมีการดำเนินงานตามวัตถุประสงค์ดังนี้

วัตถุประสงค์ที่ 1 การพัฒนาศักยภาพนักวิจัยรุ่นเยาว์และบุคลากรทางการแพทย์ด้านการประเมินเทคโนโลยีด้านสุขภาพ

งานวิจัยด้านการปะรเมินเทคโนโลยีด้านสุขภาพเป็นงานวิจัยที่เป็นศาสตร์ใหม่ในประเทศไทย และเป็นงานวิจัยที่สามารถนำไปใช้ประโยชน์ได้ในทั้งระดับประเทศ องค์กร หน่วยงาน ซึ่งโครงการประเมินเทคโนโลยีและนโยบายด้านสุขภาพได้จัดให้มีการอบรมด้านการประเมินเทคโนโลยีด้านสุขภาพให้กับบุคคลภายนอกเป็นประจำทุกปี ได้แก่ การอบรมเชิงปฏิบัติการ “การประเมินเทคโนโลยีด้านสุขภาพ (HTA Workshop)” และการอบรมเชิงปฏิบัติการ “การอบรมการประเมินความคุ้มค่าทางการแพทย์และสาธารณสุข” ซึ่งการจัดการประชุมดังกล่าวทำให้มีนักวิจัยและบุคลากรทางการแพทย์ที่สนใจด้านการประเมินเทคโนโลยีด้านสุขภาพต้องการทำวิจัยด้านการประเมินเทคโนโลยีด้านสุขภาพเพิ่มมากขึ้น รวมทั้งสิ้น 587 คน ถึงแม้ในแต่ละปีเกิดนักวิจัยรุ่นใหม่ที่มาจากการอบรมไม่มากก็ตาม นอกจากนี้โครงการประเมินเทคโนโลยีและนโยบายด้านสุขภาพยังเป็นแหล่งฝึกงาน อาจารย์พิเศษของคณะเภสัชศาสตร์ และคณะแพทยศาสตร์อีกด้วย

สำหรับบุคลากรภายในตั้งแต่ปี 2555-2558 โครงการประเมินเทคโนโลยีและนโยบายด้านสุขภาพมีนักวิจัยอยู่ในโครงการแบบเต็มเวลาจำนวน 32 คน นักวิจัยบางเวลา 4 คน ที่ปรึกษานักวิจัย 3 คน โดยมีนักวิจัยรุ่นเยาว์ที่เข้าร่วมงานวิจัยจำนวน 15 คน นอกจากนี้นักวิจัยในโครงการประเมินเทคโนโลยีและนโยบายด้านสุขภาพอยู่ระหว่างการศึกษาจำนวน 4 คน เป็นการศึกษาในระดับปริญญาโทและปริญญาเอก ทั้งในและต่างประเทศ ดังแสดงในตารางที่ 1 ในการพัฒนาศักยภาพนักวิจัยภายในโครงการจะมีการจัดอบรม “Journal club” ซึ่งเป็นการอบรมแลกเปลี่ยนความรู้ของบุคลากรภายในและการสอนจากบุคลากรภายนอก ดังแสดงในตารางที่ 2

ตารางที่ 1 รายนามนักวิจัยที่ศึกษาต่อและนักวิจัยรุ่นเยาว์ ในระหว่างการสนับสนุนของโครงการเมธีวิจัยอาวุโสฯ

ลำดับ	รายามนักวิจัย	ระดับการศึกษา	มหาวิทยาลัยและสาขา
นักวิจัยที่ศึกษาต่อ			
1	น.ส.จันทนา พัฒนเภสัช (นักวิจัย)	จบการศึกษาระดับปริญญาเอก	คณะเภสัชศาสตร์ สาขาบริหารเภสัชกิจ มหาวิทยาลัยมหิดล
2	น.ส.วรัญญา รัตนวิภาพงษ์ (ผู้ช่วยวิจัย)	จบการศึกษาระดับปริญญาโท	Health Economics and Decision Modelling (HART4) the University of Sheffield ณ สหราชอาณาจักร
3	น.ส.รุ่งนภา คำผาง (ผู้ช่วยวิจัย)	จบการศึกษาระดับปริญญาโทเอก	สาขาระบาดวิทยานานาชาติ มหาวิทยาลัยสงขลานครินทร์
4	น.ส.รักมณี บุตรชน (ผู้ช่วยวิจัย)	กำลังศึกษาระดับปริญญาเอก	สาขาระบาดวิทยานานาชาติ มหาวิทยาลัยสงขลานครินทร์
5	น.ส.จอมขวัญ โยธาสมุทร (นักวิจัย)	กำลังศึกษาระดับปริญญาเอก	Social Sciences Research (DEV), University of East Anglia ณ สหราชอาณาจักรบริเตนใหญ่และไอร์แลนด์เหนือ
6	น.ส.พัทธรา ลีฬหวรงค์ (นักวิจัย)	กำลังศึกษาระดับปริญญาเอก	Health Economics, University of Glasgow ณ ราชอาณาจักรสกอตแลนด์
7	นายกิตติพงษ์ ธิบูรณ์บุญ (ผู้ช่วยวิจัย)	กำลังศึกษาระดับปริญญาโท	Health Economics, University of York ณ สหราชอาณาจักร
8	น.ส.ปฤษฐพร กิ่งแก้ว (นักวิจัย)	กำลังศึกษาระดับปริญญาเอก	Health service research, University of Leeds ณ สหราชอาณาจักร
นักวิจัยรุ่นเยาว์			
1	น.ส.เสริมสิริ แสงรุ่งเรืองศรี (ผู้ช่วยวิจัย)	ปริญญาโท	Clinical Pharmacology จาก University of Aberdeen สหราชอาณาจักร
2	น.ส.วริทธิ์ จันทรสถาพรจิต (ผู้ช่วยวิจัย)	ปริญญาโท	สาขาวิชา Health Economics, Norwich Medical school, University of East Anglia สหราชอาณาจักร
3	น.ส.เบญจรินทร์ สันตติวงศ์ไชย (ผู้ช่วยวิจัย)	ปริญญาโท	Health Economics, Department of Economics and Related Studies, University of York สหราชอาณาจักร
4	น.ส.แก้วกุล ตันติพิสิฐกุล (ผู้ช่วยวิจัย)	ปริญญาโท	สาขาวิชาสุขภาพจิต คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย

ลำดับ	รายามนักวิจัย	ระดับการศึกษา	มหาวิทยาลัยและสาขา
5	น.ส.สุธีนุช ตั้งสถิตย์กุลชัย (ผู้ช่วยวิจัย)	ปริญญาโท	Applied Human Rights, Centre for Applied Human Rights, University of York
6	น.ส.สโรชา ชูติพงค์ชัยวัฒน์ (ผู้ช่วยวิจัย)	ปริญญาโท	Health Economics ,Policy and Law, of Erasmus University Rotterdam
7	Dr.Thant Htoo Aung (ผู้ช่วยวิจัย)	ปริญญาโท	คณะสาธารณะสุขศาสตร์ มหาวิทยาลัยมหิด
8	น.ส.ชุติมา คำดี (ผู้ช่วยวิจัย)	ปริญญาตรี	สาขาวิชาการแพทย์แผนตะวันตก การแพทย์แผนตะวันตก มหาวิทยาลัยรังสิต
9	น.ส.ศิริกาญจน์ โรจนสาโรจน์ (ผู้ช่วยวิจัย)	ปริญญาตรี	Pharmaceutical sciences คณะเภสัชศาสตร์ มหาวิทยาลัยมหิดล
10	นายวิทธวัช พันธุมงคล (ผู้ช่วยวิจัย)	ปริญญาตรี	สาขาวิชาอนามัยชุมชน คณะสาธารณสุขศาสตร์ มหาวิทยาลัยมหิดล
11	นายอุดมศักดิ์ นาคกุล (ผู้ช่วยวิจัย)	ปริญญาตรี	อนามัยชุมชน คณะสาธารณสุขศาสตร์ มหาวิทยาลัยมหิดล
12	น.ส.ธันธิมา สุวรรณถาวรกุล (ผู้ช่วยวิจัย)	ปริญญาตรี	สาขาเภสัชศาสตร์สังคมและบริหาร คณะเภสัชศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย
13	น.ส.นิธิเจน กิตติรัชกุล (ผู้ช่วยวิจัย)	ปริญญาตรี	สาขาเภสัชศาสตร์สังคมและบริหาร คณะเภสัชศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย
14	นาย ปิติพงษ์ กรรณมณีเลิศ (ผู้ช่วยวิจัย)	ปริญญาตรี	บริบาลเภสัชกรรม คณะภสัชศาสตร์ มหาวิทยาลัยนเรศวร
15	นาย เพียร เพลินบรรณกิจ (ผู้ช่วยวิจัย)	ปริญญาตรี	บริบาลเภสัชกรรม คณะภสัชศาสตร์ มหาวิทยาลัยนเรศวร

ตารางที่ 2 การจัด **Journal club**

ลำดับ	หัวข้อ	ผู้บรรยาย
1	การคัดกรองผู้มีปัญหาการดื่มสุรา ร่วมกับการให้คำแนะนำอย่างสั้น	ภญ.วริทธิ์ จันทรสถาพรจิต
2	Accuracy and Precision Evaluation of Nine Self-Monitoring Blood Glucose Systems	ภญ.ปรียานุช ดีบุกคำ
3	การเขียน Policy Briefs	ดร. ภญ.ศรีเพ็ญ ตันติเวสส
4	การขับเคลื่อนและการสื่อสารงานวิจัยทางด้านการประเมินเทคโนโลยีและนโยบายด้านสุขภาพ	คุณกรรณิการ์ กิจติเวชกุล นักจัดรายการวิทยุคลื่นความคิด FM 96.5
5	Basic clinical epidemiology topic 1: Introduction to clinical epidemiology	พญ.ธัญญรัตน์ อโนทัยสินทวี
6	Basic clinical epidemiology topic 2: Diagnostic and screening test	พญ.ธัญญรัตน์ อโนทัยสินทวี
7	Basic clinical epidemiology Topic 3: Risk and Prognostic study: Cohort and case-control	พญ.ธัญญรัตน์ อโนทัยสินทวี

ลำดับ	หัวข้อ	ผู้บรรยาย
8	Basic clinical epidemiology Topic 4: Treatment & Prevention: RCT	พญ.ธัญญรัตน์ อโนทัยสินทวี
9	Knowledge management: Maternal and Child Health Voucher Scheme Mission	ภญ.พิศพรรณ วีระยิ่งยง
10	Experience of HTAsiaLink 2014	นักวิจัย HITAP
11	How to produce a good policy brief	นายสุรเดช ดวงทิพย์สิริกุล นางสาวสุธีนุข ตั้งสถิตย์กุลชัย และ นางสาวอภิญญา มัตตเดช
12	Grading of Recommendations Assessment Development and Evaluation (GRADE)	ผศ. ดร. ภญ.มนทรัตม์ ถาวรเจริญทรัพย์ ภญ.ศิตาพร ยังคง และนางสาวชุติมา คำดี
13	Fundamental of ICH-GCP	ภญ.ธันธิมา สุวรรณถาวรกุล และ นายวิทธวัช พันธุมงคล
14	Linear programming using excel solver: a hands-on training	นางสาววรัญญา รัตนวิภาพงษ์
15	Estimating the sample size with n4Studies: a hands-on training	นางสาวสโรชา ชูติพงศ์ชัยวัฒน์ นายอุดมศักดิ์ นาคกุล และ นายดนัย ชินคำ
16	Leading a group discussion: how to become a well-plan facilitator	ภญ.พิศพรรณ วีระยิ่งยง ภญ.วริทธิ์ จันทรสถาพรจิต และ ภญ.ธันธิมา สุวรรณถาวรกุล

นอกจากการอบรมหรือเรียนรู้ภายในหน่วยงานแล้ว โครงการประเมินเทคโนโลยีและนโยบายด้านสุขภาพได้สนับสนุนให้มีนักวิจัยได้ไปอบรมภายนอกหน่วยงานทั้งภายในประเทศและต่างประเทศ ซึ่งผู้ที่ไปอบรมจะนำความรู้ที่ได้มาจัด Journal club ต่อไปเพื่อให้มีการถ่ายทอดความรู้และเป็นการเพิ่มทักษะการสอนไปในตัว โดยหัวข้อและผู้ที่ได้รับอบรมตามตารางที่ 3

ตารางที่ 3 การฝึกอบรมหลักสูตรต่างทั้งในประเทศและต่างประเทศ

ปี	หัวข้อการอบรม/การประชุม	ผู้รับการอบรม
2556	Permission for EQ-VT (software for valuation study) workshop and EQ-5D	ภญ.จันทนา พัฒนเภสัช ภญ.ปฤษฐพร กิ่งแก้ว นางสาววันทนีย์ กุลเพ็ง
	World conference on health promotion	ดร.ภญ.ศิตาพร ยังคง ภญ.พิศพรรณ วีระยิ่งยง ภญ.ธนพร บุษบาวไล
	The international health economics association	ดร.ภญ.ศิตาพร ยังคง
	Health Technology Assessment International	นายกิตติพงษ์ ธิบูรณ์บุญ นางสาวสุมาลัย สมภิทักษ์

ปี	หัวข้อการอบรม/การประชุม	ผู้รับการอบรม
	Training of Trainers on Grading of recommendation assessment development and evaluation	นางสาวชุติมา คำดี
	การประชุมวิชาการสารเสพติดระดับชาติ ครั้งที่ 8	ภญ.วริทธิ์ จันทรสถาพรจิต
2557	นำเสนองานวิจัย EQ-5D ในงานประชุมวิชาการ ISPOR	ภญ.จันทนา พัฒนเภสัช
	นำเสนองานวิจัยในการประชุม HTAi 2014	ดร.ภญ.ศิตาพร ยังคง
	การปฏิบัติการวิจัยทางคลินิกที่ดี (ICH-GCP)	ภญ.ธันธิมา สุวรรณถาวรกุล นายวิทธวัช มณีอ่อน
	นำเสนองานวิจัยงานประชุมวิชาการกระทรวงสาธารณสุข	นางสาววันทนีย์ กุลเพ็ง
	เข้ารับการอบรม Policy Communication	นายสุรเดช ดวงทิพย์สิริกุล น.ส.สุธีนุช ตั้งสถิตกุลชัย นางสาวอภิญญา มัตเดช
	Infographic Workshop: how to create Info graphic	นายวรุฒ เลิศศราวุธ
2558	การอบรมเชิงปฏิบัติการเรื่อง Facilitator and note taker	ภญ.พิศพรรณ วีระยิ่งยง ภญ.วริทธิ์ จันทรสถาพรจิต ภญ.ธันธิมา สุวรรณถาวรกุล
	Introduction to epidemiological and economic modeling of infectious diseases	ภญ.พิศพรรณ วีระยิ่งยง ภญ.นัยนา ประดิษฐ์สิทธิกร Miss Alia Luz

นอกจากการพัฒนาศักยภาพนักวิจัยโดยการฝึกอบรมแล้ว โครงการประเมินเทคโนโลยีและนโยบายสุขภาพร่วมกับเครือข่ายการประเมินเทคโนโลยีด้านสุขภาพในภูมิภาคเอเชีย (HTAsiaLInk) ได้ร่วมมือกันจัดประชุมการนำเสนอผลงานวิชาการแบบปากเปล่า เพื่อให้นักวิจัยได้พัฒนาศักยภาพด้านการนำเสนอและได้รับคำชี้แนะจากนักวิจัยอาจารย์จากมหาวิทยาลัยที่มีชื่อเสียงเพื่อใช้ในการปรับปรุงงานวิจัยเพิ่มขึ้น ทั้งนี้ในการประชุมวิชาการนานาชาติ HTAsiaLink นักวิจัยโครงการประเมินเทคโนโลยีและนโยบายด้านสุขภาพได้รับรางวัลการนำเสนอผลงานหลายรางวัล ได้แก่ ในปี 2558 รางวัลการนำเสนอดีเด่น จากการนำเสนอด้านการประเมินเทคโลยีด้านสุขภาพ คือ ภญ.พัทธรา ลีฬหวรงค์ และภญ.วรัญญา รัตนวิภาพงษ์ และการนำเสนอด้านระบบสุขภาพ คือ นางสาวสโรชา ชูติพงษ์ชัยวัฒน์ ปี 2557 รางวัลการนำเสนอดีเด่นด้านการประเมินเทคโลยีด้านสุขภาพ คือภญ.ปฤษฐพร กิ่งแก้ว โดยการนำเสนอผลงานทั้งหมดในการประชุมวิชาการนานาชาติ HTAsiaLink ตามตารางที่ 4

ตารางที่ 4 หัวข้อการนำเสนอในการประชุมวิชาการนานาชาติ HTAsiaLIn**k**

ลำดับ	หัวข้อที่นำเสนอ	นักวิจัย
การประชุมวิชาการนานาชาติ HTAsiaLink ครั้งที่ 2 ประจำปี พ.ศ. 2556 ณ เมืองปีนัง ประเทศมาเลเซีย		
1	"Assessing the accuracy and feasibility of refractive error screening by school teachers in pre-primary and primary schools in Thailand"	พญ.กัลยา ตีระวัฒนานนท์
2	Reconstructing the data from published Kaplan-Meier survival curves: the application of economic evaluation of treatments for metastatic renal cell carcinoma in Thailand	ภญ.ปฤษฐพร กิ่งแก้ว
3	Systematic Review of Population-Based Screening for Prostate Cancer	ภญ.คัคนางค์ โตสงวน
4	Epidemiological survey of mental disorders in five contracting unit for primary care areas in Thailand.	นายธีระ ศิริสมุด
5	Do seasonal influenza vaccines offer a good value for money when vaccinating to Thai school-aged children? Report on interim findings	ภญ.สุรชัย โกติรัมย์
6	Neonatal Screening for Inborn Errors of Metabolism Using Tandem Mass Spectrometry: A Cost-Effectiveness Study from Thailand	นายกิตติพงษ์ ธิบูรณ์บุญ
7	Systematic review of efficacy and economic evaluation of screening interventions to prevent road traffic accidents	ภญ.กุณฑิกา ดำรงปราชญ์
8	Access to health services for intravenous drug users in Songkhla province	นางสาวรุ่งนภา คำผาง
9	Models of HIV counseling and testing service for general population: a review"	ภญ.วรัญญา รัตนวิภาพงษ์
10	Eliciting expert opinion for model parameters and their distributions for using in the economic model of seasonal influenza vaccine	นางสาววันทนีย์ กุลเพ็ง
11	Cost-Utility Analysis of Dasatinib and Nilotinib of CML patients failed from first line treatment with Imatinib in Thailand	นางสาวสุมาลัย สมภิทักษ์
12	A review of health research priority setting in Thailand	ภญ.สุธาสินี คำหลวง
13	Developing the indicators for evaluating the development of healthy public policy in Thailand: a case study of ‘universal access to medicines for Thai people	ภญ.ธนพร บุษบาวไล
14	Cost-effectiveness of alcohol screening and brief intervention to reduce alcohol use disorder in Thailand	ภญ.วริทธิ์ จันทรสถาพรจิต
15	Development of population-based screening package in Thailand	ภญ.ธนัญญา คู่พิทักษ์ขจร

ลำดับ	หัวข้อที่นำเสนอ	นักวิจัย
16	The Economics of Pressure Ulcer Prevention in Hospitals: a systematic review and economic evaluation.	ภญ.เบญจรินทร์ สันตติวงศ์ไชย
การประชุมวิชาการนานาชาติ HTAsiaLink ครั้งที่ 3 ประจำปี พ.ศ. 2557 ณ กรุงปักกิ่ง สาธารณรัฐประชาชนจีน		
1	Reviews of economic evaluations: information for standardising methodology for the Bill and Melinda Gates Foundation (BMGF)	ภญ.วริทธิ์ จันทรสถาพรจิต
2	Assessing the feasibility and appropriateness of using surgical navigation in Thailand	ภญ.ธนพร บุษบาวไล
3	Economic evaluations of rotavirus vaccines: a systematic review of methodological variation and quality between resource-limited country studies and resource-rich country studies	นายกิตติพงษ์ ธิบูรณ์บุญ
4	A cost-utility and budget impact analysis of screening and treatment for chronic hepatitis C in HIV-infected patient	ภญ.ปฤษฐพร กิ่งแก้ว
5	Effects of assistive devices on quality of life and functional outcomes in disabled people: observational study	นางสาววันทนีย์ กุลเพ็ง
6	The evaluation of health promotion program for elderly in Thailand	นายสุรเดช ดวงทิพย์สิริกุล
7	Safety of intravitreal bevacizumab and ranibizumab injections for treatment of retinal disease patients: An observational study	ภญ.สุธาสินี คำหลวง
8	The effectiveness of diabetes control program for Thai elderly diabetic patients	นายธีระ ศิริสมุด
9	A review of the benefit packages for people with disability under main the health benefit schemes in Thailand	นางสาวแก้วกุล ตันติพิสิฐกุล
10	Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L in Thai diabetes patients	ภญ.จันทนา พัฒนเภสัช
11	Topic prioritization for developing health promotion and disease prevention policies for adults in Thailand.	นางสาวชุติมา คำดี
การประชุมวิชาการนานาชาติ HTAsiaLink ครั้งที่ 4 ประจำปี พ.ศ. 2558 ณ กรุงไทเป ไต้หวัน		
1	Cost-utility analysis of adjuvant imatinib in patients with high risk of gastrointestinal stromal tumor (GIST) recurrence in Thailand	ภญ.ธนพร บุษบาวไล
2	Economic evaluation of the use of biologic disease-modifying anti-rheumatic drugs in the treatment of patients with rheumatoid arthritis	ภญ.วริทธิ์ จันทรสถาพรจิต

ลำดับ	หัวข้อที่นำเสนอ	นักวิจัย
3	Does the WHO Package of Essential Non-communicable disease (PEN) interventions represent good value for money in resource-limited settings	ภญ.วรัญญา รัตนวิภาพงษ์
4	Identifying the priority methodological research for conducting economic evaluation in low- and middle- income countries: Finding the Holy Grail	ภญ.เบญจรินทร์ สันตติวงศ์ไชย
5	Effectiveness of interferon-free compared with interferon-based regimens for treatment naïve and null responders HCV genotype 1 infection: A systematic review and meta-analysis	ภญ.ธันธิมา สุวรรณถาวรกุล
6	Effectiveness of the risk assessment tools for cardiovascular disease prevention in adults in Thailand: A comparison between WHO/ISH prediction chart and Thai ASCVD score.	นางสาวชุติมา คำดี
7	The journey to HTA in low- and middle-income countries: conducive factors and barriers to HTA development	นางสาวสโรชา ชูติพงษ์ไชยวัฒน์
8	Review of Maternal and Child Health Voucher Scheme: Review of the First Six Months	นายทรงยศ พิลาสันต์
9	Prevalence and Factors associated with obesity among Thai elderly: the 2013 Thai elderly health survey	นายสุรเดช ดวงทิพย์สิริกุล
10	Development of health promotion program for informal sector in Thailand under Universal Health Coverage scheme	นางสาวสุธีนุช ตั้งสถิตกุลชัย
11	Effectiveness of bevacizumab and ranibizumab in the real world: An observational study in patients with retinal diseases in Thailand	ภญ.สุธาสินี คำหลวง
12	Development and validation of breast cancer risk prediction model in Thai women	พญ.ธัญญรัตน์ อโนทัยสินทวี
13	Economic loss due to inaccessibility of assistive devices in Thailand	นางสาววันทนีย์ กุลเพ็ง
14	Evidence-informed decision making for including health promotion and disease prevention interventions in the universal health coverage benefit package for Thai adults: a review of effectiveness	นายวิทวัช พันธุมงคล

วัตถุประสงค์ที่ 2 เพื่อทำงานวิจัยด้านการประเมินเทคโนโลยีด้านสุขภาพสำหรับใช้ในการตัดสินใจเชิงนโยบายในระดับชาติและสถานพยาบาล

โครงการประเมินเทคโนโลยีและนโยบายด้านสุขภาพทำงานวิจัยเพื่อใช้เป็นสนับสนุนให้ผู้กำหนดนโยบายหรือผู้บริหารในการตัดสินใจใช้ทรัพยากรด้านสุขภาพที่มีอยู่อย่างจำกัดให้เกิดประโยชน์และคุ้มค่า ซึ่งจะส่งเสริมธรรมาบาลและสร้างความเสมอภาคและความเท่าเทียมกันของประชาชนในการเข้าถึงเทคโนโลยีด้านสุขภาพ โดยการมีส่วนร่วมของทุกภาคส่วน มีโครงการที่ดำเนินการทั้งในและต่างประเทศเสร็จสิ้นในระหว่างการรับทุนเมธีวิจัยอาวุโส จำนวน 46 โครงการ ตามตารางที่ 5

ตารางที่ 5 ผลงานวิจัยที่ดำเนินการเสร็จสิ้นในช่วงเวลาที่ได้รับทุนเมธีวิจัยอาวุโส

ปีที่แล้วเสร็จ /ลำดับ	ชื่องานวิจัย	หน่วยงานที่ใช้ผลงาน
กันยายน 2555		
1	การพัฒนาระบบคัดกรองภาวะสายตาผิดปกติและประกอบแว่นสายตาสำหรับเด็กก่อนวัยประถมศึกษาและประถมศึกษาในประเทศไทย	กระทรวงสาธารณสุข สำนักงานหลักประกันสุขภาพแห่งชาติ
2	Cost-consequence Analysis of Parenchymal Stapling versus hand-sewn for pulmonary lobectomy for lung diseases in Thailand: A Randomized controlled trial	นักวิจัย
3	มาตรการตรวจคัดกรองมะเร็งต่อมลูกหมากในกลุ่มประชากรอายุ 50 ปีขึ้นไป	กระทรวงสาธารณสุข สำนักงานหลักประกันสุขภาพแห่งชาติ
4	การประเมินความคุ้มค่าทางการแพทย์ของการให้บริการตรวจคัดกรองยีน HLA-B*1502 เพื่อหลีกเลี่ยงการเกิดผื่นแพ้ยาชนิดกลุ่มอาการ Stevens-Johnson syndrome (SJS) และ toxic epidermal necrolysis (TEN) จากยา carbamazepine	สำนักงานหลักประกันสุขภาพแห่งชาติ
5	การประเมินคุณค่าของสังคมต่อเพดานความคุ้มค่าในประเทศไทยและกลุ่มประเทศในเอเชีย	ผู้กำหนดนโยบาย
2556		
1	ความคุ้มค่าของการคัดกรองมะเร็งเต้านม	กระทรวงสาธารณสุข สำนักงานหลักประกันสุขภาพแห่งชาติ
2	การประเมินความคุ้มค่าและผลกระทบด้านงบประมาณของการรักษาผู้ป่วยโกเช่ร์ด้วยเอนไซม์อิมิกลูเซอเรส	คณะอนุกรรมการบัญชียาหลักแห่งชาติ
3	การประเมินต้นทุนอรรถประโยชน์ของการตรวจกรองและ รักษาโรคพันธุกรรมเมตาบอลิกในกลุ่มสารโมเลกุลเล็ก	สำนักงานหลักประกันสุขภาพแห่งชาติ
4	การประเมินความคุ้มค่าของการรักษาโรคกระดูกพรุนในหญิงวัยหมดประจำเดือน	คณะอนุกรรมการบัญชียาหลักแห่งชาติ
5	โครงการสนับสนุนและส่งเสริมการบริการ	กรมสุขภาพจิต

ปีที่แล้วเสร็จ /ลำดับ	ชื่องานวิจัย	หน่วยงานที่ใช้ผลงาน
	ครบวงจรสำหรับผู้ป่วยจิตเวชสำหรับผู้ป่วยจิตเวช ในพื้นที่เป้าหมายเร่งรัดภายใต้ระบบประกัน สุขภาพถ้วนหน้า	สำนักงานหลักประกันสุขภาพแห่งชาติ
6	การศึกษาเพื่อพัฒนาชุดสิทธิประโยชน์ด้านการคัดกรองทางสุขภาพระดับประชากรในประเทศไทย	กระทรวงสาธารณสุข สำนักงานหลักประกันสุขภาพแห่งชาติ
7	การประเมินการพัฒนานโยบายสาธารณะเพื่อสุขภาพภายใต้การดำเนินงานของสำนักงานคณะกรรมการสุขภาพแห่งชาติ ระหว่างปี พ.ศ.2550-2554	สำนักงานคณะกรรมการสุขภาพแห่งชาติ
8	ความคุ้มค่าของการคัดกรองภาวะทุพโภชนาการของผู้ป่วยในโรงพยาบาลเพื่อลดภาวะแทรกซ้อนจากการรักษา	สำนักงานหลักประกันสุขภาพแห่งชาติ
9	การจัดทำแนวทางปฏิบัติมาตรฐานในการทำวิจัยด้านการประเมินเทคโนโลยีแนะนโยบายด้านสุขภาพ	นักวิจัย
10	การพัฒนานโยบายด้านการสร้างเสริมสุขภาพและป้องกันโรคสำหรับเด็กโตและเยาวชน	กระทรวงสาธารณสุข สำนักงานหลักประกันสุขภาพแห่งชาติ
11	การประเมินผลกระทบความตกลงการค้าเสรีระหว่างประเทศไทยกับสหภาพยุโรปต่อการค้าและการลงทุน	นักวิจัย
12	การประเมินความคุ้มค่าและผลกระทบด้านงบประมาณของยา peginterferon และ ribavirin ในข้อบ่งใช้สำหรับผู้ป่วย HCV genotype 1 และอื่นๆ ที่จำเป็นต้องใช้ยาเกิน 24 สัปดาห์	คณะอนุกรรมการพัฒนาบัญชียาหลักแห่งชาติ
13	การประเมินความคุ้มค่าและผลกระทบด้านงบประมาณของยา peginterferon และ ribavirin ในข้อบ่งใช้สำหรับผู้ป่วยไวรัสตับอักเสบซี สายพันธุ์ 6	คณะอนุกรรมการพัฒนาบัญชียาหลักแห่งชาติ
14	การประเมินความคุ้มค่าและผลกระทบด้านงบประมาณของยา peginterferon และ ribavirin ในข้อบ่งใช้สำหรับ ผู้ป่วยไวรัสตับอักเสบซีที่ติดเชื้อไวรัส HIV ร่วมด้วย (HCV/HIV co-infection)	คณะอนุกรรมการพัฒนาบัญชียาหลักแห่งชาติ
15	การประเมินความคุ้มค่าและผลกระทบด้านงบประมาณของยากลุ่ม luteinizing hormone-releasing hormone analogues (LHRH analogues) ในข้อบ่งใช้สำหรับโรคมะเร็งต่อมลูกหมากใน adjuvant therapy และ metastatic disease	คณะอนุกรรมการพัฒนาบัญชียาหลักแห่งชาติ
16	การศึกษาประสิทธิภาพและความคุ้มค่าทางการแพทย์ของยามัยโคฟีโนเลตโซเดียม ในการรักษาภาวะโรคไตอักเสบ ลูปุสที่ดื้อต่อยาหรือกลับเป็นซ้ำ : ระยะที่ 2	นักวิจัย
17	การประเมินต้นทุน-อรรถประโยชน์ของวัคซีนป้องกันโรคไข้หวัดใหญ่ฤดูกาลสำหรับเด็กวัยเรียนในประเทศไทย	WHO
18	Reviewing evidence on adolescent pregnancy : evidence for development	UNFDA

ปีที่แล้วเสร็จ /ลำดับ	ชื่องานวิจัย	หน่วยงานที่ใช้ผลงาน
19	Reviewing Health Economic Evaluations Conducted in Low- and Middle-Income Countries: Information for Standardising Methodology for Bill & Melinda Gates Foundation	Bill & Melinda Gates Foundation
2557		
1	คู่มือการประเมินเทคโนโลยีด้านสุขภาพสำหรับประเทศไทย ฉบับที่ 2 พ.ศ. 2556	นักวิจัย
2	การประเมินความคุ้มค่าของเครื่องตรวจวัดระดับน้ำตาลในเลือดด้วยตนเอง	สำนักงานหลักประกันสุขภาพแห่งชาติ
3	การประเมินความคุ้มค่าของการตรวจคัดกรองมะเร็งทวารหนักในกลุ่มชายที่มีเพศสัมพันธ์กับชาย	สำนักงานหลักประกันสุขภาพแห่งชาติ
4	การพัฒนาและประเมินประสิทธิผลของมาตรการสื่อสารเพื่อป้องกันการฆ่าตัวตาย ระยะที่ 2	กรมสุขภาพจิต
5	การพัฒนาเครื่องมือประเมินคุณภาพชีวิต EQ-5D-5L และการวัดน้ำหนักอรรถประโยชน์ในประชากรไทย	นักวิจัย
6	การประเมินความคุ้มค่าทางเศรษฐศาสตร์ของกระบวนการตรวจวินิจฉัยเพื่อป้องกันการเกิดซ้ำของทารกกลุ่มอาการดาวน์และทารกที่มีความผิดปกติทางโครงสร้างของโครโมโซม	สำนักงานหลักประกันสุขภาพแห่งชาติ
7	การประเมินต้นทุนอรรถประโยชน์ของการตรวจติดตาม PT-INR ด้วยระบบ Point of Care เพื่อปรับยาและเฝ้าระวังยาในผู้ป่วยที่ต้องรับประทานยาต้านการแข็งตัวของเลือด	สำนักงานหลักประกันสุขภาพแห่งชาติ
8	การทบทวนชุดสิทธิประโยชน์และการเข้าถึงบริการอุปกรณ์เครื่องช่วยคนพิการ	สถาบันสร้างเสริมสุขภาพคนพิการ
9	โครงการพัฒนาข้อเสนอเพื่อการปรับปรุงชุดสิทธิประโยชน์และระบบบริการด้านการสร้างเสริมสุขภาพและป้องกันโรค สำหรับผู้ใหญ่/วัยทำงาน ภายใต้ระบบหลักประกันสุขภาพแห่งชาติ	สำนักงานหลักประกันสุขภาพแห่งชาติ
10	การทบทวนวรรณกรรมอย่างเป็นระบบเรื่องมาตรการการป้องกันการพลัดตกหกล้มและโรคสมองเสื่อมสำหรับผู้สูงอายุไทย	มูลนิธิสถาบันวิจัยและพัฒนาผู้สูงอายุไทย และกรมอนามัย กระทรวงสาธารณสุข
11	การประเมินความคุ้มค่าของนโยบายร่วมจ่ายระหว่างภาครัฐและภาคเอกชน สำหรับยา sunitinib	คณะอนุกรรมการพัฒนาบัญชียาหลักแห่งชาติ
12	ความร่วมมือระหว่าง HITAP, NICE International และประเทศ Philippines	ผู้บริหารประเทศฟิลิปินส์
13	โครงการพัฒนารูปแบบการตรวจคัดกรองมะเร็งลำไส้ (มะเร็งลำไส้ใหญ่และทวารหนัก) ในประชากรกลุ่มเสี่ยง	สำนักงานหลักประกันสุขภาพแห่งชาติ
กันยายน 2558		
1	การประเมินความคุ้มค่าด้านสุขภาพของการตรวจคัดกรองมะเร็งปากมดลูกด้วยวิธี HPV DNA ในประเทศไทย	สำนักงานหลักประกันสุขภาพแห่งชาติ

ปีที่แล้วเสร็จ /ลำดับ	ชื่องานวิจัย	หน่วยงานที่ใช้ผลงาน
2	การประเมินความคุ้มค่าของการใช้สารชีวภาพในผู้ป่วยโรคข้ออักเสบรูมาตอยด์	คณะอนุกรรมการพัฒนาบัญชียาหลักแห่งชาติ
3	การประเมินต้นทุนอรรถประโยชน์และผลกระทบด้านงบประมาณของยา imatinib สำหรับการรักษาเสริมในผู้ป่วยโรคมะเร็งเนื้อเยื่อในระบบทางเดินอาหาร (GIST) ที่ได้รับการผ่าตัดและมีโอกาสเกิดโรคซ้ำสูง	คณะอนุกรรมการพัฒนาบัญชียาหลักแห่งชาติ
4	ความคุ้มค่าทางการแพทย์ของการรักษามะเร็งลำไส้ใหญ่ระยะลุกลามของประเทศไทย	คณะอนุกรรมการพัฒนาบัญชียาหลักแห่งชาติ
5	การประเมินความคุ้มค่าของการใช้สารทึบรังสี gadoxetic acid (Primovist®) ในการตรวจวินิจฉัยมะเร็งตับ (Hepatocellular Carcinoma) ด้วยเครื่องแม่เหล็กไฟฟ้า	คณะอนุกรรมการพัฒนาบัญชียาหลักแห่งชาติ
6	การประเมินความคุ้มค่าของยา Iodized oil fluid injection (Lipiodol® Ultra Fluid) สำหรับการรักษามะเร็งตับ (Hepatocellular carcinoma)	คณะอนุกรรมการพัฒนาบัญชียาหลักแห่งชาติ
7	การรักษาและการป้องกันโรคหืดในเด็ก	สำนักงานหลักประกันสุขภาพแห่งชาติ
8	โครงการพัฒนาข้อเสนอเพื่อการปรับปรุงชุดสิทธิประโยชน์และระบบบริการด้านการสร้างเสริมสุขภาพและป้องกันโรค	สำนักงานหลักประกันสุขภาพแห่งชาติ
9	โครงการพัฒนาตัวชี้วัดคุณภาพบริการปฐมภูมิในระบบหลักประกันสุขภาพถ้วนหน้า ระยะที่ ๑	กระทรวงสาธารณสุข สำนักงานหลักประกันสุขภาพแห่งชาติ

วัตถุประสงค์ที่ 3 เพื่อพัฒนาระเบียบวิธีวิจัยและคู่มือที่จำเป็นสำหรับการประเมินเทคโนโลยีด้านสุขภาพในประเทศ

การประเมินเทคโนโลยีและนโยบายด้านสุขภาพเป็นกลไกสนับสนุนการทำงานของผู้กำหนดนโยบายให้มีข้อมูลผลกระทบทั้งด้านบวกและลบของการนำเทคโนโลยีและนโยบายมาใช้ในประเทศ ซึ่งกลไกนี้จะส่งเสริมการมีส่วนร่วมของทุกภาคส่วนในการพัฒนานโยบายต่างๆ นอกจากนี้การประเมินเทคโนโลยีและนโยบายด้านสุขภาพจะช่วยเพิ่มประสิทธิภาพของระบบสุขภาพ รวมถึงกองทุนประกันสุขภาพให้ใช้ทรัพยากรอย่างมีประโยชน์และคุ้มค่า จะเห็นได้ว่าการประเมินเทคโนโลยีและนโยบายด้านสุขภาพมีความสำคัญ การทำงานต้องมีความโปร่งใส มีมาตรฐาน ดังนั้นการมีระเบียบวิธีวิจัยและคู่มือที่จำเป็นสำหรับการประเมินเทคโนโลยีด้านสุขภาพจะทำให้ผลของการประเมินเทคโนโลยีด้านสุขภาพมีมาตรฐานเป็นไปในทิศทางเดียวกัน ผู้บริหารสามารถนำข้อมูลไปเปรียบเทียบและใช้ในการตัดสินใจได้ โดยโครงการประเมินเทคโนโลยีและนโยบายด้านสุขภาพได้พัฒนาการวัดคุณภาพชีวิต EQ-5D-5L สำหรับประชากรไทยและคู่มือการประเมินเทคโนโลยีด้านสุขภาพ ที่ได้รับการรับรองจากคณะอนุกรรมการบัญชียาหลักแห่งชาติสำหรับการทำข้อมูลที่ใช้ในการตัดสินใจของคณะอนุกรรมการบัญชียาหลักแห่งชาติและคณะทำงานต่างๆ ด้วย

เครื่องมือประเมินคุณภาพชีวิต EQ-5D-5L: การทดสอบคุณสมบัติการวัดและค่าน้ำหนักอรรถประโยชน์ในประชากรไทย

ในการประเมินความคุ้มค่าทางการแพทย์ เป็นการประเมินเทคโนโลยีด้านการแพทย์อย่างหนึ่ง ที่เปรียบเทียบผลลัพธ์ทางสุขภาพได้กับต้นทุนที่ใช้ไป ตามคู่มือการประเมินเทคโนโลยีด้านสุขภาพแนะนำให้ใช้เครื่องมือวัดคุณภาพชีวิตที่เป็นการวัดค่าอรรถประโยชน์ (Utility) จากแบบสอบถาม EuroQol ED-5D-3L ซึ่งมีการแปลเป็นภาษาไทยและมีคะแนนอรรถประโยชน์สำหรับคนไทยด้วยเช่นกัน ต่อมาในต่างประเทศ โดย EuroQol group ได้พัฒนาแบบสอบถามให้มีมิติการตอบได้ 5 ระดับเป็น EuroQol ED-5D-5L โดยโครงการประเมินเทคโนโลยีและนโยบายด้านสุขภาพได้สนับสนุนให้มีการพัฒนาแบบสอบถามและคะแนนอรรถประโยชน์ของ EQ-5D-5L สำหรับคนไทยและเปรียบเทียบกับ EQ-5D-3L ในด้านคุณสมบัติการวัดและผลการประเมินความคุ้มค่าทางเศรษฐศาสตร์

ในการพัฒนาคะแนนอรรถประโยชน์จากประชากรมีการดำเนินงานด้วยการสัมภาษณ์กลุ่มตัวอย่างจำนวน 1,207 ราย แบบตัวต่อตัวใน 12 จังหวัดทั่วประเทศ โดยใช้โปรโตคอล EQ-VT สุ่มตัวอย่างด้วยแผนการสุ่มตัวอย่างหลายขั้นและเลือกหน่วยตัวอย่างแบบโควต้าตามสัดส่วนของอายุและเพศ เพื่อให้กลุ่มตัวอย่างเป็นตัวแทนของประชากรไทย ประเมินคะแนนอรรถประโยชน์ด้วยวิธีการแลกเปลี่ยนเวลา (time trade-off, TTO) ดำเนินการโดยใช้สถานะสุขภาพจำนวน 86 สถานะที่แบ่งเป็น 10 กลุ่ม แต่ละกลุ่มประกอบด้วยสถานะสุขภาพ 10 สถานะ ประเมินคะแนนอรรถประโยชน์ของสถานะสุขภาพด้วยวิธีการ discrete choice experiment (DCE) ดำเนินการโดยใช้สถานะสุขภาพจำนวน 196 สถานะ ที่แบ่งเป็น 28 กลุ่ม แต่ละกลุ่มประกอบด้วยสถานะสุขภาพ 7 คู่ กลุ่มตัวอย่างแต่ละรายประเมินคะแนนอรรถประโยชน์ด้วยวิธี TTO และ DCE โดยใช้สถานะสุขภาพเพียงกลุ่มเดียว ซึ่งสุ่มโดยโปรแกรม EQ-VT สำหรับการเปรียบเทียบคุณสมบัติการวัดดำเนินการโดยสัมภาษณ์กลุ่มตัวอย่างที่เป็นโรคเบาหวานและรักษาด้วยอินซูลินจำนวน 117 รายด้วย แบบสอบถาม 3L 5L และ SF-36 ประเมินคุณสมบัติการวัดจากการกระจายของคำตอบ อิทธิพลเพดาน ความตรงเชิงเหมือน อำนาจการจำแนก ความเชื่อมั่นแบบสอบซ้ำ และความพึงพอใจของผู้ตอบแบบสอบถาม ส่วนการเปรียบเทียบผลการประเมินความคุ้มค่าทางเศรษฐศาสตร์จากการใช้ค่าอรรถประโยชน์ที่ได้จากแบบสอบถาม 5L และ 3L ทำการพิจารณาจากอัตราส่วนต้นทุนประสิทธิผลส่วนเพิ่ม (incremental cost-effectiveness ratio, ICER) และ กราฟระดับความคุ้มค่าที่ยอมรับได้ (cost-effectiveness acceptability curve, CEAC)

ผลการศึกษาพบว่าคะแนนอรรถประโยชน์ของสถานะสุขภาพทั้งหมดที่เป็นไปได้ของ 5L จำนวน 3,125 สถานะ มีความสอดคล้องกัน แบบจำลองที่ใช้ทำนายคะแนนอรรถประโยชน์สำหรับประชากรไทยคือแบบจำลองอิทธิพลแบบสุ่ม (random effect model) ที่ประกอบด้วยอิทธิพลหลักเพียงอย่างเดียว ผลการศึกษาพบว่ามิติการเคลื่อนไหวมีผลต่อคะแนนอรรถประโยชน์มากที่สุด สถานะสุขภาพที่คะแนนที่ดีที่สุดเป็นลำดับที่สองคือ 11112 มีคะแนน 0.970 ส่วนสถานะสุขภาพที่คะแนนน้อยที่สุดคือ 55555 มีคะแนน -0.290 ผลการศึกษาคุณบัติการวัดพบว่า 5L มีอิทธิพลเพดานน้อยกว่า 3L (33% และ 29%) นอกจากนี้ยังพบว่า 5L มีคุณสมบัติที่ดีกว่า 3L ในด้านอำนาจการจำแนก ความเชื่อมั่นแบบสอบซ้ำของคะแนนดัชนี และความพึงพอใจของผู้ตอบแบบสอบถาม ส่วนความตรงเชิงเหมือนไม่แตกต่างกันระหว่าง 5L และ 3L ในด้านการประเมินความคุ้มค่าทางเศรษฐศาสตร์พบว่าการใช้คะแนนอรรถประโยชน์ที่คำนวณจาก 5L ให้ค่าICER ต่ำกว่า 3L และช่วยลดความไม่แน่นอนของผลการศึกษา ดังนั้น 5L ควรได้รับการแนะนำให้เป็นแบบสอบถามคุณภาพชีวิตด้านสุขภาพสำหรับประเทศไทย

คู่มือการประเมินเทคโนโลยีด้านสุขภาพสำหรับประเทศไทย ฉบับที่ 2 พ.ศ. 2556

การพัฒนาคู่มือการประเมินเทคโนโลยีด้านสุขภาพจัดเป็นโครงการหนึ่งในยุทธศาสตร์เพื่อวิจัยและพัฒนาฐานรากของการประเมินเทคโนโลยีด้านสุขภาพ คู่มือการประเมินเทคโนโลยีด้านสุขภาพสำหรับประเทศไทยฉบับที่ 1 ดำเนินการแล้วเสร็จและได้รับการเผยแพร่ตั้งแต่ปี พ.ศ. 2551 โดยมีวัตถุประสงค์เพื่อใช้เป็นแนวทางสำหรับผู้ผลิตและผู้ใช้ข้อมูลการประเมินเทคโนโลยีด้านสุขภาพ เพื่อใช้ในการตรวจสอบความถูกต้องและคุณภาพของงานวิจัยสำหรับใช้ในการจัดสรรปันส่วนทรัพยากรด้านสุขภาพ คู่มือฯ ฉบับที่ 1 นี้ได้เสนอแนะแนวทางปฏิบัติเพื่อการพัฒนาคุณภาพของงานวิจัยด้านการประเมินความคุ้มค่าทางสาธารณสุข (Health economic evaluation) รวมทั้งเสนอแนะประเด็นสำคัญทั้งหมดของวิธีวิจัย และตระหนักถึงความจำกัดของทรัพยากรและข้อมูลที่มีความจำเพาะเจาะจงกับระบบสุขภาพในประเทศไทย นอกจากนั้น คู่มือฯ ฉบับแรกนี้ยังเสนอแนะแนวทางการเลือกวิธีการและแหล่งข้อมูลที่ใช้ในงานวิจัย จึงทำให้งานวิจัยเพิ่มความโปร่งใสมากยิ่งขึ้น หากปราศจากคู่มือดังกล่าวย่อมส่งผลให้เกิดความหลากหลายในคุณภาพของงานวิจัย และผู้ตรวจสอบผลงานวิจัยไม่สามารถประเมินคุณภาพและความถูกต้องของงานวิจัยได้ อย่างไรก็ตาม การมีคู่มือการประเมินเทคโนโลยีด้านสุขภาพสำหรับประเทศไทย ก็ไม่สามารถรับรองว่าจะมีการนำข้อมูลเหล่านี้ไปใช้ในการตัดสินใจเชิงนโยบาย แต่การตัดสินใจเชิงนโยบายโดยใช้หลักฐานทางวิชาการจะเป็นไปได้มากยิ่งขึ้นหากมีข้อมูลการประเมินเทคโนโลยีด้านสุขภาพที่มีคุณภาพและเป็นข้อมูลของประเทศไทยเตรียมพร้อมไว้แล้ว แม้ว่าคู่มือการประเมินเทคโนโลยีด้านสุขภาพฉบับแรกนี้จะได้รับการรับรองจากคณะอนุกรรมการพัฒนาบัญชียาหลักแห่งชาติและคณะอนุกรรมการพัฒนาชุดสิทธิประโยชน์และระบบบริการของสำนักงานหลักประกันสุขภาพแห่งชาติ อย่างไรก็ตาม สืบเนื่องจากเป็นผลงานที่เกิดขึ้นในระยะแรก ดังนั้นจึงยังคงมีจุดอ่อนสองประการประการแรกคือ คู่มือนี้เป็นคู่มือสำหรับการประเมินเทคโนโลยีด้านสุขภาพที่มุ่งเน้นการเสนอแนะแนวทางสำหรับการประเมินความคุ้มค่าทางสาธารณสุข จึงยังไม่ครอบคลุมเนื้อหาเกี่ยวกับแนวทางสำหรับการประเมินเทคโนโลยีด้านสุขภาพในประเด็นอื่นๆ ประการที่สองคือ เนื่องจากคู่มือฯ นี้ถูกพัฒนาขึ้นตั้งแต่ปี พ.ศ. 2551 จึงอาจมีเนื้อหาที่ไม่ทันสมัย ดังนั้นจึงมีการพัฒนาคู่มือฯ ฉบับที่ 2 คือเพื่อพัฒนาและปรับปรุงคู่มือฯ นี้อย่างต่อเนื่องและทำให้มีความทันสมัยอยู่ตลอดเวลา เพื่อใช้เป็นแนวทางในการวิจัยและประเมินเทคโนโลยีด้านสุขภาพให้สอดคล้องกับบริบทของระบบสุขภาพที่เปลี่ยนแปลงไป

กระบวนการพัฒนาคู่มือฯ ฉบับที่ 2 เริ่มต้นตั้งแต่เดือนมิถุนายน พ.ศ. 2555 โดยนักวิจัยจากโครงการประเมินเทคโนโลยีด้านสุขภาพศึกษาทบทวนงานวิจัยด้านการประเมินเทคโนโลยีด้านสุขภาพ โดยเฉพาะอย่างยิ่งการประเมินความคุ้มค่าทางสาธารณสุขในระยะที่ผ่านมา ทั้งก่อนและหลังการมีคู่มือการประเมินเทคโนโลยีด้านสุขภาพสำหรับประเทศไทย เพื่อเปรียบเทียบคุณภาพของงานวิจัยและความสอดคล้องกับข้อเสนอแนะที่ระบุไว้ในคู่มือฯ ฉบับที่ 1 ซึ่งเป็นการวัดผลกระทบของคู่มือฯ ที่ได้ทำขึ้นตั้งแต่เดือนมกราคม พ.ศ. 2549 จนถึงเดือนกันยายน พ.ศ. 2555 จากข้อมูลเบื้องต้นพอสรุปได้ว่า งานวิจัยด้านการประเมินความคุ้มค่าทางสาธารณสุขในประเทศไทยในระยะหลังการเผยแพร่คู่มือฯ ฉบับที่ 1 มีคุณภาพเพิ่มสูงขึ้น ทั้งในด้านการรายงานผลการศึกษาและคุณภาพของแหล่งข้อมูล เมื่อเปรียบเทียบกับระยะก่อนการเผยแพร่คู่มือฯ ฉบับที่ 1 โดยคู่มือฯ ฉบับที่ 1 ได้ให้แนวทางในการวิจัยที่เป็นมาตรฐานและยกระดับคุณภาพงานวิจัยในประเทศได้ระดับหนึ่ง อย่างไรก็ดี ยังคงมีช่องว่างสำหรับการพัฒนา และยกระดับคุณภาพงานวิจัยในด้านนี้อย่างต่อเนื่อง เพื่อตอบสนองการใช้ประโยชน์จากงานวิจัยในการตัดสินใจเชิงนโยบาย

ในเดือนกรกฎาคม พ.ศ. 2555 โครงการประเมินเทคโนโลยีและนโยบายด้านสุขภาพทำหน้าที่เป็นผู้ประสานงานของการพัฒนาคู่มือฯ ฉบับที่ 2 จัดประชุมปรึกษา/ระดมสมองผู้เชี่ยวชาญและผู้เกี่ยวข้อง/กลุ่มผู้ใช้ประโยชน์จากคู่มือฯ เช่น คณะกรรมการพัฒนาชุดสิทธิประโยชน์ต่างๆ คณะอนุกรรมการพัฒนาบัญชียาหลักแห่งชาติ อาจารย์ นักศึกษาในมหาวิทยาลัย นักวิจัย นักวิชาการ และผู้มีส่วนได้ส่วนเสียอื่น ๆ ทั้งภาครัฐและเอกชน โดยจะพิจารณาถึงความครอบคลุมของประเด็นอื่นๆ ในคู่มือฯ ฉบับที่ 1 นอกเหนือจากการประเมินความคุ้มค่าทางสาธารณสุข การทบทวนงานวิจัยด้านการประเมินเทคโนโลยีด้านสุขภาพที่ผ่านมาของโครงการประเมินเทคโนโลยีและนโยบายด้านสุขภาพ ความทันสมัยของเนื้อหา การประยุกต์ใช้คู่มือฯ นี้ในการผลิตและการใช้ข้อมูลการประเมินเทคโนโลยีด้านสุขภาพ ฯลฯ เพื่อทราบถึงประโยชน์และข้อจำกัดของคู่มือฯ และเพื่อให้ข้อเสนอแนะสำหรับการพัฒนาและปรับปรุงคู่มือการประเมินเทคโนโลยีทางการแพทย์ในประเทศไทย ฉบับที่ 2 หลังจากนั้นคณะทำงานดำเนินการพัฒนาคู่มือฉบับที่ 2 ตามข้อเสนอแนะ และในเดือนพฤศจิกายน พ.ศ. 2555 จึงมีการจัดประชุมปรึกษา/ระดมสมองผู้เชี่ยวชาญและผู้เกี่ยวข้อง/กลุ่มผู้ใช้ประโยชน์จากคู่มือฯ เช่น คณะกรรมการพัฒนาชุดสิทธิประโยชน์ต่างๆ คณะอนุกรรมการพัฒนาบัญชียาหลักแห่งชาติ หรืออาจารย์ นักศึกษาในมหาวิทยาลัย นักวิจัย นักวิชาการ และผู้มีส่วนได้ส่วนเสียอื่น ๆ ทั้งภาครัฐและเอกชน เพื่อพิจารณาความเหมาะสมในการนำคู่มือฯ ฉบับที่ 2 ไปใช้สำหรับประเทศไทย ซึ่งข้อคิดเห็นทั้งหมดจะนำมาปรับปรุง เพิ่มเติม แก้ไข คู่มือการประเมินเทคโนโลยีด้านสุขภาพสำหรับประเทศไทย ฉบับที่ 2 ก่อนการตีพิมพ์ฉบับสมบูรณ์ โดยคู่มือการประเมินเทคโนโลยีด้านสุขภาพสำหรับประเทศไทย ฉบับที่ 2 เสร็จสมบูรณ์และตีพิมพ์ฉบับภาษาไทย เมื่อเดือนมกราคม 2557 ส่วนฉบับภาษาอังกฤษตีพิมพ์ในวารสารจดหมายเหตุทางการแพทย์แพทยสมาคมแห่งประเทศไทย (Journal of the Medical Association of Thailand) เมื่อเดือนพฤษภาคม 2557

วัตถุประสงค์ที่ 4 เพื่อวิจัยและพัฒนาระบบ กลไก การนำผลการประเมินเทคโนโลยีด้านสุขภาพไปใช้ในการตัดสินใจด้านสุขภาพ รวมถึงการจัดสรรงบประมาณ

โครงการประเมินเทคโนโลยีและนโยบายด้านสุขภาพ โดย น.พ.ยศ ตีระวัฒนานนท์ เมธีวิจัยอาวุโส พร้อมด้วยนักวิจัยอาวุโสและนักวิจัย ได้รับเชิญเป็นกรรมการ เลขานุการ และผู้ช่วยเลขานุการตามคำสั่งของกระทรวงสาธารณสุขเพื่อพัฒนาการประเมินเทคโนโลยีด้านสุขภาพ กระทรวงสาธารณสุขและช่วยสนับสนุนกระทรวงสาธารณสุขขับเคลื่อนการประเมินเทคโนโลยีด้านสุขภาพให้มีความเข้มแข็ง ซึ่งนอกจากจะเป็นกรรมการและเลขานุการในคณะกรรมการพัฒนาการประเมินเทคโนโลยีด้านสุขภาพแล้ว โครงการประเมินเทคโนโลยีและนโยบายด้านุสขภาพได้ให้คำปรึกษากับบุคลากรสุขภาพได้มีความสนใจการทำประเมินเทคโนโลยีด้านสุขภาพและฝึกอบรมแบบ on the job training ซึ่งจะทำให้ผู้เข้าร่วมโครงการมีประสบการณ์และสามารถทำการประเมินได้ด้วยตนเอง ในขั้นแรกมีการนำเสนอโครงการทั้งหมดจำนวน 12 โครงการ หลังจากนี้จะมีการปรับปรุงโครงร่างโครงการและดำเนินการวิจัยต่อไป

โครงการประเมินเทคโนโลยีและนโยบายด้านสุขภาพทำวิจัยเพื่อมุ่งหวังให้มีการผลการวิจัยไปใช้ในเชิงนโยบาย โดยผู้แทนของโครงการประเมินเทคโนโลยีและนโยบายด้านสุขภาพเป็นอนุกรรมการในคณะอนุกรรมการพัฒนาบัญชียาหลักแห่งชาติ และเลขานุการในคณะทำงานเศรษฐศาสตร์สาธารณสุข ภายใต้คณะอนุกรรมการพัฒนาบัญชียาหลักแห่งชาติ และมีการเสนองานวิจัยให้กับคณะอนุกรรมการ และคณะทำงานของคณะอนุกรรมการพัฒนาบัญชียาหลักแห่งชาติ นอกจากนี้ผลงานวิจัยที่ได้นำเสนอกับผู้บริหารของกระทรวงสาธารณสุข สำนักงานหลักประกันสุขภาพแห่งชาติ กรมบัญชีกลาง กระทรวงการคลัง สำนักงานประกันสังคม กระทรวงแรงงาน และหน่วยงานต่าง ๆ โดยแสดงในตารางที่ 6 ซึ่งผลการวิจัยที่นำเสนอกับคณะอนุกรรมการพัฒนาบัญชียาหลักแห่งชาติได้ถูกนำไปใช้ประโยชน์ในการ

บรรจุหรือไม่บรรจุยาในบัญชียาหลักแห่งชาติ ในขณะที่ผลงานวิจัยบางเรื่องถูกนำไปใช้ประโยชน์ในเชิงนโยบายตามตารางที่ 7 ทั้งนี้ผลงานวิจัยบางส่วนอยู่ระหว่างการพิจารณาของคณะกรรมการ คณะอนุกรรมการ คณะทำงาน หรือผู้กำหนดนโยบายเพื่อใช้ในการพิจารณาตัดสินใจต่อไป

ตารางที่ 6 การนำเสนองานวิจัยกับผู้กำหนดนโยบาย

ลำดับ	หน่วยงาน	เรื่อง
1	คณะอนุกรรมการ/คณะทำงาน ภายใต้คณะอนุกรรมการพัฒนาบัญชียาหลักแห่งชาติ	การประเมินความคุ้มค่าของการคัดกรองและการรักษาโรคกระดูกพรุนในผู้หญิงวัยหมดประจำเดือน การทบทวนวรรณกรรมอย่างเป็นระบบและการวิเคราะห์เชิงอภิมานของการใช้ยา Bevacizumab ในการรักษาโรคจุดภาพชัดของจอตา การประเมินต้นทุนอรรถประโยชน์ของยารักษาภาวะความดันหลอดเลือดแดงในปอดสูง การประเมินต้นทุนอรรถประโยชน์ของยารักษาโรคมะเร็งเม็ดเลือดขาวเรื้อรัง การประเมินความคุ้มค่าของยารักษาโรคมะเร็งเนื้อเยื่อในระบบทางเดินอาหาร การประเมินความคุ้มค่าของยารักษาโรค Gaucher's disease Imiglucerase การประเมินต้นทุน-อรรถประโยชน์ และผลกระทบด้านงบประมาณของการรักษาโรคมะเร็งไตชนิด clear cell renal cell carcinoma ระยะแพร่กระจาย การประเมินความคุ้มค่าทางเศรษฐศาสตร์และผลกระทบด้านงบประมาณของการใช้ยา Peg-interferon และ Ribavirin ในข้อบ่งใช้สาหรับผู้ป่วยไวรัสตับอักเสบซีเรื้อรังชนิดสายพันธุ์ 1 การประเมินความคุ้มค่าทางเศรษฐศาสตร์และผลกระทบด้านงบประมาณของการใช้ยา Peg-interferon และ Ribavirin ในข้อบ่งใช้สาหรับผู้ป่วยไวรัสตับอักเสบซีเรื้อรังชนิดสายพันธุ์ 6 การประเมินความคุ้มค่าทางเศรษฐศาสตร์และผลกระทบงบประมาณของการใช้ยา peg-interferon และ ribavirin ในข้อบ่งใช้สาหรับผู้ป่วยไวรัสตับอักเสบซีเรื้อรังในกลุ่มผู้ติดเชื้อ HIV ร่วมด้วย (HIV/HCV co-infection) การประเมินต้นทุนอรรถประโยชน์และผลกระทบทางด้านงบประมาณของยากลุ่ม Luteinizing hormone-releasing hormone analogues ในข้อบ่งใช้สาหรับมะเร็งต่อมลูกหมากใน Adjuvant therapy และระยะ Metastatic disease

ลำดับ	หน่วยงาน	เรื่อง
		การประเมินความคุ้มค่าของนโยบายร่วมจ่ายระหว่างภาครัฐและภาคเอกชน สำหรับยา sunitinib การประเมินความคุ้มค่าของการใช้สารชีวภาพในผู้ป่วยโรคข้ออักเสบรูมาตอยด์ การประเมินต้นทุนอรรถประโยชน์และผลกระทบด้านงบประมาณของยา imatinib สำหรับการรักษาเสริมในผู้ป่วยโรคมะเร็งเนื้อเยื่อในระบบทางเดินอาหาร (GIST) ที่ได้รับการผ่าตัดและมีโอกาสเกิดโรคซ้ำสูง การความคุ้มค่าทางการแพทย์ของการรักษามะเร็งลำไส้ใหญ่ระยะลุกลามของประเทศไทย การประเมินความคุ้มค่าของการใช้สารทึบรังสี Gadoxetic acid (Primovist®) ในการตรวจวินิจฉัยมะเร็งตับ (Hepatocellular Carcinoma) ด้วยเครื่องแม่เหล็กไฟฟ้า ประเมินความคุ้มค่าของยา lodized old fluid injecttion (Lipiodol® Ultra Fluid) สำหรับการรักษามะเร็งตับ (Hepatocellular carcinoma)
2	กระทรวงสาธารณสุข	การประเมินความคุ้มค่าของวัคซีน HPV การพัฒนาชุดสิทธิประโยชน์การตรวจร่างกาย สำหรับประชากรไทย สำรวจสุขภาวะผู้สูงอายุไทย ปี 2556 ภายใต้แผนงานส่งเสริมสุขภาพผู้สูงอายุและผู้พิการ
3	สำนักงานหลักประกันสุขภาพแห่งชาติ	การพัฒนาชุดสิทธิประโยชน์การตรวจร่างกาย สำหรับประชากรไทย การพัฒนานโยบายด้านการสร้างเสริมสุขภาพและป้องกันโรคสำหรับเด็กและเยาวชน การประเมินความคุ้มค่าทางการแพทย์ของการให้บริการตรวจคัดกรองยีน HLA-B*1502 เพื่อหลีกเลี่ยงการเกิดผื่นแพ้ยาชนิดกลุ่มอาการ Stevens-Johnson syndrome (SJS) และ toxic epidermal necrolysis (TEN) จากยา carbamazepine
4	คณะกรรมการวัคซีนแห่งชาติ	การพัฒนายุทธศาสตร์และนโยบายสำหรับการป้องกันและควบคุมโรคมะเร็งปากมดลูก
5	สำนักงานคณะกรรมการสุขภาพแห่งชาติ	การพัฒนาชุดสิทธิประโยชน์การตรวจร่างกาย สำหรับประชากรไทย
6	สำนักงานคณะกรรมการวิจัยแห่งชาติ	การจัดลำดับความสำคัญของหัวข้อวิจัยด้านสุขภาพสำหรับประเทศไทย การพัฒนาชุดสิทธิประโยชน์การสร้างเสริมสุขภาพป้องกันโรคสำหรับเด็ก 0-5 ปี

ลำดับ	หน่วยงาน	เรื่อง
7	ศูนย์ความเป็นเลิศด้านชีววิทยาศาสตร์ (TCELS)	ข้อเสนอแนะสำหรับแผนยุทธศาสตร์ advance bio-health technology
8	สำนักงานคณะกรรมการนโยบายวิทยาศาสตร์ เทคโนโลยีและนวัตกรรมแห่งชาติ (สวทน.)	ข้อเสนอแนะสำหรับแผนยุทธศาสตร์ advance bio-health technology
9	สำนักงานกองทุนสนับสนุนการสร้างเสริมสุขภาพ	การพัฒนาชุดสิทธิประโยชน์การตรวจร่างกาย สำหรับประชากรไทย
10	Bill & Melinda Gates Foundation	Methods for economic evaluation Project (MEEP) To assess decision maker needs/ Transferability on economic evaluation (especially in LMIC)
11	Ministry of Health of Myanmar	MCH voucher scheme
12	Ministry of Health of Philippines	Economic evaluations of PCV and HPV vaccine
13	National Institute for Health and Clinical Excellence (NICE) International	Priority Setting Institution
14	Center for Global Development (CGD)	Priority Setting Institution
15	Global Fund	Value for money of the Global Fund
16	Ministry of Health and Welfare of the Netherlands	evaluation of screening and treatment of HBV and HCV in Thailand
17	World Health Organization (WHO)	Systematic review of influenza preparedness Economic evaluation of seasonal influenza vaccine among pregnant women in Thailand

ตารางที่ 7 งานวิจัยที่ถูกนำไปใช้ในเชิงนโยบาย

ลำดับ	หน่วยงาน	เรื่อง
1	กระทรวงสาธารณสุข	สิทธิประโยชน์การตรวจร่างกาย สำหรับประชากรไทยตามกลุ่มวัย การสำรวจสุขภาวะผู้สูงอายุไทย ปี 2556
2	สำนักงานคณะกรรมการวิจัยแห่งชาติ	การจัดลำดับความสำคัญของหัวข้อวิจัยด้านสุขภาพสำหรับประเทศไทย
3	คณะกรรมการสุขภาพแห่งชาติ	นโยบายการตรวจสุขภาพที่จำเป็นและเหมาะสมสำหรับประชาชน
4	สำนักงานหลักประกันสุขภาพถ้วนหน้า	การบรรจุยา 4 รายการในสิทธิประโยชน์ของหลักประกันสุขภาพถ้วนหน้า ได้แก่ ยา Trastuzumab รักษามะเร็งเต้านม ยา Peginterferon รักษาโรคไวรัสตับอักเสบซีเรื้อรัง ยา Nilotinib รักษามะเร็งเม็ดเลือดขาว และยา Dasatinib รักษามะเร็งเม็ดเลือดขาว

ลำดับ	หน่วยงาน	เรื่อง
		การเพิ่มสิทธิประโยชน์การตรวจคัดกรองยีน HLA-B*1502 เพื่อหลีกเลี่ยงการเกิดผื่นแพ้ยาชนิดกลุ่มอาการ Stevens-Johnson syndrome (SJS) และ toxic epidermal necrolysis (TEN) จากยา carbamazepine การเพิ่มสิทธิประโยชน์การตรวจวัดสายตาในเด็กอนุบาลและปฐมวัย การเพิ่มมาตรการการสร้างเสริมสุขภาพและป้องกันโรค ในปีงบประมาณ 2559 จำนวน 10 มาตรการ
5	สำนักงานประกันสังคม	การบรรจุยา 4 รายการในสิทธิประโยชน์ของประกันสังคม ได้แก่ ยา Trastuzumab รักษามะเร็งเต้านม ยา Peginterferon รักษาโรคไวรัสตับอักเสบซีเรื้อรัง ยา Nilotinib รักษามะเร็งเม็ดเลือดขาว และยา Dasatinib รักษามะเร็งเม็ดเลือดขาว

การเผยแพร่ผลงานวิจัย

การเผยแพร่ความรู้และผลงานการวิจัยถือได้ว่าเป็นอีกหนึ่งกิจกรรมที่โครงการประเมินเทคโนโลยีและนโยบายด้านสุขภาพให้ความสำคัญ เนื่องจากเป็นช่องทางที่ใช้ในการสื่อสารและให้ความรู้ด้านการประเมินเทคโนโลยีด้านสุขภาพให้กับสาธารณะ บุคลากรทางการแพทย์ นักวิชาการทั้งในและต่างประเทศผ่านเว็บไซต์ จดหมายข่าว จุลสาร Policy brief และการตีพิมพ์ผลงานวิจัยในวารสารทั้งภายในประเทศและต่างประเทศ ในระยะเวลาที่ได้รับการสนับสนุนภายใต้โครงการเมธีวิจัยอาวุโส สกว. เพื่อพัฒนาศักยภาพการประเมินเทคโนโลยีด้านสุขภาพ มีการผลิตสื่อต่างๆ ตามกลุ่มเป้าหมายดังนี้

- จุลสาร HITAP มีวัตถุประสงค์เพื่อเผยแพร่ความรู้และสร้างความตระหนักด้านการประเมินเทคโนโลยีด้านการแพทย์ โดยมีกลุ่มเป้าหมายเป็น ประชาชนทั่วไป โดยมีการเผยแพร่จุลสาร ดังนี้
  - จุลสาร ปีที่ 6 ฉบับที่ 18 เรื่อง เช็คระยะสุขภาพ
  - จุลสาร ปีที่ 6 ฉบับที่ 19 เรื่อง ชัดแจ๋ว ตรวจตาเด็ก เตรียมอนาคตไทย
  - จุลสาร ปีที่ 6 ฉบับที่ 20 เรื่อง เช็คระยะสุขภาพ ภาค 2 ตรวจดีได้ ตรวจร้ายเสีย
  - จุลสาร ปีที่ 7 ฉบับที่ 21 เรื่อง วัยรุ่น วุ่นโรค
  - จุลสาร ปีที่ 7 ฉบับที่ 22 เรื่อง สุขภาพดีไม่มีแก่
  - จุลสาร ปีที่ 8 ฉบับที่ 23 เรื่อง The Power of HTA
  - จุลสาร ปีที่ 8 ฉบับที่ 24 เรื่อง บทบาทของ HTA ในการพัฒนาบัญชียาหลักแห่งชาติ
- HTAsiaLink Newsletter มีวัตถุประสงค์เพื่อเผยแพร่การทำงานการประเมินเทคโนโลยีด้านสุขภาพของเครือข่าย HTAsiaLink ให้กับผู้ที่สนใจ มีการจัดทำเอกสารจะเน้นการเผยแพร่ผ่านระบบอิเล็คทรอนิกซ์ ไม่มีการจัดพิมพ์เป็นรูปเล่มเพื่อให้ผู้ที่สนใจได้ใช้ประโยชน์ได้สะดวก
  - HTAsiaLink Newsletter 3rd issue: Finding the right topic for Health Technology Assessment

- HTAsiaLink Newsletter 4th issue: Communication HTA
- HTAsiaLink Newsletter 5th issue: Capacity building for HTA organization in Asia
- HTAsiaLink Newsletter 6th issue: Sharing information
- HTAsiaLink Newsletter 7th issue: HTA to support UHC

- Policy brief มีวัตถุประสงค์เพื่อสรุปงานวิจัยให้กระชับและเหมาะกับผู้บริหารหรือผู้กำหนดนโยบายที่จะนำไปใช้ประโยชน์ได้สะดวก ซึ่งผลงานวิจัยทุกเรื่องจะถูกจัดทำเป็น Policy brief ทั้งหมด

ลำดับที่	ชื่อ Policy brief	ชื่อโครงการวิจัย
ปี 2555		
1	ข้อเสนอแนะเชิงนโยบายโครงการ “อนาคตไทย” เพื่อการสร้างเสริมสุขภาวะเด็กอายุ 0-5 ปี	การพัฒนาข้อเสนอเชิงนโยบายด้านการสร้างเสริมสุขภาพและป้องกันโรคในกลุ่มเด็กอายุ 0-5 ปี
2	ข้อเสนอแนะเชิงนโยบายการประเมินผลลัพธ์ของการดำเนินมาตรการสร้างเสริมสุขภาพ	การประเมินผลลัพธ์ของการดำเนินมาตรการสร้างเสริมสุขภาพ: 1) การประเมินความเต็มใจจ่ายของครัวเรือนต่อมาตรการสร้างเสริมสุขภาพของ สสส. 2) การพัฒนาแนวทางการกำหนดเป้าหมายและตัวชี้วัดของการดำเนินงานสร้างเสริมสุขภาพของ สสส. โดยใช้ข้อมูลจากการศึกษาต้นทุนความเจ็บป่วย
ปี 2556		
3	“เติมเต็มช่องว่าง” การเข้า (ไม่) ถึงบริการของผู้มีปัญหาสุขภาพจิต	โครงการสนับสนุนและส่งเสริมการบริการครบวงจร สำหรับผู้ป่วยจิตเวชในพื้นที่เป้าหมายเร่งรัดภายใต้ระบบประกันสุขภาพถ้วนหน้า (โครงการบริการสุขภาพจิตครบวงจร)
4	เรื่องไม่เล็กของไข้หวัดใหญ่...ไทยจะรับมืออย่างไรให้คุ้มค่า”	การประเมินต้นทุน-อรรถประโยชน์ของวัคซีนป้องกันไข้หวัดใหญ่ฤดูกาลในเด็กวัยเรียนของประเทศไทย
5	โครงการชัดแจ๋ว: ตรวจตาเด็ก...เพื่ออนาคตไทย	การพัฒนาระบบคัดกรองภาวะสายตาผิดปกติและประกอบแว่นสายตาสำหรับเด็กก่อนวัยประถมศึกษาและประถมศึกษาในประเทศไทย
6	เภสัชพันธุศาสตร์ถอดรหัสปัญหาแพ้ยารุนแรงในคนไทย	การประเมินความคุ้มค่าทางการแพทย์ของการให้บริการตรวจคัดกรองยีน HLA-B*1502 เพื่อหลีกเลี่ยงการเกิดผื่นแพ้ยาชนิดกลุ่มอาการ Stevens-Johnson syndrome (SJS) และ toxic epidermal necrolysis (TEN) จากยา carbamazepine
7	ภาวะโภชนาการในโรงพยาบาลเรื่องสำคัญที่ไม่ควรมองข้าม	ความคุ้มค่าของการคัดกรองภาวะทุพโภชนาการของผู้ป่วยในโรงพยาบาลเพื่อลดภาวะแทรกซ้อนจากการรักษา

ลำดับที่	ชื่อ Policy brief	ชื่อโครงการวิจัย
8	การพัฒนานโยบายสาธารณะเพื่อสุขภาพในประเทศไทย:ความสำเร็จและความท้าทาย	การประเมินการพัฒนานโยบายสาธารณะเพื่อสุขภาพภายใต้การดำเนินงานของสำนักงานคณะกรรมการสุขภาพแห่งชาติ ระหว่างปี พ.ศ. 2550-2554
9	การคัดกรองสุขภาพที่เหมาะสมสำหรับสังคมไทย	การศึกษาเพื่อพัฒนาชุดสิทธิประโยชน์ด้านการคัดกรองทางสุขภาพระดับประชากรในประเทศไทย
ปี 2557		
10	“ASSIST” เครื่องมือคัดกรองการเสพสารเสพติดที่ใช้ง่ายและคุ้มค่า	การศึกษาเพื่อพัฒนาชุดสิทธิประโยชน์ด้านการคัดกรองทางสุขภาพระดับประชากรในประเทศไทย
11	ให้เครื่องตรวจวัดระดับน้ำตาลในเลือดด้วยตนเองแก่ผู้ป่วยเบาหวาน คุ้มหรือไม่?	การประเมินความคุ้มค่าของการตรวจวัดระดับน้ำตาลในเลือดด้วยตนเองในผู้ป่วยเบาหวานชนิดที่ 1 และ 2 ที่ฉีดอินซูลินในบริบทประเทศไทย
12	ตรวจกรองอาการดาวน์ในหญิงตั้งครรภ์ทุกรายเป็นไปได้	ต้นทุนผลได้ของการตรวจกรองและวินิจฉัยก่อนคลอดของกลุ่มอาการดาวน์ในประเทศไทย
13	ความผิดปกติทางโครงสร้างของโครโมโซม: คุ้มค่าที่จะป้องกัน	การประเมินความความคุ้มค่าทางเศรษฐศาสตร์ของกระบวนการตรวจวินิจฉัยเพื่อป้องกันการเกิดซ้ำของทารกกลุ่มอาการดาวน์และทารกที่มีความผิดปกติทางโครงสร้างของโครโมโซม
14	GSP และการเจรจาเขตการค้าเสรี อาจไม่มีผลกระทบรุนแรงต่อการค้าและการลงทุนของไทย	การประเมินผลกระทบความตกลงการค้าเสรีระหว่างประเทศไทยกับสหภาพยุโรปต่อการค้าและการลงทุน
15	MS/MS เทคโนโลยีใหม่ ตรวจหลายโรคพันธุกรรมได้ในครั้งเดียว: คุ้มค่าหรือไม่ หากใช้ตรวจเด็กทารกไทยทุกคน	การประเมินต้นทุนอรรถประโยชน์ของการตรวจกรองและ รักษาโรคพันธุกรรมเมตาบอลิกในกลุ่มสารโมเลกุลเล็ก
16	บริหารจัดการระบบวิจัยอย่างมีคุณภาพ – เพื่อสุขภาพที่ดีของคนไทย	การจัดลำดับความสำคัญของหัวข้อวิจัยด้านสุขภาพ สำหรับประเทศไทย
17	ผลกระทบจากการตั้งครรภ์ในวัยรุ่นไทย	สถานการณ์การตั้งครรภ์ในวัยรุ่นในประเทศไทย 2556 ; Adolescent Pregnancy Thailand 2013
18	LHRH analogues ยาใหม่ รักษามะเร็งต่อมลูกหมาก ไม่ต้องตัดทิ้ง	การประเมินความคุ้มค่าและผลกระทบด้านงบประมาณของยากลุ่ม LHRH analogues ในข้อบ่งใช้สำหรับโรคมะเร็งต่อมลูกหมากใน Adjuvant therapy และระยะ Metastatic disease
19	ข้อเสนอแนะเชิงนโยบายเพื่อการปรับปรุงชุดสิทธิประโยชน์และระบบบริการ ด้านการสร้างเสริมสุขภาพและป้องกันโรค สำหรับผู้ใหญ่/วัยทำงานภายใต้หลักประกันสุขภาพถ้วนหน้า	โครงการพัฒนาข้อเสนอเพื่อการปรับปรุงชุดสิทธิประโยชน์และระบบบริการ ด้านการสร้างเสริมสุขภาพและป้องกันโรคสำหรับผู้ใหญ่/วัยทำงานภายใต้หลักประกันสุขภาพถ้วนหน้า

ลำดับที่	ชื่อ Policy brief	ชื่อโครงการวิจัย
20	ข้อเสนอแนะเชิงนโยบายโครงการ “อนาคตไทย” เพื่อการสร้างเสริมสุขภาวะเด็กและเยาวชนอายุ 6-25 ปี	การพัฒนานโนบายด้านการสร้างเสริมสุขภาพและป้องกันโรคสำหรับเด็กโตและเยาวชน
21	สังคมผู้สูงอายุ...กับความท้าทายของการจัดการด้านสุขภาพ	โครงการสำรวจสุขภาวะผู้สูงอายุไทย ปี 2556
22	ระบบสุขภาพไทยที่พึงประสงค์ในอีก 20 ปีข้างหน้า	การจัดลำดับความสำคัญของหัวข้อวิจัยด้านสุขภาพ สำหรับประเทศไทย
23	ข้อมูลสถานการณ์การตั้งครรภ์ในวัยรุ่นไทย	สถานการณ์การตั้งครรภ์ในวัยรุ่นในประเทศไทย 2556 ; Adolescent Pregnancy Thailand 2013
24	เกณฑ์ความคุ้มค่าต่อ 1 ปีสุขภาวะ คืออะไร และมีค่าเท่าใด	การประเมินคุณค่าของสังคมต่อเพดานความคุ้มค่าในประเทศไทยและกลุ่มประเทศในเอเชีย
ปี 2558		
25	ผลเสียจากการบริหารจัดการอุปกรณ์เครื่องช่วยคนพิการที่ขาดประสิทธิภาพ	การทบทวนชุดสิทธิประโยชน์และการเข้าถึงบริการอุปกรณ์เครื่องช่วยคนพิการ
26	ฐานข้อมูลคนพิการ: กลไกสำคัญที่รอการพัฒนา	
27	สิทธิประโยชน์ด้านสุขภาพสำหรับคนพิการ : อีกหนึ่งความเหลื่อมล้ำในระบบประกันสุขภาพไทย	
28	แบบสอบถามคุณภาพชีวิต EQ-5D-5L ฉบับภาษาไทย	เครื่องมือประเมินคุณภาพชีวิต EQ-5D-5L: การทดสอบคุณสมบัติการวัดและค่าน้ำหนักอรรถประโยชน์ในประชากรไทย
29	DAAs ยาใหม่รักษาตับอักเสบซีได้ดีกว่าเดิม แต่แพงกว่าเดิม และยังขาดข้อมูลความคุ้มค่า	การประเมินความคุ้มค่าและผลกระทบด้านงบประมาณของยา sofosbuvir ในการรักษาโรคติดเชื้อไวรัสตับอักเสบซีชนิดเรื้อรัง

- Publication เป็นการเผยแพร่ความรู้ในกลุ่มนักวิชาการที่มีความสนใจเฉพาะ โดยโครงการประเมินเทคโนโลยีและนโยบายด้านสุขภาพมีการตีพิมพ์งานในวารสารวิชาการทั้งในประเทศและต่างประเทศ ซึ่งบางฉบับเป็นวารสารที่มี impact factor สูง ทั้งนี้โครงการประเมินเทคโนโลยีและนโยบายด้านสุขภาพได้ตีพิมพ์ผลงานในวารสารวิชาต่างประเทศ ภายใต้การสนับสนุนของโครงการเมธีวิจัยอาวุโส สกว. เพื่อพัฒนาศักยภาพการประเมินเทคโนโลยีด้านสุขภาพ ทั้งสิ้น 23 ฉบับ ดังนี้

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RESEARCH ARTICLE

An Economic Evaluation of Neonatal Screening for Inborn Errors of Metabolism Using Tandem Mass Spectrometry in Thailand

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Abstract

Background

Inborn errors of metabolism (IEM) are a rare group of genetic diseases which can lead to several serious long-term complications in newborns. In order to address these issues as early as possible, a process called tandem mass spectrometry (MS/MS) can be used as it allows for rapid and simultaneous detection of the diseases. This analysis was performed to determine whether newborn screening by MS/MS is cost-effective in Thailand.

Method

A cost-utility analysis comprising a decision-tree and Markov model was used to estimate the cost in Thai baht (THB) and health outcomes in life-years (LYs) and quality-adjusted life year (QALYs) presented as an incremental cost-effectiveness ratio (ICER). The results were also adjusted to international dollars (I$) using purchasing power parities (PPP) (1 I$ = 17.79 THB for the year 2013). The comparisons were between 1) an expanded neonatal screening programme using MS/MS screening for six prioritised diseases: phenylketonuria (PKU); isovaleric acidemia (IVA); methylmalonic acidemia (MMA); propionic acidemia (PA); maple syrup urine disease (MSUD); and multiple carboxylase deficiency (MCD); and 2) the current practice that is existing PKU screening. A comparison of the outcome and cost of treatment before and after clinical presentations were also analysed to illustrate the potential benefit of early treatment for affected children. A budget impact analysis was conducted to illustrate the cost of implementing the programme for 10 years.

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Results

The ICER of neonatal screening using MS/MS amounted to 1,043,331 THB per QALY gained (58,647 I$ per QALY gained). The potential benefits of early detection compared with late detection yielded significant results for PKU, IVA, MSUD, and MCD patients. The budget impact analysis indicated that the implementation cost of the programme was expected at approximately 2,700 million THB (152 million I$) over 10 years.

Conclusion

At the current ceiling threshold, neonatal screening using MS/MS in the Thai context is not cost-effective. However, the treatment of patients who were detected early for PKU, IVA, MSUD, and MCD, are considered favourable. The budget impact analysis suggests that the implementation of the programme will incur considerable expenses under limited resources. A long-term epidemiological study on the incidence of IEM in Thailand is strongly recommended to ascertain the magnitude of problem.

Introduction

Inborn errors of metabolism (IEM) comprise more than 30 genetic disorders that can lead to several serious long-term complications to neonatal and young children [1]. Without rapid diagnosis and appropriate treatment, these diseases can cause mental retardation (MR), physical disabilities, and even death [2]. Although the incidence of IEM seems to be low and varied among different ethnicities [3], high incidences are found in the North American and European populations with an incidence of 40.00 and 29.51 cases per 100,000 live births respectively [4, 5] whereas the incidences of IEM in Asian populations range between 16.08–26.35 in 100,000 live births [6–8].

Tandem mass spectrometry (MS/MS) is an advanced technology that has the ability to identify more than 30 diseases [9] by testing compounds from a single dried blood sample collected from infants during their second to third days of life [10]. Analysis for identifying each condition is simultaneous and rapid with high specific sensitivity (100%) and specificity (100%) [11]. With this technology, many high- income countries such as Italy, Denmark, Canada, Australia, Qatar, and Taiwan have expanded their neonatal screening programme in order to cover more IEM, which in the past consisted of only phenylketonuria (PKU) [12].

In Thailand, a neonatal screening programme was introduced in 1996 to screen for PKU [13]. Currently, PKU is the only disease screened among the IEM group and the screening method used is the Guthrie test due to its simplicity and inexpensiveness. For other diseases, to date, no study has been carried out to identify the magnitude of the problem especially in terms of incidence and/or prevalence of the diseases in a systematic way. Without such fundamental information to support the necessity of advanced and expensive technology, convincing policy-makers to introduce MS/MS as a population-based screening tool in Thailand will be very challenging.

So far, many studies have shown that MS/MS is cost-effective in their specific country settings [14–22]. However, due to generalizability and transferability issues, the results of the economic evaluations in the original country of study cannot be transferred to other countries because of the differences in multiple factors (e.g. demography, epidemiology of disease, health infrastructure, clinical practice, and healthcare cost) [23–25]. Thus, this study was conducted

to determine the cost-effectiveness of screening and treatment for selected IEM in Thailand. The result of this study will be mainly used to support policy-makers of the National Health Security Office (NHSO) to determine whether this screening intervention should be included into the benefits package of the country's Universal Health Coverage (UHC) scheme.

Materials and Methods

Selection of IEM disorders

By recognising that screening all diseases detectable by MS/MS may not be possible in Thailand where healthcare resources are limited. For example, with a small number of physicians who specialise in IEM treatment, managing medical care for all detected patients is impracticable. Therefore, only most significant diseases will be screened for an initiative period of the programme. Among the diseases detectable by MS/MS, we prioritised which diseases are appropriate to be included in the study. We first held an expert panel of IEM specialists (DW, NV, PW, VS, SP, and CK) from four major hospitals in Bangkok where most of the IEM patients are treated to help with the selection of the diseases, including Siriraj Hospital, Ramathibodi Hospital, Chulalongkorn Hospital, and the Queen Sirikit National Institute of Child Health. The selection criteria were modified from the principle of population-based screening proposed by the World Health Organization (WHO) based on the recommendations of Wilson and Jungner [26] which included the magnitude of the health problem, availability of technology (screening and treatment), safety, and effectiveness of the treatment. As a result, six diseases consisting of PKU, isovaleric acidemia (IVA), methylmalonic acidemia (MMA), propionic acidemia (PA), maple syrup urine disease (MSUD), and multiple carboxylase deficiency (MCD) were selected for an economic evaluation.

Study design

The cost-effectiveness analysis followed the standard guidelines of economic evaluations [27, 28] with present health technology services as the comparator. Thus, the analysis compared: 1) the current practice—or "pre-expanded newborn screening programme"—where only PKU is screened using the Guthrie test and PKU patients received early treatment whereas the other diseases detected were treated after symptomatic presentation; and 2) the "expanded newborn screening programme using MS/MS" where the six prioritised diseases were screened and treatment was given early or before symptomatic presentation. The costs and health outcomes of these alternatives were then compared by taking the societal perspective into account as suggested by Thai Health Technology Assessment guidelines [29].

The health outcomes of interest were measured in life-year gained (LY) and quality-adjusted life year (QALY) gained. A discount rate of 3% was applied for both the cost and outcome [30]. All costs were subsequently converted to year 2013 adjusted using the consumer price index medical care for medical goods and services and general consumer price index for those non-medical and other costs as recommended in the Thai health technology assessment guidelines [31]. The analyses were performed in Microsoft Excel 2007 (Microsoft Corp., Redmond, WA) and the results were presented as an incremental cost-effectiveness ratio (ICER) in Thai baht (THB) per QALY gained. For intercountry comparisons, costs can be converted into international dollars (I$) using the purchasing power parity (PPP) exchange rate of 1 I$ = 17.79 THB (2013) [32]. This analysis used the cost-effectiveness ceiling threshold of one times the gross domestic product (GDP) per capita (120,000 THB ≈ 6,745 I$) per QALY gained as recommended by the Health Economic Working Group under the Subcommittee for Development of the National List of Essential Drugs and the Subcommittee for Development of the Health Benefit Package and Service Delivery of the NHSO, Thailand [33].

Analytical model

A probabilistic multivariate model was conducted using a combination of a decision-tree and Markov model that followed a cohort of newborns with a cycle-length of one year. Our model consisted of newborns at birth starting either at the stage of being at risk for one of the six selected diseases or the normal newborn stage. Next, these newborns were able to transit through three possible scenarios consisting of early diagnosis, late diagnosis, and normal newborns (Fig 1). After that, the affected newborns were followed by applying a Markov model to capture possible changes in the health status for each year of life within the designated cycle-length for 100 years or lifetime. This is to ensure that all cost and outcomes related to the disease and intervention were comprehensively accounted for.

Although the six prioritised IEM diseases have the potential to cause several severe clinical manifestations, only the most common long-term complications were taken into account as health states in this analysis (Fig 2). Since it was highly possible that a majority of IEM patients would have neurological complications, this complication was deemed integral to the model [1]. The other important long-term complications represented in the model were renal failure in MMA and cardiomyopathy in PA [34]. Thus, the health states applied in each disease were divided into three different groups based on the most common long-term complications: 1) PKU, IVA, MSUD, and MCD (Fig 2A) were designated the health states of living without any complications, having neurological complications, and death; 2) MMA (Fig 2B) was consisted of the health states of living without any complications, having neurological complications, having renal failures, having both neurological and renal complications, and death; and 3) PA (Fig 2C) was presented the health states of living without any complications, having neurological complications, having cardiomyopathy, having both neurological complications and cardiomyopathy, and death.

Estimation of disease incidences

The incidence of PKU in the Thai population is 2.22 per 100,000 live births. This data was obtained through a newborn screening programme at Siriraj Hospital—which had screened over 180,000 infants born in Bangkok Metropolitan—as well as a continuity programme for screening-positive cases [35]. Due to the lack of existing data on the incidences of the other IEM in Thai setting, the present study adopted the incidences of other Asian populations—specifically the Chinese and Japanese—which were considered comparable to Thai ethnicity. The incidence of the remaining five IEM ranged from 0.54 to 2.69 cases per 100,000 live births [7] [8] (Table 1).

Transitional probabilities of long-term complications and mortality

Transitional probabilities, or *tp(u)* (i.e., transition to long-term complications and/or death), are required for the Markov model to simulate the events of patients entering each health state (Table 1). Our base-case analysis mainly estimated a baseline rate of long-term complications using a retrospective review of the registered medical records of patients with the six IEM diseases at the four hospitals from 1992 to 2012. The data consisted of clinical variables such as the survival time, demographics, clinical complications, and patient status (alive/dead) of 119 patients (IVA = 23, MMA = 20, PA = 8, PKU = 26, MSUD = 32, and MCD = 10). The annual transitional probabilities of long-term complications were estimated by employing nonparametric methods and the annual probabilities of mortality were estimated using survival analysis.

A parametric survival-time model was applied in order to derive a time-dependent probability of mortality for IVA, MMA, PA, and MSUD. In particular, a Weibull model which was

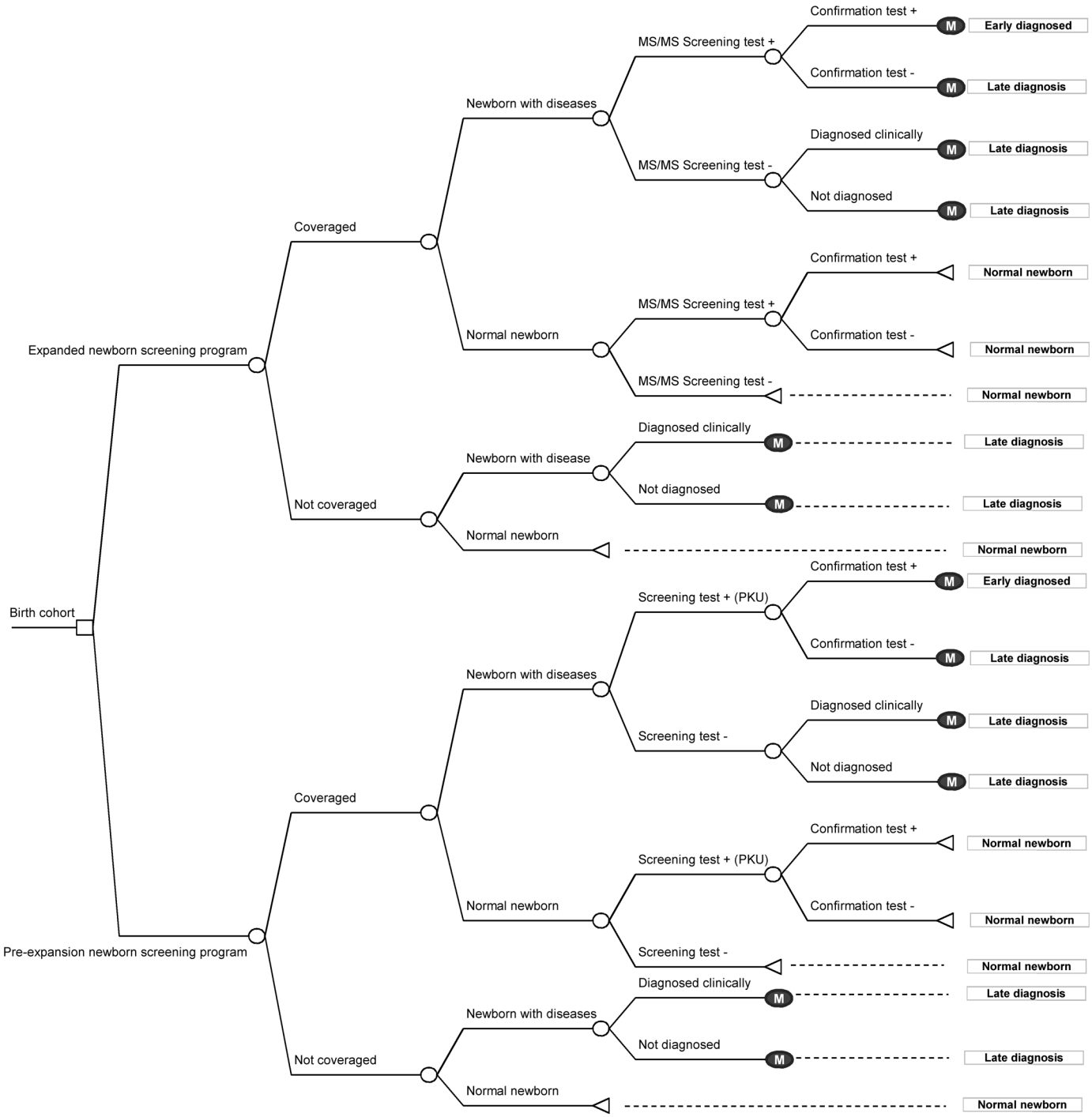

Fig 1. Simplified-decision-tree. Comparing the strategies of expanding the newborn screening programme with the pre-expanded newborn screening programme. MS/MS = Tandem mass spectrometry; PKU = phenylketonuria; M = Markov model.

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compared with exponential model was used as the AIC (Akaike information criterion) indicated that it was more fit to the actual data. The survival function, *S(t)* which describes the

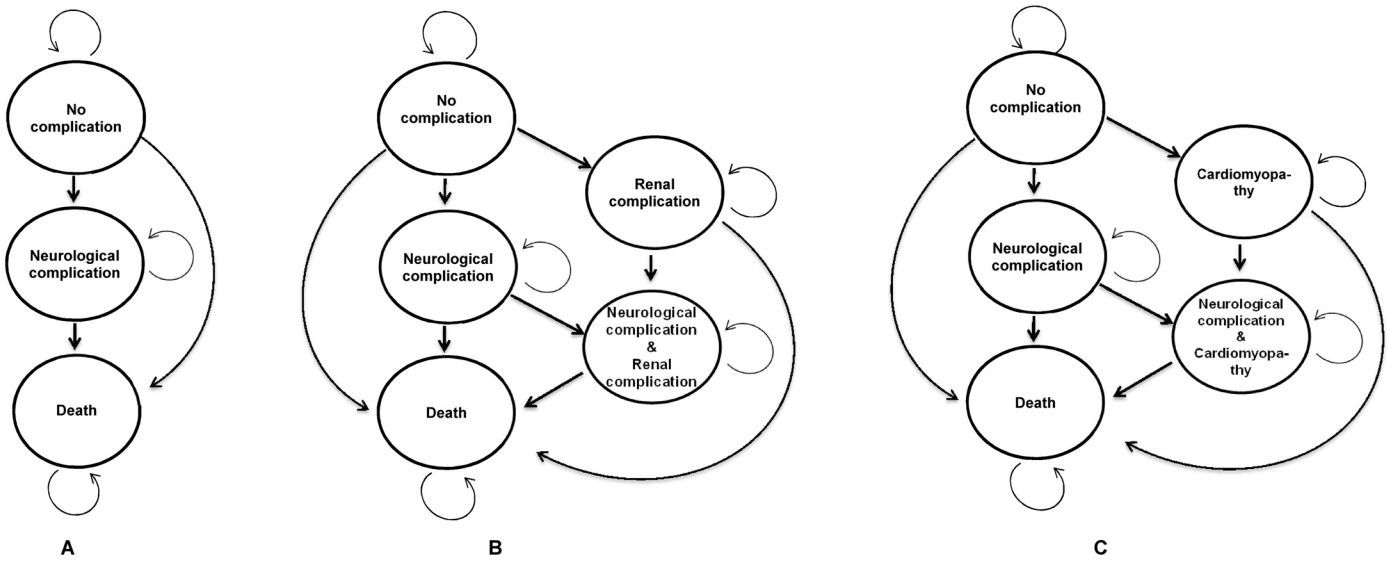

Fig 2. Markov model. Health states transition of selected IEM. (A) represents PKU, IVA, MSUD and MCD; (B) represents MMA; and (C) represents PA. PKU = phenylketonuria; IVA = isovaleric acidemia; MMA = methylmalonic acidemia; PA = propionic acidemia; MSUD = maple syrup urine disease; MCD = multiple carboxylase deficiency.

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probability of survival as a function of time is [48]:

$$S(t) = \exp\{-H(t)\} \quad (1)$$

and

$$H(t) = \lambda t^{\gamma} \quad (2)$$

where $H(t)$ which is the cumulative hazard; λ (lambda) is the scale parameter; t is time in years; and and ancillary or γ (gamma) is the shape parameter that describes the instantaneous death rate, the hazard rate $h(t)$, which increase which time if $\gamma > 1$.

The transitional probability of dying during the cycle, $tp(u)$, is therefore estimated from the following formula (where u is the cycle-length of the model):

$$tp(u) = 1 - \exp\{\lambda(t-u)^{\gamma} - \lambda t^{\gamma}\} \quad (3)$$

For PKU and MCD, the reviewed data showed that patients who were admitted to hospitals were all still alive which prevented us from capturing their lifespan by applying survival analysis. In the case of PKU, the probability was adopted from the data of the United States' national survey on PKU[36] whereas the lack of long-term literature on MCD patients required the experts to make the assumption that their mortality is equivalent to the normal population. In addition, for all six IEM, apart from the probability of mortality caused specifically by the diseases, the model also included death from other causes estimated from the Thai life table [49] (S1 Table).

Sensitivity and specificity

At present, only PKU is screened using the Guthrie test. This traditional method yielded a sensitivity of 98.50% and specificity of 99.50% [39] as shown in Table 1.

Due to a prior systematic review supporting the high accuracy of MS/MS [19], we assumed a screening test sensitivity of 100% and specificity of 100% (Table 1). The expert panel also

Table 1. Mean and standard error (SE) of transitional probabilities used in the model.

Parameter		Distribution	Mean	SE	Reference
Uptake rate		Beta	0.97	0.0001	[38]
MS/MS sensitivity		Beta	1.00	-	[19]
MS/MS specificity		Beta	1.00	-	[19]
Guthrie sensitivity		Beta	0.9850	0.01	[39]
Guthrie specificity		Beta	0.9995	0.01	[39]
Incidence of diseases					
PKU		Beta	$2.22\ 10^{-5}$	$1.11\ 10^{-5}$	[35]
IVA		Beta	$1.08\ 10^{-5}$	$5.38\ 10^{-6}$	[8]
MMA		Beta	$2.69\ 10^{-5}$	$8.50\ 10^{-6}$	[8]
PA		Beta	$5.40\ 10^{-6}$	$3.80\ 10^{-6}$	[8]
MSUD		Beta	$1.08\ 10^{-5}$	$5.38\ 10^{-6}$	[8]
MCD		Beta	$6.60\ 10^{-6}$	$3.30\ 10^{-6}$	[7]
Death from the disease[a]					
Yearly probability					
PKU	Age 0 to < 10 years	Beta	$2.53\ 10^{-3}$	-	Estimated from [36]
	Age 10 to < 20 years	Beta	$2.88\ 10^{-2}$	-	
	Age 20 to < 30 years	Beta	$4.57\ 10^{-3}$	-	
	Age 30 to < 40 years	Beta	$4.39\ 10^{-3}$	-	
	Age 40 to < 50 years	Beta	$3.54\ 10^{-3}$	-	
	Age 50 to < 60 years	Beta	3.24 10–3	-	
	Age $\geq$ 60	Beta	1.13 10–1	-	
Survival analysis					
IVA	Constant for baseline hazard	Lognormal	-2.515	0.721	Medical record review
	Ancillary parameter in Weibull distribution	Lognormal	-1.424	0.371	Medical record review
MMA	Constant for baseline hazard	Lognormal	-4.070	1.690	Medical record review
	Ancillary parameter in Weibull distribution	Lognormal	-0.865	0.532	Medical record review
PA	Constant for baseline hazard	Lognormal	-3.970	1.662	Medical record review
	Ancillary parameter in Weibull distribution	Lognormal	-0.745	0.477	Medical record review
MSUD	Constant for baseline hazard	Lognormal	-4.790	1.123	Medical record review
	Ancillary parameter in Weibull distribution	Lognormal	-0.665	0.289	Medical record review
Long-term complications (Yearly probability)					
PKU	Neurological complication	Beta	0.1340	0.0852	[37]
IVA	Neurological complication	Beta	0.0509	0.0549	Medical record review
MMA	Neurological complication	Beta	0.0897	0.0730	Medical record review
	Renal failure	Beta	0.0339	0.0487	Medical record review
PA	Neurological complication	Beta	0.6838	0.2080	Medical record review
	Cardiomyopathy	Beta	0.0468	0.1056	Medical record review
MSUD	Neurological complication (Age 0 to <1 year)	Beta	0.2778	0.1056	Medical record review
	Neurological complication (Age 1 to < 2 years)	Beta	0.3846	0.1147	Medical record review
	Neurological complication (Age = >2)	Beta	0.6250	0.1122	Medical record review
MCD	Neurological complication (Age 0 to < 3 years)	Beta	0.0572	0.0774	Medical record review
	Neurological complication (Age 3 to < 7 years)	Beta	0.0646	0.0819	Medical record review
	Neurological complication (Age = > 7 years)	Beta	0.0218	0.0487	Medical record review
Relative risk of early compared with clinical diagnosis					
PKU	Mortality	Beta	0.67	-	[36]
	Neurological complication (RR)	Lognormal	0.02	0.03	[37, 40, 41]
IVA	Mortality reduction	Beta	0.20	-	[42]

(*Continued*)

Table 1. (*Continued*)

Parameter		Distribution	Mean	SE	Reference
	Neurological complication (RR)	Lognormal	0.28	0.11	[43]
MMA	Mortality reduction	Beta	0.25	-	[42]
	Neurological complication (RR)	Lognormal	0.63	0.41	[34]
	Renal failure (RR)	Lognormal	0.33	0.31	[34]
PA	Mortality reduction	Beta	0.25	-	[42]
	Neurological complication (RR)	Lognormal	0.73	0.30	[34]
	Cardiomyopathy (RR)	Lognormal	0.46	0.95	[44]
MSUD	Mortality reduction	Beta	0.20	-	[42]
	Neurological complication (RR)	Lognormal	0.23	0.11	[45, 46]
MCD	Mortality reduction	Beta	1.00	-	[47]
	Neurological complication (RR)	Lognormal	0.00	-	[14, 47]

[a] See S1 Table for death from other causes.

PKU = phenylketonuria; IVA = isovaleric acidemia; MMA = methylmalonic acidemia; PA = propionic acidemia; MSUD = maple syrup urine disease; MCD = multiple carboxylase deficiency; RR = Relative risk of early-diagnosed patients compared with clinical diagnosed patients

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agreed with this assumption that a sensitivity and specificity of 100% for both should be used. As such, this meant that no IEM cases were missed by the MS/MS screening programme.

Outcome of early detection

A relative risk (RR) was used as the main outcome measure. The RR of the experimental or screened group compared with the clinical diagnosed group on neurological complications or other complications of each IEM disease—was obtained based on a systematic search through Ovid MEDLINE and Embase. Detailed information about the systematic search is available in (S1 Search Strategy). Where data was available, pooling RR was performed (Table 1). The effectiveness in the reduction of neurological complication of patients with early detection of PKU was calculated based on data from three cohort studies consisting of: a collaborative study of children treated for PKU in the US [41]; a study in Italy from the Regional Center for Inborn Errors of Metabolism [40]; and a retrospective study of PKU patients diagnosed and controlled in Spain [37] (RR 0.02, 95%CI (0.00–0.09)). For IVA patients, the reduction in risk of neurological complications was estimated based on a literature review investigating 155 IVA patients worldwide (RR 0.28, 95%CI (0.07–0.50)) [43]. Two case series reports of MSUD patients diagnosed in the US [46] and Japan [45] were pooled to estimate the reduction of neurological complications (RR 0.23, 95%CI (0.01–0.45)). For MMA and PA patients, the review study of cases around the world comparing symptomatic cases and those diagnosed through newborn screening [34] was used to calculate the RR of neurological complications (RR 0.63, 95%CI (0.00–1.00) for MMA, and RR 0.73, 95%CI (0.00–1.00) for PA) as well as the RR of renal failure in MMA patients (RR 0.33, 95%CI (0.00–0.93)). The RR of cardiomyopathy in PA patients was 0.46 (95%CI (0.00–1.00)) based on a German study comparing PA patients diagnosed through newborn screening and those obtained through clinical diagnosis [44]. In the case of MCD, we assumed no long-term complications if early detection and treatment was provided as results according to the report of American Academy of Paediatrics [47] and previously published data [14] showed.

An extensive search of literature was also conducted to determine the benefit of early detection for reduction of mortality in patients but no any robust evidence-based information was found. Nevertheless, the potential data found could be an estimation of UK paediatrician on reduction on death of early-diagnosed IVA, MMA, PA, and MSUD patients ranged between 20%-25% given to a previous study [42]. So, the information was adopted into the model. For PKU and MCD patients, normal life expectancy was assumed for the effectiveness of early detection which was supported by the data from medical record reviews which showing no PKU and MCD patients died due to the disease (Table 1).

Screening costs

Two sample quotations of MS/MS manufacturers and distributors were obtained to estimate the capital and material costs of the MS/MS screening programme. In terms of human resources, a proportion of labour costs to capital and material costs from international publications [15, 16, 19] were estimated and applied to the analysis (Table 2).

To screen around 750,000 births per year, we estimated that Thailand requires 7 to 9 MS/MS machines. When requesting for the sample quotations, we received a difference in terms of price. The cost per MS/MS machine ranged from 9.8 to 15 million THB in addition to an annual maintenance fee of 1.8 to 4.8 million THB. To calculate for depreciation, the equipment would have a lifetime of 7–8 years life without the salvage value. The prices of reagent per sample were also considerably dissimilar at 111 and 300 THB per sample. Meanwhile, the labour cost accounted for approximately 28% of the screening cost and was calculated to be 64 THB per sample. Thus, from this information, the cost of MS/MS screening per sample was estimated to be 294 THB per sample (Table 2).

Treatment costs

This study was approached from a societal perspective so all costs relevant to patient, health care system, and society were analysed. A cost analysis was conducted specifically for each of the six prioritised diseases. Treatment costs mainly included hospitalisation expenses and dietary management. Retrospective information of the treatment costs for the IEM patients was collected from each of the four hospitals' databases, and then the resulting data were pooled and analysed together (Table 2).

From the data, it was evident that the cost of inpatient care (IPD) was very high in the first year of treatment due to an acute phase. The treatment cost decreased dramatically in the second year of treatment. Thus, the IPD cost was divided into two periods: 1) the first year of treatment; and 2) the second year of treatment onwards. Regarding the cost of outpatient care (OPD), the cost per year was estimated by multiplying the cost per visit by the number of outpatient visits per year (S2 Table).

Additionally, the cost of the supplemental metabolic formula was calculated based on the assumption that patients needed a special formula for their lifespan to maintain normal metabolic function. Price of this special product was provided by manufacturer and the data of quantity used for patients was obtained from the IEM specialists. Regarding the cost of other supplemental products such as orphan drugs, vitamins, and cofactors, the IEM specialists were asked to answer a set of questions on a provided questionnaire survey about the type, the quantity, and the unit price of the product being used to treat their IEM patients. For productivity loss and direct-non medical costs, data were collected via face-to-face interviews with the patients' families using a structured questionnaire. The parents of the IEM patients were asked about the time spent to look after their children who have been disabled due to complications caused by IEM. The average wage in Thailand [50]—classified by gender and age—was used

Table 2. Means and standard error (SE) of cost parameters presented in 2013 Thai Baht. 1 I$ = 17.79 THB.

Parameter		Distribution	Mean	SE	Reference
Screening cost for MS/MS (per sample)		Gamma	294	126	Survey
Screening cost for Guthrie (per sample)		Gamma	5.00	-	NSCO
Confirmation cost (per sample)		Gamma	2,349	168	Hospital database
Hospital inpatient care (IPD) cost per year					
First year of treatment					
PKU		Gamma	80,316	19,899	Hospital database
IVA		Gamma	174,006	53,349	Hospital database
MMA		Gamma	252,457	81,466	Hospital database
PA		Gamma	284,718	91,965	Hospital database
MSUD		Gamma	252,859	53,281	Hospital database
MCD		Gamma	92,070	25,721	Hospital database
Second year of treatment onward					
IVA		Gamma	21,290	3,712	Hospital database
MMA		Gamma	191,729	73,046	Hospital database
PA		Gamma	160,951	44,432	Hospital database
MSUD		Gamma	52,580	15,029	Hospital database
MCD		Gamma	69,615	60,111	Hospital database
Hospital outpatient care (OPD) cost per year					
PKU		Gamma	16,366	321	Hospital database
IVA		Gamma	44,925	1,335	Hospital database
MMA		Gamma	108,671	2,272	Hospital database
PA		Gamma	61,328	2,142	Hospital database
MSUD		Gamma	17.928	519	Hospital database
MCD		Gamma	4,055	362	Hospital database
Pharmaceutical product per year[a]					
L-carnitine (IVA, MMA)		Gamma	1,470	-	Survey
L-glycine (IVA)		Gamma	276	-	Survey
Cobalamin (MMA, PA)		Gamma	7,350	-	Survey
Biotin (PA)		Gamma	13,597	-	Survey
Biotin for (MCD)		Gamma	10,198	-	Survey
Metabolic formula per year					
PKU	Age 0 to < 4 years	Gamma	75,511–81,552	-	Survey
	Age ≥4 years	Gamma	45,306	-	Survey
IVA	Age 0 to < 5 years	Gamma	51,347–78531	-	Survey
	Age ≥5 years	Gamma	45,306		Survey
MMA	Age 0 to < 7 years	Gamma	51,347–75,511	-	Survey
	Age ≥7 years	Gamma	45,306		Survey
PA	Age 0 to < 7 years	Gamma	51,347–75,511	-	Survey
	Age ≥7 years	Gamma	45,306		Survey
MSUD	Age 0 to < 4 years	Gamma	55,878–86,082	-	Survey
	Age ≥4 years	Gamma	45,306		Survey
Direct non-medical cost per year					
PKU	with long-term complications	Gamma	27,704	-	Survey
	without long-term complications	Gamma	12,941	9,768	Survey
IVA	with long-term complications	Gamma	27,704	-	Survey
	without long-term complications	Gamma	15,781	4,924	Survey
MMA	with long-term complications	Gamma	46,516	20,107	Survey

(*Continued*)

Table 2. (*Continued*)

Parameter		Distribution	Mean	SE	Reference
	without long-term complications	Gamma	22,408	15,429	Survey
PA	with long-term complications	Gamma	36,348	26,618	Survey
	without long-term complications	Gamma	22,408	15,429	Survey
MSUD	with long-term complications	Gamma	45,770	22,843	Survey
	without long-term complications	Gamma	22,408	15,429	Survey
MCD	with long-term complications	Gamma	27,704	-	Survey
	without long-term complications	Gamma	14,361	7,346	Survey
Productivity cost per year					
PKU	with long-term complications	Gamma	26,522	2,235	Survey
	without long-term complications	Gamma	127,896	-	Survey
IVA	with long-term complications	Gamma	129,930	-	Survey
	without long-term complications	Gamma	43,944	5,469	Survey
MMA	with long-term complications	Gamma	177,404	20,107	Survey
	without long-term complications	Gamma	50,880	11,493	Survey
PA	with long-term complications	Gamma	128,784	11,010	Survey
	without long-term complications	Gamma	50,880	11,493	Survey
MSUD	with long-term complications	Gamma	105,717	9,573	Survey
	without long-term complications	Gamma	50,880	11,493	Survey
MCD	with long-term complications	Gamma	129,930	-	Survey
	without long-term complications	Gamma	35,444	85,000	Survey

[a]Calculated at patient weight 1 kilogram.

NSCO = Neonatal Screening Operation Centre; PKU = phenylketonuria; IVA = isovaleric acidemia; MMA = methylmalonic acidemia; PA = propionic acidemia; MSUD = maple syrup urine disease; MCD = multiple carboxylase deficiency

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for calculating the productivity loss or opportunity cost. We also inquired about costs relevant to hospitalisation such as travel costs from home to the hospital. From the data obtained, the differences between the cost of mild and severe cases were observed, and the costs for these cases were therefore classified into two groups according to the severity/complication of the disorder(s), including without complications and with complications (Table 2).

Utility measurement

There are several concerns about assessing health utility weight from children, especially an available and appropriate measuring instrument allowing children to complete their health status [51]. In addition, both small number of living patients and their intellectual disabilities status are factors that make it possibly impossible to perform primary data collection. Therefore, the estimation of health utility was conducted by holding an expert panel consisting of the six IEM specialists as proxies.

EuroQoL Five-Dimension Questionnaire (EQ-5D) was applied as a tool to estimate health utility weight of each health stage of each disease. The IEM specialists were then asked to recall from their current as well as previous IEM patients. Then, they filled out a score onto the prepared paper sheet. Subsequently, the average score was presented and discussed among the experts. As a result, a consensus for health utility weight was reached and applied into the model (Table 3).

Uncertainty analysis

To investigate the robustness of the cost-effectiveness results, we performed two types of uncertainty analysis. The first was a one-way sensitivity analysis which examined the effect of changes in key parameters on the ICERs of the base-case scenario. These variables included: the incidence of six selected IEM; probability of long-term complications; the effectiveness of the screening intervention (RR); health utility weight of six selected IEM; first year IPD and OPD costs; second year direct medical costs; metabolic formula and pharmaceutical product costs; direct non-medical cost of patients with complication; direct non-medical cost of patients without complication; productivity loss of patients with complication; productivity loss of patients without complication; uptake rate of screening; and MS/MS screening cost. Since each of these variables (except for the uptake rate and the screening cost) comprised six different values which varied by disease, we assumed that these values simultaneously changed in the same direction to the lower or upper bound once each variable was examined. The value being tested varied based on a 95% confidence interval (CI) of these parameters with standard errors. The costs of the metabolic formula and pharmaceutical products—which are parameters without standard error—were assumed to be varied by 50% from their mean value. Other parameters (not one being tested) were randomly generated by using a probabilistic sensitivity method.

The second, a probabilistic sensitivity analysis (PSA), was also conducted to assess the uncertainty involving all model parameters according to their mean, standard error (SE), and distribution shown in Tables 1 to 3. Probability distributions were defined as follows: (1) beta-distributions were assigned where parameter values ranged from zero to one, such as transition probabilities and utility parameters; (2) gamma-distributions were specified when parameter values were above zero and positively skewed by costs variables; and (3) a log-normal distribution was used for survival parameters and RR. A Monte Carlo simulation performed in Microsoft Excel 2007 (Microsoft Corp., Redmond, WA) was employed to generate 1,000 rounds of the simulation to demonstrate a range of plausible lifetime costs, health outcomes (LYs and QALYs), and ICERs. The result of the analysis was plotted in a cost-effectiveness plane. Moreover, the result was further analysed for a relationship between the values of the ceiling ratio and the likelihood of favouring each screening strategy as the result is illustrated using cost-effectiveness acceptability curves showing.

Budget impact analysis

Based on the model, a budget impact analysis (BIA) was also conducted by following the standard BIA frameworks for healthcare intervention in Thailand [52] along with international protocol [53]. The analysis applied the perspective of the budget holder in Thailand, i.e. the NHSO, and aimed to project the financial plans between the implementation of the new screening programme and the status quo. The costs were analysed and reported into two categories: screening cost and treatment cost. The costs were inflated at 0.5% each year [31] with a time horizon of 10 years. Since there is a stable trend for population growth in Thailand, the annual cohort of newborns was fixed at 750,000 per year [54]. The analysis was based on the important assumption that the new programme will be managed by the existing screening organization, i.e. the neonatal screening operation centre, and will replace the current PKU screening. Therefore, there is no cost of setting up a new department in order to handle the programme. The machine cost was considered as a fixed capital cost and was spread out equally throughout each year of the programme based on the concept of equivalent annual cost [55], while reagent and administrative costs were variable costs dependent on the number of participants. We conservatively assumed that the uptake for the new screening programme was

Table 3. Health utility weight of IEM patients.

Utility estimated		Distribution	Mean	SE	Reference
PKU	without long-term complication	Beta	0.71	0.02	Expert panel
	with mental retardation	Beta	0.13	0.19	Expert panel
IVA	without long-term complication	Beta	0.71	0.07	Expert panel
	with mental retardation	Beta	0.00	0.15	Expert panel
MMA	without long-term complication	Beta	0.62	0.06	Expert panel
	with mental retardation	Beta	0.16	0.18	Expert panel
	with renal failure	Beta	0.45	0.16	Expert panel
	with mental retardation and renal complication	Beta	0.14	0.22	Expert panel
PA	without long-term complication	Beta	0.49	0.13	Expert panel
	with mental retardation	Beta	0.05	0.21	Expert panel
	with cardiomyopathy	Beta	0.41	0.20	Expert panel
	with mental retardation and cardiomyopathy	Beta	0.00	0.28	Expert panel
MSUD	without long-term complication	Beta	0.60	0.07	Expert panel
	with mental retardation	Beta	0.00	0.04	Expert panel
MCD	without long-term complication	Beta	0.84	0.11	Expert panel
	with mental retardation	Beta	0.51	0.07	Expert panel

PKU = phenylketonuria; IVA = isovaleric acidemia; MMA = methylmalonic acidemia; PA = propionic acidemia; MSUD = maple syrup urine disease; MCD = multiple carboxylase deficiency

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80% for the first year of the implementation and then increased it to 85%, 90%, 95%, and 100% in subsequent years. The minimum cost and maximum cost scenarios of the screening budget was examined based on the range of 95% CI of screening costs, while the scenario of the treatment budget was tested based on the incidence of disease (varying the incidence of all diseases simultaneously to the lower and upper bounds).

Results

Cost-effectiveness analysis of the pre-expanded and the expanded newborn screening programme

The cost-effectiveness analysis via the adoption of a new screening strategy compared with the existing screening programme indicate ICERs of 602,606 THB per LY gained (33,873 I$ per LY gained) and 1,043,331 THB per QALY gained (58,647 I$ per QALY gained) (Table 4), both of which are above the agreed threshold currently used in Thailand.

In order to understand the potential benefit of screening at the individual diseases level, Table 5 illustrates the lifetime outcome of each affected child once they are detected early or

Table 4. Costs, health outcomes, and incremental cost-effectiveness ratios (ICERs) of two neonatal screening programmes. 1 I$ = 17.79 THB. THB = Thai baht; LYs = life-years; ICER = incremental cost effectiveness ratio; QALYs = quality-adjusted life year.

Strategy	Total cost (THB)	Incremental Cost (THB)	LYs	LY gained	ICER (THB/LY gained)	QALYs	QALY gained	ICER (THB/QALY gained)
Pre-expanded newborn screening programme	153.27	—	66.42256	—	—	66.42229	—	—
Expanded newborn screening programme	676.55	523.28	66.42343	0.00087	602,606	66.42279	0.00050	1,043,331

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late. The analysis suggests that early medical treatment substantially improves the health outcome in PKU patients resulting in 9.60 QALY higher than those with late detection. IVA patients also noticeably benefit from early detection which extends their QALY by 3.69. In MSUD patients, early detection also yields better health outcomes that help prolong QALY by 2.73. In terms of lifetime costs, the difference between providing early healthcare and late healthcare to those with MSUD, IVA, and PKU ranges between 200,045 THB (11,245 I$) and 502,913 THB (28,269 I$) per patient. MCD patients gain 1.66 QALY from early detection and it is the only disease where early medical management reduces the patient's lifetime costs (-256,779 THB (-14,434 I$)). However, in most diseases, the costs of giving lifetime care in patients detected early are higher than those in clinically diagnosed patients; it is clear that being detected early requires significantly much more costs in MMA and PA patients (1,783,826 THB (100,271 I$) and 1,241,945 THB (69,811 I$), respectively), which is obviously high relative to their health outcome gained (2.83 QALY and 0.81 QALY for MMA and PA, respectively).

Uncertainty analysis

The results of the one-way sensitivity analysis using probabilistic model was further elaborated upon using a tornado diagram as shown in Fig 3, indicating that the most sensitive factor to ICER (THB per QALY gained) was the incidence. This was followed by: the MS/MS screening cost; RR reduction; and health utility. Among the factors least sensitive to the results were the uptake rate, productivity loss, and direct non-medical costs.

Fig 4 shows the result of the probabilistic sensitivity analysis. Monte Carlo simulation indicated that compared to the 'current practice' strategy, the 'expanded newborn screening' strategy was more costly but more effective in more than 95% of the simulated cases. The average patient with screening accrued 0.00048 (95% CI: 0.00023–0.00077), and THB 484.09 (95% CI: 218.25–839.59) more QALYs and costs than that without screening, giving an ICER of THB 1,060,240 (95% CI: 534,228–2,195,143) per QALY which, however, exceeds the threshold for cost-effective intervention in Thailand (THB 120,000 per QALY).

Fig 5 illustrates the cost-effectiveness acceptability curves representing the probability of both screening programme scenarios at different thresholds or willingness to pay being cost-effectiveness. When considering willingness to pay at less than Thailand's value of one times the 2013 GDP per capita per QALY gained, the current screening programme has the potential to be more cost-effective. However, if the threshold is higher than approximately 1,100,000 THB per QALY gained, the MS/MS screening programme becomes a better option.

Budget impact analysis

From Table 6, it can be expected that the screening programme will have a total cost of 191.9 million THB per year in the earlier period and continually increase to above 300 million THB after seven years of implementation. In detail, the cost of screening is estimated to be 179.8 million THB in the first year and stays roughly at 200 million THB after three years of operation. Whereas the treatment cost is only a small proportion compared to the total cost in the earlier years (e.g. 12.1 million THB in 2013), it subsequently grows rapidly and is estimated to reach 93.9 million THB in the tenth year; this amount accounts for nearly one-third of the total cost in that year. It is obvious that the total expense of the screening programme is expected to increase overtime and the costs of treatment will be more and more substantial for the overall budget as illustrated in Fig 6. The analysis also found that there is a considerable switching cost from the current practice to the new programme, amounting to 2,539.6 million THB for the ten-year period.

Table 5. Difference of lifetime health outcomes and costs per patient after early detection or late detection. 1 I$ = 17.79 THB. The result was under adjusting of 3.0% discounting rate. Undiscounted version was provided as (S3 Table). PKU = phenylketonuria; IVA = isovaleric acidemia; MMA = methylmalonic acidemia; PA = propionic acidemia; MSUD = maple syrup urine disease; MCD = multiple carboxylase deficiency; RR = Relative risk of early-diagnosed patients compared with clinical diagnosed patients.

Disease	Cost (THB)			Life-years			QALYs		
	Early diagnosis	Late diagnosis	Difference	Early diagnosis	Late diagnosis	Difference	Early diagnosis	Late diagnosis	Difference
PKU	3,145,203	2,642,290	502,913	29.55	19.57	9.99	20.91	11.31	9.60
IVA	3,728,014	3,409,629	318,384	17.63	14.84	2.79	11.51	7.82	3.69
MMA	7,685,602	5,901,776	1,783,826	16.33	12.14	4.19	8.67	5.84	2.83
PA	3,838,684	2,596,739	1,241,945	8.82	5.70	3.12	1.25	0.74	0.81
MSUD	3,462,620	3,262,575	200,045	14.88	12.64	2.24	3.93	1.20	2.73
MCD	2,544,647	2,801,427	-256,779	29.59	28.77	0.81	24.75	23.09	1.66

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Discussion

Based on the current threshold recommended in Thailand, the results of the present study suggest that implementing the MS/MS screening programme does not meet the criteria for cost-effectiveness. The incidence rate and the MS/MS screening cost are some of the major parameters influencing the cost-utility results followed by the RR reduction and health utility weight. A one-way sensitivity analysis shows that changing the parameters' values did not affect the conclusion of the study. The result of the probabilistic analysis suggests that the better option is to continue implementing the Guthrie test for PKU. However, the benefits of early management for IVA, MSUD, PKU, and MCD patients are attractive. The budget impact analysis suggests that the likely costs of implementing the programme is about 2,700 million THB over a projection of 10 years.

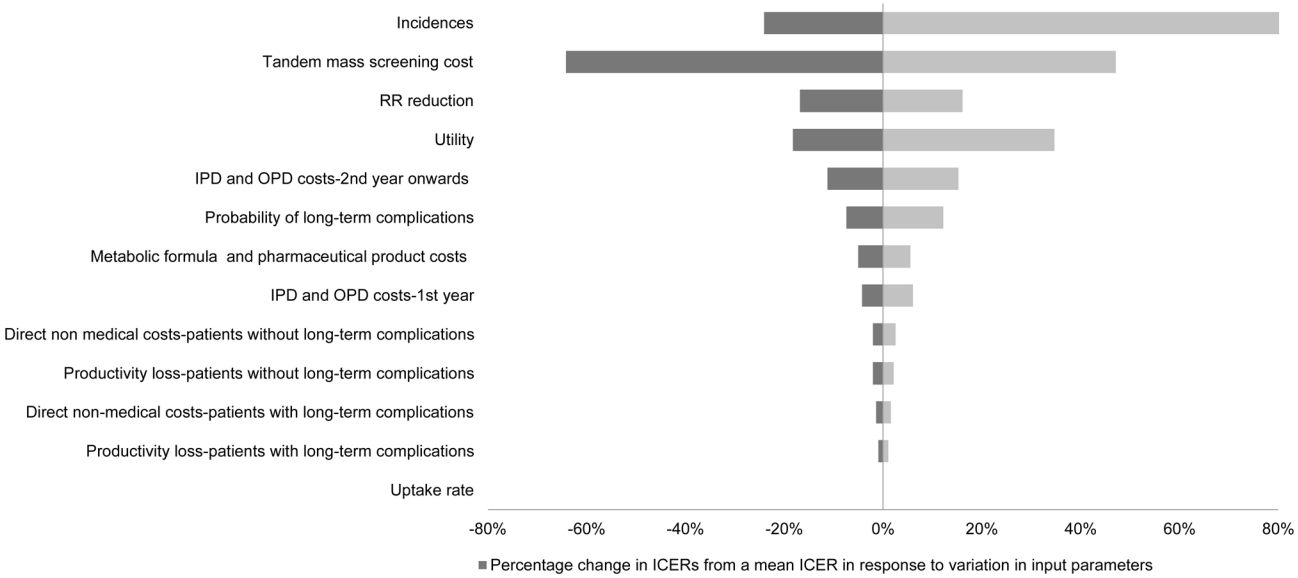

Fig 3. One-way sensitivity analysis. Tornado graph showing results of one-way sensitivity analysis derived from probabilistic method. These figures indicating parameters which have the largest effect on incremental cost effectiveness ratio or ICER (THB per QALY gained) when they are varied individually. IPD = cost of inpatient care; OPD = cost of outpatient care.

doi:10.1371/journal.pone.0134782.g003

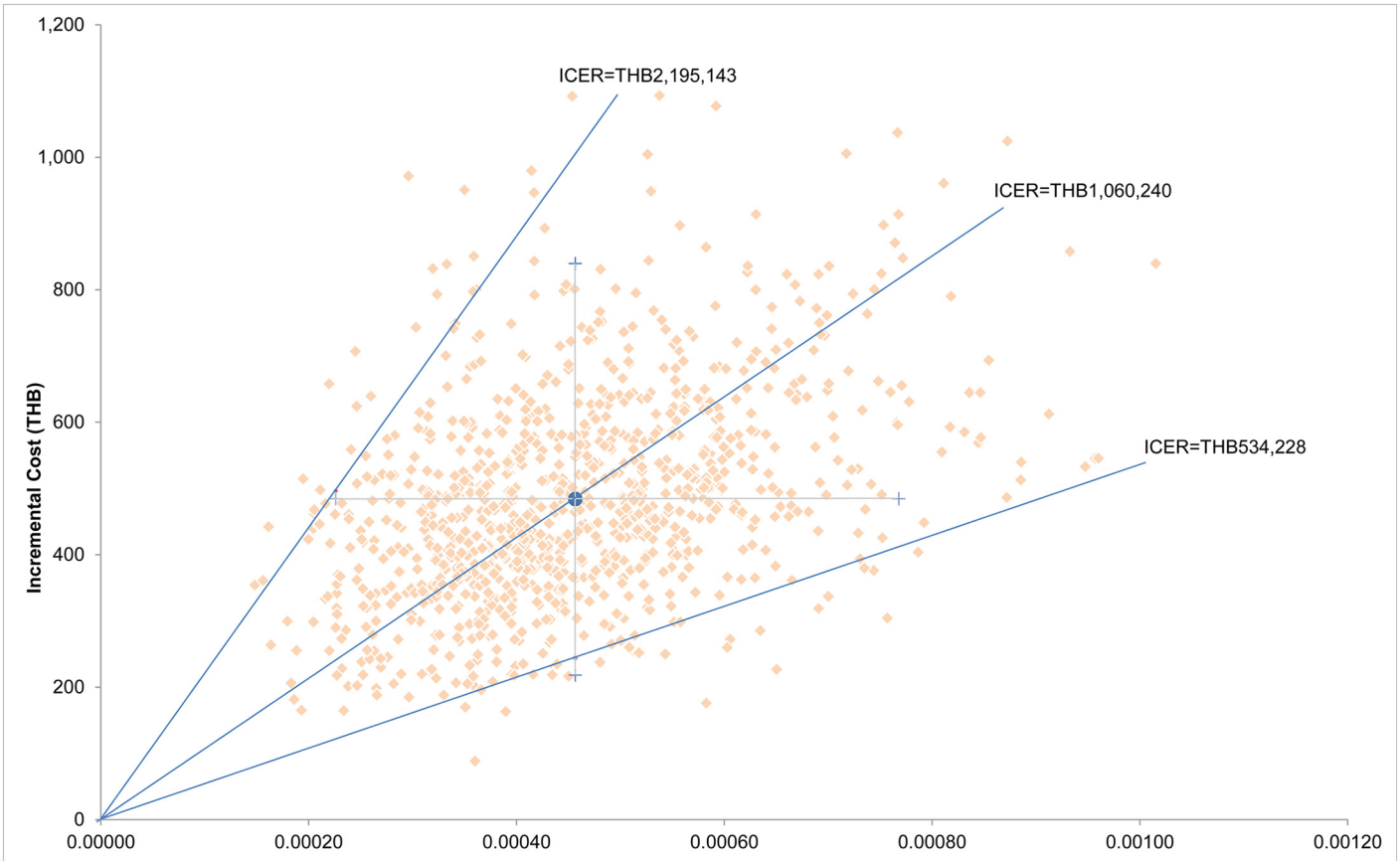

Fig 4. Cost-effectiveness plane. Monte Carlo simulation results on cost-effectiveness plane for the expanded newborn screening showing interval estimates for cost, outcome and incremental cost-effectiveness ratio. The figure shows the horizontal I-bar representing the 95% uncertainty interval on life-year gained, the vertical I-bar representing the 95% uncertainty interval on incremental cost, and the wedge represent the 95% uncertainty interval on the ICER. THB = Thai baht; ICER = incremental cost effectiveness ratio.

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To our knowledge, this is the first study that comprehensively evaluated the cost-effectiveness of MS/MS in low- and middle-income countries (LMICs). All previous economic evaluations of MS/MS were conducted in high-income countries. Of those evaluations, most of studies represented cost-utility analyses [14, 16, 17, 20, 22, 56] followed by cost-effectiveness analyses [15, 18, 19, 42, 57]. Most studies also adopted a societal perspective [14, 15, 19, 56] or used a health care provider's perspective [17, 19, 20, 42], while a few applied the purchaser view [16, 22]. The most frequently used comparator in the studies is the no screening programme [14, 16–18, 20], followed by offering only PKU using the Guthrie test [15, 19, 42]. The result found in this study is not comparable with studies in other settings where most of the studies concluded that the screening programme is cost-effective either in screening for a combination diseases like in the US (California [16, 20], Wisconsin [17], Texas [22]), Australia [18], and UK [42] or screening for only some preferred disease like in UK [19] Canada [15]. As such, there are several differences between our study and the previous studies which need to be addressed.

Firstly, one important factor highly sensitive to the cost-effectiveness results of the screening programme is the incidence of diseases [14, 17]. A high burden in some particular diseases tends to make the intervention favourable, especially for diseases with effective outcomes of treatment such as PKU and medium-chain acyl-coenzyme A dehydrogenase deficiency

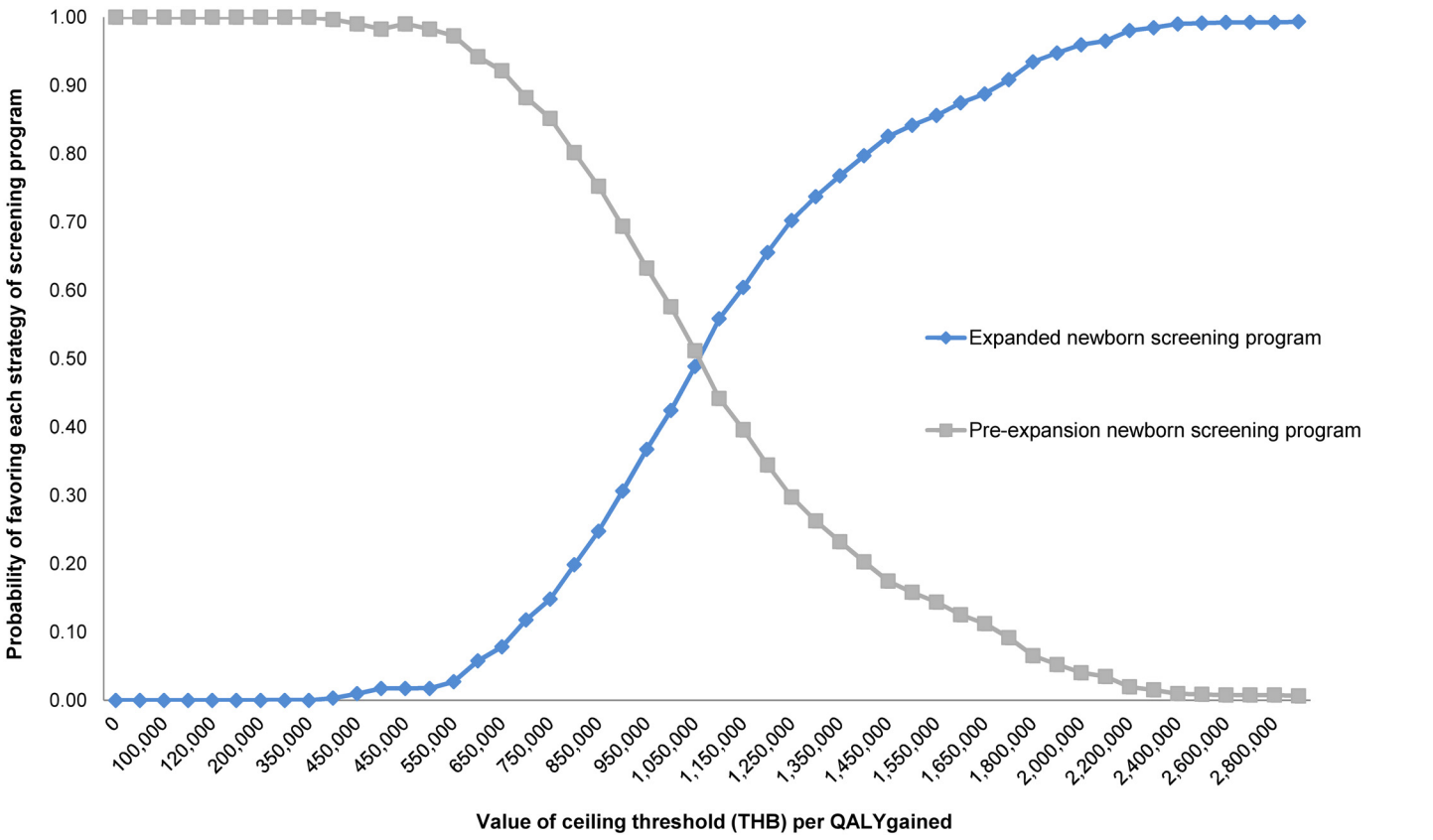

Fig 5. Acceptability curve. The graph shows the probabilities of each strategy being cost-effective at a given ceiling ratio. The dashed lines represent the willingness to pay thresholds for the adoption of health interventions in Thailand.

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Table 6. Estimated annual budget impact during 2013 to 2022 of the MS/MS screening programme implementation compared with the status quo (million THB). 1 I$ = 17.79 THB

Year[a]	Expanded newborn screening programme							Status quo							Difference
	Screening cost			Treatment cost			Total	Screening cost			Treatment cost			Total	Total
	Base case	Min	Max	Base case	Min	Max	(Base case)	Base case	Min	Max	Base case	Min	Max	(Base case)	(Base case)
2013	**179.8**	102.8	256.8	**12.1**	8.5	15.8	**191.9**	**3.6**	3.6	3.6	**3.2**	2.8	3.6	**6.8**	**185.0**
2014	**190.8**	109.4	272.3	**20.5**	14.4	26.7	**211.3**	**3.6**	3.6	3.6	**5.2**	4.4	6.0	**8.8**	**202.5**
2015	**202.0**	116.1	287.9	**29.4**	20.6	38.3	**231.4**	**3.7**	3.7	3.7	**7.1**	5.9	8.2	**10.7**	**220.7**
2016	**213.2**	122.9	303.6	**39.2**	27.5	51.0	**252.5**	**3.7**	3.7	3.7	**6.9**	7.4	10.5	**10.6**	**241.9**
2017	**224.6**	129.8	319.4	**49.6**	34.7	64.4	**274.1**	**3.7**	3.7	3.7	**10.3**	8.5	12.1	**14.0**	**260.1**
2018	**225.6**	130.8	320.4	**58.8**	41.2	76.5	**284.4**	**3.7**	3.7	3.7	**11.7**	9.7	13.8	**15.5**	**269.0**
2019	**226.7**	131.9	321.5	**67.7**	47.4	88.1	**294.4**	**3.7**	3.7	3.7	**13.1**	10.8	15.4	**16.9**	**277.5**
2020	**227.7**	132.9	322.5	**76.5**	53.6	99.5	**304.2**	**3.8**	3.8	3.8	**14.5**	11.9	17.1	**18.3**	**286.0**
2021	**228.8**	134.0	323.6	**85.2**	59.7	110.7	**314.0**	**3.8**	3.8	3.8	**15.9**	13.0	18.7	**19.7**	**294.3**
2022	**229.8**	135.0	324.6	**93.9**	65.7	122.0	**323.7**	**3.8**	3.8	3.8	**17.2**	14.2	20.3	**21.0**	**302.6**
Total	**2148.9**	1245.6	3052.3	**533.0**	373.3	692.8	**2681.9**	**37.1**	37.1	37.1	**105.2**	88.6	125.9	**142.4**	**2539.6**

[a] The uptake rate was assumed at 80%, 85%, 90%, 95%, and 100% in 2013, 2014, 2015, 2016, and 2017–2022, respectively.

Min = minimum; Max = maximum

doi:10.1371/journal.pone.0134782.t006

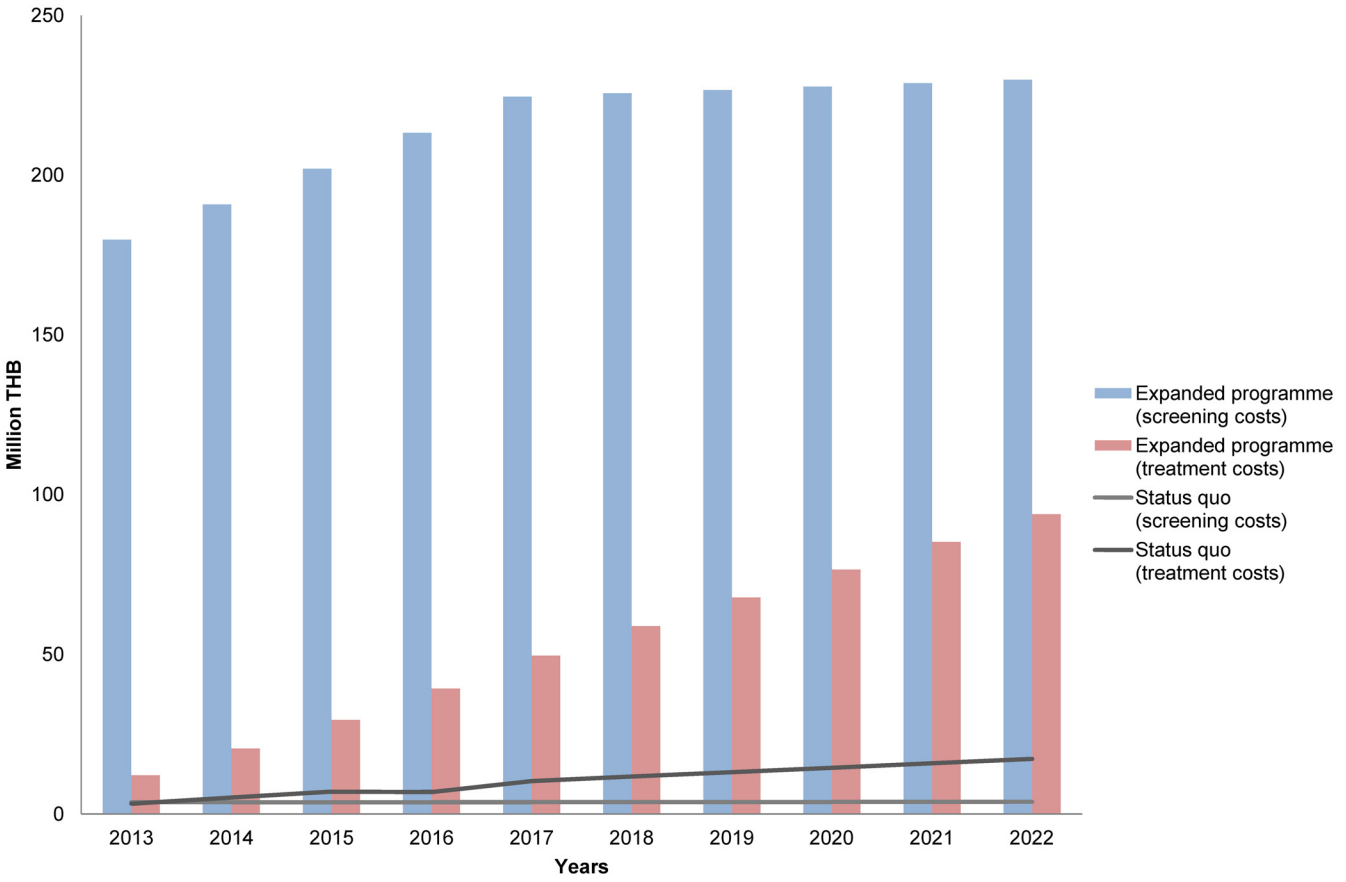

Fig 6. Budget Trend. The trend of the budget required for the screening programme compared with the current situation over ten years. THB = Thai baht.

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(MCAD) [17, 19]; all previous studies were conducted in countries with a high incidence of PKU. For example, in the UK, the incidence of PKU used in that study was 9.00 cases per 100,000 live births while the incidence of MCAD claimed in the UK and American studies were 8.00 and 4.50 per 100,000 live births [17, 19], respectively. In contrast, the incidence of PKU adopted in our study was 2.22 in 100,000 live births or about four times lower than the UK incidence. Furthermore, MCAD was not included due to it being uncommon in Thai and Asian population [58]. In relation to this point, a systematic literature review of the economic evaluation of an MS/MS screening programme also mentioned that the dissimilarity in the demography of the countries and regions led to different MS/MS cost-effectiveness results [57].

Secondly, the cost of treatment is another key variable influencing the difference in findings. Ideally, an early diagnosis will prevent patients from serious clinical consequences resulting in less health resources required for treatment. If this is the case, it will lead to a programme that is more economically favourable. For example, in US, Schoen et al 2002 [20] indicated that if glutaric aciduria type I (GA1) patients were diagnosed early, the cost of treatment will be decreased about 46% compared with patients who were diagnosed late. The same amount of reduction was applied with other diseases such as MMA and PA [20]. In contrast, based on the treatment costs analysed from the hospitals, we did not find a difference between the costs of patients diagnosed early or late. This could be because even though early detection can prevent patients from severe clinical consequences at an acute period and help avoid some unnecessary

costs for treatment, patients will still need more for preventive treatment in order to maintain their health. Therefore, patients diagnosed earlier can live longer and require more expensive treatment, some of which are required for a lifetime. This is agreeable with a previous study by Pandor et al 2004. [19] in the UK which found that there was no difference in treatment costs between the early diagnosis group and late diagnosis group for GA type I. This could be because the nature of the disease is extremely severe even though it was detected and treated early. Moreover, the effective treatment for this disease was not yet available. We believe that unless there is strong evidence, the assumption that early detection can reduce the cost of treatment should not be held.

Thirdly, there were huge differences in the outcome measurement, particularly the life-years gained between the early diagnosis and late diagnosis group. In a study by Schoen et al 2002 [20], the assumption of life-years gained of 20 years is added into the early detection group [20]. In an Australian study, it is assumed that patients who lived until 4 years of age could live up to the age of 66.2 [18]. Accordingly, those values used might be key factors which supported the favour of screening. However, a more conservative option was applied in a Canadian study where clinical data and the assumption about life expectancy were both used in the analysis [15]. In this case, it found that the average life-year gained was about 11 years (ranging from 4–25 years). In our analysis, using Markov modelling to follow the patients for lifetime estimated that having a screening programme will yield an average life-year gained of 13 years (ranging 4–40 years without outcome discounting). In particular, if the life expectancy gained by PKU patients was excluded, the average life-year gained for the rest of the IEM patients was only 8 years. We believe that from the scarcity of evidence, a conservative assumption for life expectancy should be the better option to apply to the model.

Lastly, the patient's quality of life is one of most sensitive parameters to the result. The higher the quality of life achieved by patients diagnosed early, the more favourable screening became. From reviewing previous studies, we found that a relatively high value of health utility weight was applied to the studies which concluded that interventions were cost-effective. The utility weight of asymptomatic patients of 0.90 is used in the models by Feuchtbaum et al 2006 [16] as well as Tiwana et al 2012 [22], and 0.92 is used in the model by Autti-Roma et al 2005 [56] conducted in California and Texas in the US and Finland, respectively. It is important to note that those data were obtained from expert opinion [22, 56] or even research assumption [16] without reporting or mentioning the method of eliciting the utility weight of the patients. In our study, a more systematic approach was used for an analysis even though we had a small number of patients and most of them had mental retardation which resulted in difficulties in trying to extract utility weight data. As suggested by the Thai guidelines for conduction economic evaluations [59], the utility data was elicited by a proxy which is the group of people with knowledge of the diseases through the application of Indirectly measured utility methods (EQ-5D). This systematic tool for collecting the data was unique in that it can reduce the bias of the value of quality of life used [60, 61]. From the expert panel, we found that the utility of asymptomatic patients ranged from 0.49–0.84 for the six selected diseases (mostly under 0.71, only MCD was higher at 0.84). Obviously, the health utility weight applied for our analysis is lower than those of other studies which might plausibly result in the unfavourable outcome of the new intervention.

To argue about whether or not the number of diseases added into the analysis affected the results of study, we primarily believe that due to the variation of diseases, particularly in the incidence, level of severity, effective treatment, and costs of treatment, an individual assessment of the diseases is needed. The theory that including more diseases into the analysis would lead to favourable results really depends on whether the incremental benefit of the added diseases is above its incremental cost. If not, the added diseases can create a burden of costs for the whole

screening programme. Thus, it can be concluded that it is not necessary to include all of the diseases into the model but instead give priority to evidence-based prioritised diseases and more attention to the details of each individual disease such as the effectiveness of treatment and relevant costs. The studies in Wisconsin [17] and the UK [19] proved that even screening for one or two diseases instead of a combination of 30 diseases may provide for a cost-effective intervention. In the same way, it does not mean that if the analysis indicates one or more of the diseases are economical for screening, another can be added to the programme and still be justified as cost-effective for the reason that there is no additional cost for screening. This is because the variable costs that come attached to expensive treatments can distort the results of study. By holding an expert panel, we believe that we have included the most significant diseases into the analysis, and that adding more diseases will not result in a more economical result unless there is new evidence such as high incidence of the diseases and effectiveness of treatment.

This study showed a zero utility weight (the equivalent of death) in three groups of patients including IVA, MSUD with neurological complications, PA with neurological and cardiomyopathy complications. This result is in line with a previous study which showed that Thai patients with a mental retardation combined with a complication, have a very low health utility that is close to zero [62]. For the three groups of patients, the zero utility can occur because the diseases are extremely severe. It is also important to address that apart from the main complications used as health states in the model, patients can also have other complications. In addition, combining these factors with the algorithm of the Thai EQ-5D could also explain the low score of patients. The observational study estimated a tariff-a coefficient that was used to subtract full health utility weight (1.00). It was found that in Thailand the tariff is high compared to other countries (i.e. UK and Japan) [63, 64]. For example, a tariff of constant term is valued -0.202 in Thailand and -0.081 in the UK. As for the utility score for state 33222, the calculated utility weight is -0.039 in Thailand compared with 0.161 in the UK.

The budget impact analysis points out that if the screening programme is implemented, the national healthcare payer must prepare a budget of at least 200 million THB each year. That amount can be considered substantial because it is comparable to almost one-tenth of the total healthcare budget allocated to all current screening activities financed by public sources in Thailand [65]. Therefore, implementing this screening seems to be very challenging under the rationale of affordability, a core concept of budget impact analysis. Another important point is that while the annual expenses of screening does not change much each year—thereby reflecting the relatively stable trend of population growth in Thailand—the treatment expenses is expected to rise sharply and will comprise a significant part of the entire budget in the future. This reveals that there are higher numbers of cumulative patients each year, each of which require lifelong treatment. This can be a crucial message delivered to policy makers when considering all aspects of providing the programme.

There are some limitations regarding the availability of data used in the model. Firstly, most of the incidences adopted in the analysis were foreign data of Asian countries. Nevertheless, the studies [6–8] indicated a similarity between uncommon IEM in Asia. So based on our current knowledge, the incidence should not be much different as Thailand is comparable with those countries in terms of ethnicity.

Secondly, although this study had advantages in using actual patient data to estimate the baseline clinical data, the information on the health outcomes of early-diagnosed patients still rely on unsubstantial evidence. Without existing well-established studies to observe the potential benefits of MS/MS screening for IEM, this study had to use information from observational studies that consisted of a small number of cases as well as expert opinion. However, we believe

that we performed an extensive search in order to seek for the most credible evidence and used very conservative assumptions where information was limited.

Thirdly, the estimated cost of the screening programme did not include the cost of setting up a new screening unit to perform IEM screening and confirmation, transportation, and other logistics costs. Other potential expenses were also not included, example, human resources training such as the training of IEM specialists and related paramedics/metabolic dieticians/ metabolic nurses. Nevertheless, we believe that if a new screening programme was provided, it is likely to be a part of the existing newborn screening institute in Thailand. Thus, it might not require lots of resource to set up a new centre for the screening programme.

Fourthly, the health utility weight was elicited from expert opinion. There were also many challenging issues about using QALY measurements in infants and children [66–68]. Nevertheless, given the lack of incidence and extreme difficulties of eliciting health from babies or patients with mental retardation, we believe that using an expert panel is a viable substitution.

Lastly, while there are several methods to measure health-related quality of life, based on the pros and cons of each method, the EQ-5D was selected as the most appropriate method for eliciting quality of life for economic evaluation by the Thai guidelines and this lead to the establishment of the national EQ-5D tariffs [69]. However, there are issues that needs to be addressed when using the EQ-5D, especially when it is used to estimate the utility of IEM patients. There are concerns for the generic health utility measures, for instance, the EQ-5D may not be sufficiently sensitive for people with mental health problems [70]. It is also possible that the EQ-5D does not assess some key health-related quality of life domains such as peer relations or family functioning [60]. In addition, as specific health problems of a certain disease may not be captured, it is possible to overestimate the utility weight which can potentially hamper the estimation of the incremental QALYs especially if the differences in effectiveness between comparators are marginal [70].

Conclusions

In conclusion, the results of the study indicate that screening for inborn errors of metabolism in Thailand using MS/MS is economically unattractive given the threshold of cost-effectiveness in Thailand. Continuing the current screening programme as well as prioritising treatment for MCD, PKU, MSUD, and IVA patients diagnosed early is the appropriate action to take in order to deal with IEM. The budget impact analysis suggests that implementing the screening programme will incur considerable expenses. In addition, a nation-wide epidemiological study on the incidence of IEM in Thailand was strongly recommended to understand more about the magnitude of the diseases. Thus, we recommend that Thailand should perform a large-scale pilot study for an IEM screening programme as a further study.

Supporting Information

S1 Table. Yearly probability of death from other causes.
(DOCX)

S2 Table. Probability of admission as inpatient and average number of visit of outpatient per year.
(DOCX)

S3 Table. Difference of lifetime health outcomes and costs per-patient after early detection or late detection (without discounting).
(DOCX)

S1 Search Strategy. Search strategy.
(DOCX)

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Author Contributions

Conceived and designed the experiments: KT PL YT SP DW NV PW VS CK SC. Performed the experiments: KT PL DW NV VS CK PW SP YT. Analyzed the data: KT PL YT. Contributed reagents/materials/analysis tools: DW NV VS CK PW SP. Wrote the paper: KT PL YT DW NV PW VS SP CK SC.

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EFFECTIVENESS OF DIAPERS AMONG PEOPLE WITH CHRONIC INCONTINENCE IN THAILAND

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Objectives: The aim of this study was to assess effect of adult diapers on health-related quality of life (HRQOL) and the independent level of performing activities of daily living (ADLs) in people with urinary or fecal incontinence. Psychological consequences of patients' caregivers were also measured.
Methods: This quasi-experimental study was conducted at two rehabilitation centers in Thailand. People aged 15 years or greater with chronic urinary or fecal incontinence were eligible. Study participants received adult diapers for 10 weeks after recruitment. Thai EuroQol Five Dimensions (EQ-5D) and the Barthel Index were measured at baseline and weeks 2, 6, and 10 to evaluate HRQOL and the independent level of performing ADLs, respectively. The Braden Scale was used to assess the risk of having pressure ulcers. Mean differences in the Thai EQ-5D, the Barthel Index, and the Braden Scale, before and after receiving adult diapers, were estimated using a multilevel linear regression model.
Results: There were ninety patients and forty-eight caregivers who took part in this study. HRQOL and independent level of performing ADLs had improved significantly by week 10 after receiving adult diapers with mean differences of 0.102 (95% confidence interval [CI], 0.046–0.158) and 4.40 (95% CI, 1.74–7.07), respectively. The risk of having pressure ulcers had significantly decreased by 67 percent (95% CI, 16 percent–78 percent) by week 10 after receiving adult diapers.
Conclusions: The results indicate a significant improvement of HRQOL and the independent level of performing ADLs among incontinent patients after receiving adult diapers. These results were used to inform the development of the health benefits package under the Universal Health Coverage Scheme in Thailand.

Keywords: Urinary incontinence, Fecal incontinence, Diaper, Quality of life

Urinary and fecal incontinence are defined as the involuntary loss of urine or feces due to uncontrolled bladder or bowel functions, respectively. Both urinary and fecal incontinence are major causes of poor health-related quality of life (HRQOL) among men and women worldwide (1). Incontinence affects not only biological health but also social and psychological well-being. Compared with the normal population, persons with urinary incontinence have higher levels of depression and anxiety, feel more stigmatized, and have poorer life satisfaction (1;2).

It is estimated that the prevalence of urinary incontinence is as high as 30 percent, 36 percent, and 15 percent in European, U.S., and Asian populations, respectively (3). The prevalence of fecal incontinence in the United States and Australia were found to be 8 percent (4) and 6 percent (5), respectively. Although there has been progress in the treatment of urinary and fecal incontinence, none of these anti-incontinence solutions have been proven to help people to fully control their bowel or bladder functions (6). Therefore, most patients require support from products that can contain urine and fecal leakages, enabling them to maintain their lives confidently (6).

Absorbent products are pads or garments that absorb urine and stool fluid and are used to keep skin and clothing dry. Because they reduce wetness and odor from incontinence, using these items can help patients continue with their social activities and daily lives while avoiding the stigmatizing consequences of incontinence. Therefore, these products are used together with anti-incontinence therapy and play an important role in the care of incontinence, especially for people with chronic and untreatable incontinence.

However, there are many disadvantages of using absorbent products. The long-term use of absorbent products may introduce urinary tract infection (UTI) or dermatitis due to skin

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contact with stool and urine (6). Moreover, some people—especially men—are reluctant to use these products as they have connotations with babies or female sanitary ware (7). Most surprisingly, although absorbent products have been widely available and used in both resource-rich and resource-poor settings, their effectiveness in terms of improving quality of life and increasing independence level of activities daily living (ADLs) has not been studied.

Given that many of the causes of urinary and/or fecal incontinences are incurable, people require long-term—if not lifetime—use of absorbent products, thereby making the cost of using them very high compared to standard living expenses. It is estimated that 9 percent of the annual costs of incontinence treatment in the United States comes from absorbent products; this accounts for US$1.75 billion (8;9). In several countries, including Thailand, the costs of absorbent products cannot be reimbursed from public programs. As such, these costs are not subsidized by any of the three health benefit schemes available in Thailand. The reason for withholding financial reimbursement may, in part, be due to the partially large budget requirement for absorbent products, although their benefit is still uncertain.

In a review of relevant literature, we identified no studies assessing the effectiveness (quality of life and adverse effects) of adult diapers in new users with untreatable urinary or fecal incontinence. In a recent Cochrane review (10), the performance and patient's acceptance between different types of absorbent product (i.e., insert pads, T-shaped diaper, pull-up diaper) were compared. Therefore, this quasi-experiment aims to assess the effectiveness of absorbent products in terms of improving the quality of life in people with untreatable urinary or fecal incontinence. The adverse effects of using these products (including pressure ulcers and dermatitis) and the effects of the products on symptoms of anxiety and depression of patients' caregivers were also approached. This study was requested by the subcommittee for the health benefits package and service delivery development of the National Health Security Office (NHSO). This is to consider whether adult diapers should be part of the health benefits package of the Universal Health Coverage in Thailand.

MATERIALS AND METHODS

Study Settings and Participants

The quasi-experiment was conducted from July to October 2010 at two health facilities that claim to be the national authorities for rehabilitation in Thailand—the Sirindhorn National Medical Rehabilitation Centre and the Department of Rehabilitation, Phramongkutklao Hospital. People with urinary or fecal incontinence were eligible for the study if they met the following criteria: age ≥ 15 years; untreatable incontinence for longer than 1 month or urine leakage despite using an indwelling catheter; no previous use of more than two adult diapers per week; able to communicate in Thai; and no cognitive impairment. Patients were excluded if they were severely ill or unwilling to participate in the study. All participants provided written informed consent and the study's protocol was reviewed and approved by both the Institute for Development of Human Research Protection and the Institutional Review Board of each hospital.

Intervention

There are several varieties of absorbent products currently on the market, with differences in the types of materials used (i.e., disposable or washable) and form (e.g., inserts, diapers, T-shaped diapers and pull-ups). In this study, disposable diapers were selected as an intervention of interest because they can be used for all disabled patients (i.e., those who are bedridden and those in wheelchairs) and for both males and females. Seven brands of disposable diapers sold in Thailand were evaluated for their ability to contain urine and fluid leakage, by applying the Rothwell method (11). Only the disposable diapers that had the highest water absorption capacity, measured as the weight of water absorbed (in grams) per cost of diaper, were used in this study. Depending on the health condition of the participants, as assessed by physical therapists, each participant received three to six diapers per day for 10 weeks after recruitment.

Outcome Measurement

The primary outcome of interest was HRQOL in people with urinary and/or fecal incontinence before and after receiving adult diapers. HRQOL was measured by means of a standardized quality measure—the Thai EuroQol five dimensions (EQ-5D) questionnaire. The Thai EQ-5D consists of five domains (i.e., mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), with each domain containing three response levels (i.e., no, some, and severe problems), and a visual analogue scale (VAS). This tool is recommended by the national Health Technology Assessment (HTA) guidelines to be used across HTA studies to ensure consistency of results (12). After completing the questionnaires, the total scores from the five domains were converted into a single EQ-5D index score using the Thai population-specific preference weights (13). The EQ-5D index score ranges from -0.452 to 1, in which -0.452 indicates the poorest health state worse than death and 1 indicates perfect health state.

The respondents' level of independence in ADLs was also measured using the Barthel Index (14), which contains 10 activities (i.e., bowel control, bladder control, personal hygiene, toilet transfer, bathtub transfer, feeding, dressing, wheelchair transfer to and from the bed, walking, and descending and ascending the stairs). The total score can range from 0 (unable to perform task) to 100 (fully independent). In addition, the potential adverse effects of using diapers on skin was measured by applying the Braden Scale for Predicting Pressure Sore Risk (15). This tool can be used to assess the risk of developing pressure ulcers and

comprises of six subscales (i.e., sensory perception, moisture, activity, mobility, friction and shear). Each subscale is scored from 1 to 4 and the total score ranges from 6 to 23, with a lower score indicating higher risk. The number and severity of pressure ulcers after using diapers were also determined.

As mentioned earlier, urinary and fecal incontinence impact not only on the physical and mental health of affected individuals but also on the quality of life of their caregivers. The emotional and psychological disturbances of the caregivers must therefore also be taken into account (16;17). Thus, we measured the symptoms of anxiety and depression of the participants' caregivers by using the Hospital Anxiety and Depression Scale (HADS) (18). The HADS is divided into Anxiety and Depression subscales and the final score of each subscale ranges from 0 to 21, with a higher score indicating more distress.

Data Collection

The demographics of the studied participants and their caregivers, that is, age, sex, marital status, educational level, occupation, income, place of living, and underlying diseases, which caused incontinence, were gathered during recruitment. All the outcomes of interest—that is, the Thai EQ-5D, the Barthel Index, the Braden Scale, the number and severity of pressure ulcers for study participants and the HADS for caregivers—were collected at baseline and weeks 2, 6, 10 after receiving the diapers. All information was collected by well-trained interviewers using structural data record forms at the two health facilities where participants attended study appointments and received additional diapers. The traveling costs of each individual were subsidized during the study period.

Sample Size Estimation

Because the primary objective of the study was to compare the Thai EQ-5D before and after diapers use in the same participants, the sample size was estimated based on the two dependent means method.

From the pilot study, the standard deviation (SD) of the Thai EQ-5D in incontinence patients before using diapers was 0.181, with a type I error set at 0.05 and power, to detect the difference, was set at 80 percent. Therefore, 73 patients were required to detect a 0.06 difference in Thai EQ-5D before and after diaper use. There was an expected drop-out rate of 20 percent. Therefore, 90 patients were enrolled in this study.

Statistical Analysis

The demographics of the studied participants and caregivers were presented in terms of frequencies and percentages for categorical variables and means with SDs for continuous variables. Differences in the mean Thai EQ-5D, Barthel Index, Braden Score, and HADS between each visit, before and after receiving diapers, were compared using a multilevel linear mixed-regression model. The time variable was treated with a fixed effect model, whereas the subject variable was treated with a random effect model. The probability of reporting severe problems between visits for each domain of the Thai EQ5D was compared by applying a multi-level logistic regression model. The odd ratios (OR) along with their 95 percent confidence intervals (CIs) between the 2^{nd}, 3^{rd}, and 4^{th} visits were estimated by the exponential coefficients. The number of pressure ulcers on each visit were compared by applying a mixed-effect hierarchical model with a log-link function using the "xtpoisson" command. The relative risks (RRs) of having pressure sores between visits with 95 percent CIs were calculated by the exponential coefficients. Version 12 of the STATA software program was used for analyzing the data. A two-sided test with a p-value < 0.5 was considered statistically significant.

RESULTS

Among the ninety eligible subjects, seventy-one participants completed the study and were assessed for the outcomes at week 10, while seventeen patients were lost to follow-up and two patients died during the study period. A flow chart of the participant recruitment is presented in Supplementary Figure 1. Forty-eight caregivers agreed to participate in the study but only thirty-five of them completed the assessment.

Demographics and Baseline Data

The demographics of the study participants are described in Table 1. More than half of the patients (60 percent) were affected by both urinary and fecal incontinence, whereas 38 percent and 2 percent suffered from urinary and fecal incontinence, respectively. The major cause of incontinence was spinal cord injury (46 percent) and approximately half of the participants had suffered from incontinence for longer than 5 years.

The mean age of the caregivers was 47.02 (SD = 14.16) years. The majority of caregivers were female (73 percent). Almost half of the caregivers (46 percent) had only graduated from primary school, while 29 percent and 23 percent had graduated from secondary school and higher than secondary school, respectively; only 2 percent of the caregivers were not educated.

At the baseline, the mean Thai EQ-5D, VAS, and Barthel Index of patients were 0.18 (SD = 0.35), 66.19 (SD = 23.47), and 47.15 (SD = 25.13), respectively. Approximately 70 percent of the patients had no pressure ulcers and the mean Braden Scale was 15.15 (SD = 2.95). The mean anxiety and depression subscales of the caregivers were 7.30 (SD = 3.86) and 5.47 (SD = 3.68), respectively.

Effects of universal access to diapers on health utility

EQ-5D. The mean difference of the Thai EQ-5D between baseline and weeks 2, 6, and 10 were 0.060 (95% CI, 0.007–0.114), 0.057 (95% CI, 0.002–0.112) and 0.102 (95% CI, 0.046–0.158), respectively, see Figure 1 and Supplementary Table 1. In addition, the VAS also increased significantly after the participants

Table 1. Demographic Data of Study's Participants

Characteristic	Incontinence patients ($N = 90$)
Male (%)	40 (44)
Age, years, mean (SD)	49.13 (21.19)
Marital status (%)	
- Single	45 (50)
- Married	21 (23)
- Divorced	21 (23)
- Separated	3 (3)
Education level (%)	
- None	8 (9)
- Primary school	31 (35)
- Secondary school	29 (33)
- Higher than secondary school	21 (24)
Income (%)	
- No income	55 (61)
- 500–5,000 Bath	16 (18)
- 5,100–10,000 Bath	14 (16)
- 10,100–30,000 Bath	5 (6)
Health benefit schemes (%)	
- Universal health coverage	66 (73)
- Social security	6 (7)
- Civil servant	16 (18)
- Self-payment	2 (2)
Type of incontinence (%)	
- Urinary incontinence	34 (38)
- Fecal incontinence	2 (2)
- Both urinary and fecal incontinence	54 (60)
Cause of incontinence (%)	
- Spinal cord injury	38 (46)
- Cerebrovascular accident	17 (20)
- Others	28 (34)
Duration of incontinence (%)	
- ≤1 year	7 (8)
- 1–2 years	13 (15)
- 2–5 years	22 (26)
- >5 years	43 (51)
Barthel Index, mean (SD)	47.15 (25.13)
EQ-5D, mean (SD)	0.18 (0.35)
VAS, mean (SD)	66.19 (23.47)
History of having pressure ulcer (%)	
- Yes	25 (30)
- No	59 (70)
Braden Scale, mean (SD)	15.15 (2.95)

received the diapers, with mean differences of 8.00 (95% CI, 4.04–11.94), 7.34 (95% CI–3.30, 11.43), and 9.65 (95% CI–5.51, 13.78) when comparing the baseline VAS to weeks 2, 6, and 10, respectively.

The percentages of patients reporting severe problems in each domain of the EQ-5D during each visit are presented in Supplementary Figure 2 and Supplementary Table 2. There were only significant decreases in the "self-care" and "usual activities" domains after receiving the diapers during the 10th week with ORs of 0.15 (95% CI, 0.04–0.57) and 0.23 (95% CI, 0.07–0.78), respectively.

In the subgroup analysis, providing adult diapers for those with a Barthel Index score in the range of 25–49 significantly changed the EQ5D score compared to other groups (with Barthel Indexes in ranges lower or higher than 25–49). An uncertainty analysis was performed as there were some missing EQ-5D values, due to patient loss to follow-up. A worst case scenario analysis was performed by assuming that patients without follow-up data had no change from the initial EQ-5D values. The results show similar findings with the complete case analysis. In the worst case scenario analysis, the mean difference of EQ-5D between baseline and weeks 2, 6, and 10 were 0.052 (95% CI, 0.004–0.100), 0.049 (95% CI, 0.001–0.097), and 0.080 (95% CI, 0.032–0.128), respectively.

Barthel Index

Using the Barthel Index to measure the ability to perform ADLs, incontinent patients showed a significant improvement after receiving the diapers. The mean differences when comparing the baseline scenario with the 2nd, 6th, and 10th weeks were 2.92 (95% CI, 0.38–5.47), 2.56 (95% CI, -0.06–5.18), and 4.40 (95% CI, 1.74–7.07), respectively (see Supplementary Table 1 and Figure 1). This suggests that using diapers can significantly improve an incontinent patient's ability to perform ADLs independently.

Risk of having pressure sores and other adverse effects on the skin. The number of pressure ulcers in incontinent patients dropped significantly during the 6th week and 10th week (see Supplementary Figure 3). When compared with the baseline, the risk of having pressure ulcers during the 6th week and 10th week significantly decreased around 58 percent (95% CI, 8 percent–75 percent) and 67 percent (95% CI: 16 percent–78 percent), respectively. While the risk of having pressure sores decreased during the 2nd week as well (relative risk reduction = 30 percent (95% CI, -22 percent–60 percent)), it was not statistically significant when compared with baseline.

Using the Braden Scale, to assess skin health and the potential adverse effects of using diapers, the results did not differ significantly from baseline and also slightly increased during the 2nd and 10th weeks with respective mean differences of 0.27 (95% CI, -0.31–0.85) and 0.19 (95% CI, -0.42–0.79), see Supplementary Table 1 and Figure 1. This suggests that using diapers does not increase the risk of developing pressure ulcers in incontinent patients.

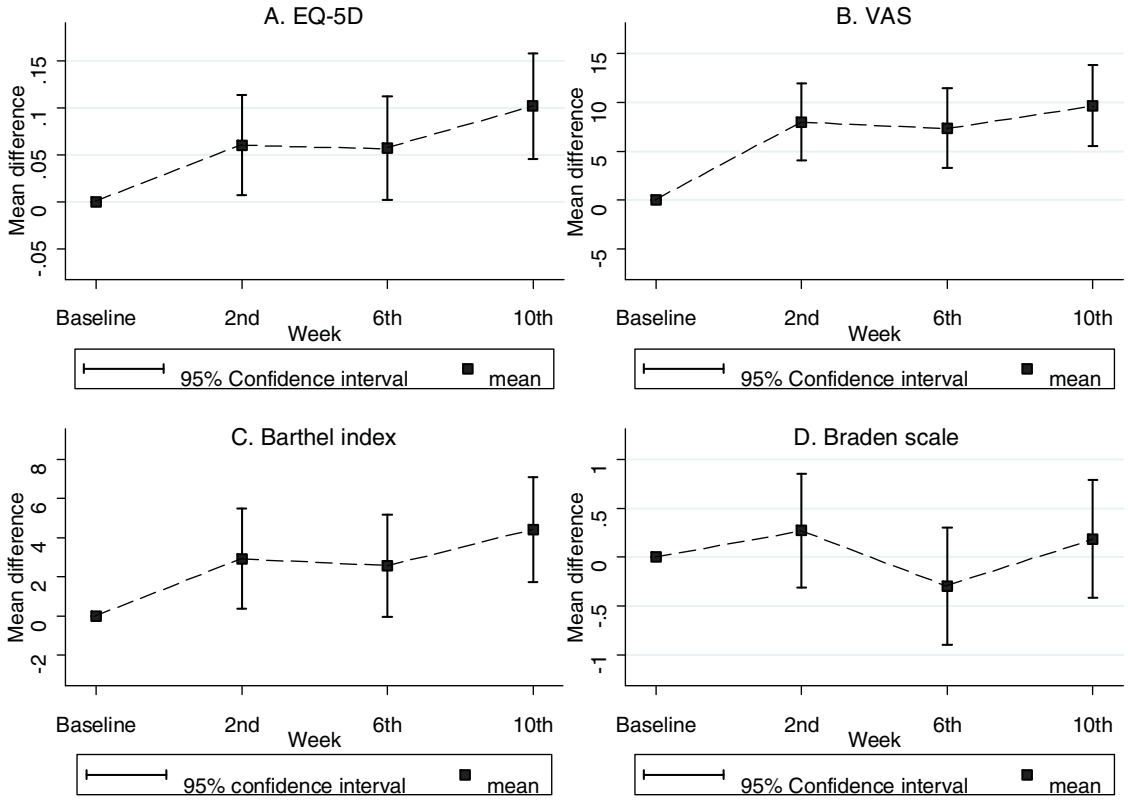

Figure 1. Mean difference of outcomes of interest between baseline and 2nd, 6th, and 10th weeks.

Hospital Anxiety and Depression Scale. The mean differences of the caregivers' anxiety and depression subscales between baseline and weeks 2, 6, and 10 are presented in Supplementary Table 3 and Figure 2. Overall, the anxiety and depression subscales decreased after the participants received diapers. These results, however, were not statistically significant. Only the mean difference of the anxiety subscale during the 2nd week was significantly improve from baseline with a mean difference of -1.053 (95% CI, -1.826—0.281). This means that the anxiety subscale of the caregiver significantly decreased by -1.053 after the patients had received diapers for 2 weeks.

DISCUSSION

To the best of our knowledge, this is the first study that evaluates HRQOL and adverse events of providing adult diapers for patients with permanent urinary and fecal incontinence. This study does not only focus on the outcomes for patients, but also takes into account caregivers' psychological consequences. The quasi-experiment indicates that, compared to the preintervention period, in which the patients had limited or no access to adult diapers, HRQOL improves significantly from the first 2 weeks after access to adult diapers. Although there was no study determining a minimal clinically important difference in EQ-5D among Thais, the change of 0.06 can be seen as clinically significant, based on international literature (19–21). The subgroup analysis also shows that those with Barthel Index scores in the range of 25–49 have the most benefit from access to adult diapers, though this interpretation should be used with caution, due to results being based on a limited number of samples. In addition, HRQOL and the respondents' independence in performing ADLs increase over time, although no significant adverse effects were observed among respondents. The increase of HRQOL is mainly due to an improvement of self-care and usual activities, in which the latter had an earlier and higher impact. The study illustrates no significant effect, of providing adult diapers, on caregivers.

Considering each domain of the improved HRQOL, increased access to adult diapers significantly enhanced the self-care and usual activities domains only. These findings were confirmed by the significant change in the Barthel Index after receiving diapers. In our study, the Barthel Index in incontinent patients increased significantly after receiving diapers for all visits. From a psychological perspective, anxiety and depression symptoms did not change significantly in either patients or their caregivers. As most participants had suffered from incontinence for longer than 2 years, they may have already found ways to manage, control, and cope with the emotional and psychological difficulties associated with these symptoms (22–24). Therefore, ever at baseline, we found that both patients and caregivers reported low rates of anxiety, depression and psychological problems.

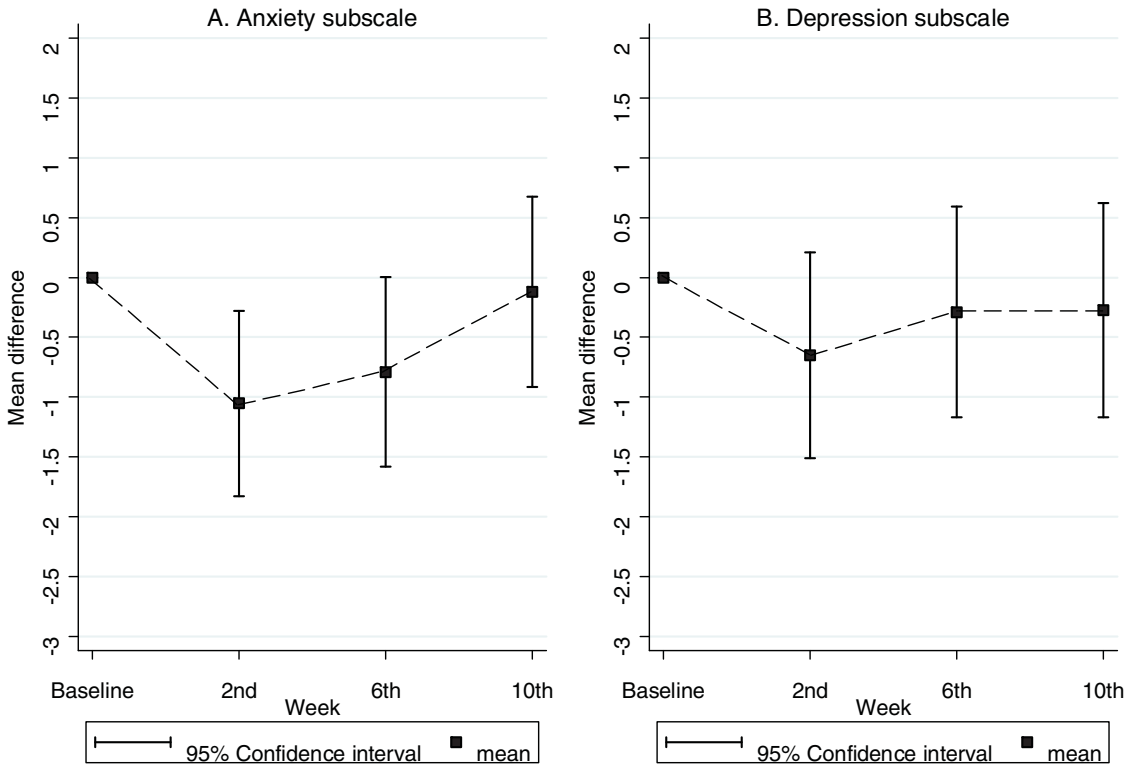

Figure 2. Mean difference of anxiety and depression subscales of caregivers between baseline and 2nd, 6th, and 10th weeks.

Although using diapers can help incontinent patients perform their daily activities, including self-care, wearing them increases the contact of skin, around the perianal and genital areas, with urine and feces. While this contamination results in a loss of skin integrity and increased skin pH, which causes susceptibility to a variety of biological, chemical and physical insults and can eventually leads to diaper dermatitis and ulcers, our study did not find this adverse effect. Moreover, the Braden Scale did not show any significant difference from baseline to post diaper access. In addition, the risk of having pressure ulcers decreased significantly after using diapers. Nevertheless, this adverse outcome was only measured at weeks 2, 6, and 10 of the study. Thus, the long term adverse effects of using diapers are still undetermined.

Our study has some notable strengths. First, the effectiveness of using diapers was measured in terms of both health and nonhealth aspects. Moreover, the data concerning the outcomes of interest were collected by well-trained interviewers and with the employment of standard tools with high validity and reliability. In addition, we collected data from 90 patients and 48 caregivers, which is considered to be a relatively large sample size, compared to other HRQOL studies.

However, our study also has some limitations. First, our study was not a randomized controlled trial, which is the best study design for evaluating the effectiveness of healthcare interventions. Other constraints of our intervention include the inability to blindly conduct the experiment with the patients. However, incontinence is an unresolvable problem after time passed. Therefore, performing this quasi-experimental study—which repeatedly measured the outcomes for several visits compared with the baseline—did not have much bias and was suitable for answering our research question. Because the aim of our study did not include the measurement of therapeutic effects of diapers, the majority of the participants included in our study had untreatable incontinence resulting from a physical disability, such as a cerebral vascular accident or a spinal cord injury. Accordingly, our results on HRQOL improvement for patients and caregivers are applicable to patients with permanent incontinence and may not be relevant to other temporary causes of incontinence. Also, these findings should be used with caution outside of the Thai setting, as socioeconomic and cultural differences may influence the study's conclusions. Lastly, our study measured the outcomes for 10 weeks after the patients had received the diapers, thus the benefits and adverse effects of diapers in long-term use are still inconclusive.

The results of this study have been presented to the subcommittee, who are now confident about significant benefits and minimum risks of providing adult diapers. Nevertheless, several discussions have arisen. As it is expected that 360 thousand Thai people are in need of adult diapers, which would cost US$650 million per year, the potential budget implication of providing adult diapers on a national scale is 13 percent of the total Universal Health Coverage Scheme budget (25). Although decision makers recognized that providing free-of-charge adult diapers can improve equity, addressing the unmet needs of the poor by improving accessibility to adult diapers, they also

considered the unsustainability of the program and decided not to include adult diapers in the health benefits package.

CONCLUSIONS

This study confirms the significant benefit of adult diapers in terms of increasing the HRQOL and the independent level of performing ADLs in people with untreatable incontinence. However, due to economic constrains, this intervention has not been adopted in the health benefit package of the Universal Health Coverage Scheme in Thailand.

SUPPLEMENTARY MATERIAL

Supplementary Figures 1–3
http://dx.doi.org/10.1017/S0266462315000343
Supplementary Tables 1–3
http://dx.doi.org/10.1017/S0266462315000343

CONFLICTS OF INTEREST

All authors have no conflict of interest to declare.

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Discussion

A learning experience from price negotiations for vaccines

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1. Context

Vaccines are regarded as one of the most successful health measures to date and there is no doubt that vaccination is ideal for health decision makers, health practitioners, and the public because it is a preventive measure that is in most cases – once provided – effective in the long-term. However, although there have been a number of newly developed vaccines available in the market over the past few decades, many of them have not been widely taken up, especially in low- and middle-income countries (LMICs), which comprise approximately 80% of the world population. Many scholars have found that the affordability of vaccination is among other important constraining factors, including a lack of local policy-relevant information for making decisions and political prioritization of vaccination or vaccine-preventable disease [1].

As a result, the GAVI Alliance was established to ensure equitable access to new and underused vaccines by negotiating for significantly lower prices compared to the market price. However, these negotiated prices are provided only to eligible GAVI countries. In addition, the UNICEF Supply Division introduced a vaccine procurement program to make some vaccines available for GAVI ineligible countries at a relatively low cost by tapping into economies of scale through a call for tender. However, some vaccines, such as PCV and rotavirus, are still unaffordable for some countries, which result in relatively low uptake through UNICEF. Similarly, the Pan American Health Organization's (PAHO) Revolving Fund negotiates vaccine prices for countries in Latin America [2]. While these initiatives are regarded as effective methods for price negotiation, limitations persist; for example, countries with different levels of economies, such as Haiti and Chile, pay the same vaccine costs under this regional price negotiation.

For countries that are unable to procure vaccines at affordable prices through the above mentioned mechanisms and instead anticipate price drops in vaccines over time, evidence indicates that price drops are usually less than expected [3]. This leads to unnecessary delays in vaccine adoption by countries. As a result, vaccine price negotiation is very important, although vaccine price negotiation principles and processes at the country level are either not practiced or well documented in literature. This paper aims to discuss the experiences of medicine price negotiations in Thailand with the aspiration of adapting these experiences to vaccine price negotiation.

2. The experience of medicine price negotiation in Thailand

The Thai government has systematically established price negotiation mechanisms for medicines, which is recognized as a successful example in an LMIC. The government can introduce previously unaffordable medicines into public programs from the process and make its universal healthcare coverage scheme sustainable. The success of this process can be attributed to three core principles:

1. Establishing reliable and manageable process and mechanism.

   Price negotiation is often seen by the public as a mysterious and endless process that industry uses to lobby decision makers to introduce new technologies. Therefore, it is important to make the price negotiation process trustworthy and manageable by being transparent about who is responsible for the negotiation, how to manage potential conflicts of interest, and what the timeline is for each step of the process. For example, the Thai government established the Working Group on Price Negotiation, comprising multiple stakeholders such as representatives from health insurance agencies, academics, and health professionals, under the national body responsible for designing the pharmaceutical reimbursement list in Thailand [4]. The working group members need to declare conflicts of interest and publicly document the process and information used.

   The working group begins the process of price negotiation once the national body has expressed interest in a particular medicine without yet committing to include the medicine in the reimbursement list. This makes price negotiation more meaningful and effective because industry is aware that the government has not yet decided on inclusion of the particular medicine. This is contrary to common practice in many countries, which conduct price negotiations after the decision has already

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Box 1: Experience of using evidence to lower the price of HPV vaccine in Thailand.

In 2007, when two companies were applying for Human papillomavirus vaccine (HPV) licensing in Thailand, the Thai government knew that the vaccine could have a potential role to reduce the high burden of cervical cancer. The Health Intervention and Technology Assessment Program (HITAP) was requested to conduct an economic evaluation and budget impact analysis in order to inform the government about the introduction of the vaccine as part of public health programs in Thailand. The findings were revealed in 2009, showing that at the price of US$450 per course (three doses), HPV does not represent good value for money for public investment. The report indicated that the price of the vaccine needed to be reduced by approximately 60% in order for the vaccine to become cost-effective at the threshold of 1 Gross Domestic Product/capita/Quality-adjusted Life Year gained [5]. The results were made publicly available and the government decided not to include the vaccine, rather emphasizing cervical cancer screening (a comparator to the vaccine in this study) as a preventive measure. The two companies examined the report and agreed with the findings. Three months later, the companies reduced the price of the vaccine as per the recommendation of the report [6]. Although the government still has not included the vaccine in the public program as of 2014 due to high budget implications, Thai households benefited from the significant price reduction in the private market, from US$450 to US$200 per course. This illustrates how evidence can persuade the private sector to reconsider price strategies of vaccines in a country.

been made to adopt a particular medicine, giving industry the advantage.

2. Making evidence-based price negotiation.

   Although many people recognize price negotiation as an art rather than a science, the Thai experience suggests that price negotiation can be more effective with evidence-based negotiations (see example in Box 1). The working group always requests for economic analyses from health technology assessment (HTA) agencies on value for money and potential budget impact of introducing new medicines in the reimbursement list. If the medicine does not represent good value for money, the working group will request for an assessment to be carried out on the price at which the medicine would become good value for money. Although in other countries the reference prices of medicines in similar classes or in other settings are often used, information on value for money and budget impact analyses that incorporate the costs and benefits of introducing new medicines in comparison to other alternatives as well as the size of the problem signify whether the medicine is necessary and affordable. Using this information ensures that the working group negotiates for medicines that are conclusively needed by the population.

3. Creating incentives for industry.

   While the above two principles may seem stringent, it is necessary to recognize the importance of industry's innovations and productions for health systems. Therefore, in negotiating prices it is critical to create incentives to lower prices as well as ensure the sustainability of industry. Thailand has created incentives by committing to procuring large amounts of products so that the company can still make profits from lower price margins and increased quantity of products sold. This issue has been taken very seriously by the Thai government in introducing and adopting a "one choice" policy for medicine negotiations, which means that the winner of the request for tender is entitled to providing medicines for all public health providers.

3. Conclusion and challenges

The three principles mentioned above are likely to be applicable for vaccine price negotiation, although it has some challenges. For example, the market for newly developed vaccines is more likely to be a monopoly or oligopoly compared to the medicines market due to the lack of alternatives. Another challenge is that there are fewer available vaccines compared to medicines, resulting in mechanisms that are put in place that are not used often; therefore, price negotiation for vaccines may need to be part of medicines price negotiation. The difficulty is that vaccines and medicines are different in many ways, including the need for special supply chain and logistics for vaccines that should be included as part of vaccine procurement. Similarly, price negotiation plays a role in vaccine procurement.

As long as affordability is a major factor in making vaccines available in public programs, vaccine price negotiation will become a more important and significant process. As such, it is important to make the price negotiation process more effective than it is currently. Thus, global organizations, both public and private, and academics should provide better support and conduct more research in order to increase scientific evidence as well as document the process for better implementation of vaccine price negotiation.

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Original Contribution

Mortality Attributable to Seasonal Influenza A and B Infections in Thailand, 2005–2009: A Longitudinal Study

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Influenza epidemiology differs substantially in tropical and temperate zones, but estimates of seasonal influenza mortality in developing countries in the tropics are lacking. We aimed to quantify mortality due to seasonal influenza in Thailand, a tropical middle-income country. Time series of polymerase chain reaction–confirmed influenza infections between 2005 and 2009 were constructed from a sentinel surveillance network. These were combined with influenza-like illness data to derive measures of influenza activity and relationships to mortality by using a Bayesian regression framework. We estimated 6.1 (95% credible interval: 0.5, 12.4) annual deaths per 100,000 population attributable to influenza A and B, predominantly in those aged ≥60 years, with the largest contribution from influenza A(H1N1) in 3 out of 4 years. For A(H3N2), the relationship between influenza activity and mortality varied over time. Influenza was associated with increases in deaths classified as resulting from respiratory disease (posterior probability of positive association, 99.8%), cancer (98.6%), renal disease (98.0%), and liver disease (99.2%). No association with circulatory disease mortality was found. Seasonal influenza infections are associated with substantial mortality in Thailand, but evidence for the strong relationship between influenza activity and circulatory disease mortality reported in temperate countries is lacking.

Bayesian regression; burden; developing country; influenza; middle-income country; mortality; seasonal variation; tropics

Abbreviation: ICD-10, *International Classification of Diseases, Tenth Revision*.

The World Health Organization asserts that seasonal influenza results in 250,000–500,000 deaths annually in industrialized countries (1). Estimates are lacking from low- and middle-income countries but might differ substantially because of reduced health-care resources, differences in influenza transmission dynamics, poorer nutrition, differences in chronic illnesses, and lower levels of vaccine coverage against influenza and interacting pathogens, such as *Streptococcus pneumoniae* (2, 3). Differences in the pattern of person-to-person contacts that spread influenza may also lead to different patterns of epidemic spread that could potentially affect influenza-related mortality. Such differences in contact patterns may relate to the degree of urbanization and the demographic structure of the population. Finally, many developing countries are in tropical or subtropical zones, where influenza seasonality and strain diversity can differ substantially from those of temperate regions (3). Very little is currently known about mortality due to seasonal influenza in the tropics with the exception of one very highly developed and fully urbanized population, Singapore (4, 5).

Although routine influenza vaccination programs have previously been limited to higher-income settings, there is increasing interest in expanding such programs in developing countries. Estimating influenza-related mortality in such settings is essential for quantifying the likely impact of such vaccination programs (1). However, a major challenge in estimating seasonal influenza mortality is that symptoms are nonspecific, and few patients are tested for active influenza

infection. It is also evident that, for most deaths where influenza is likely to have played a causal role, no mention of influenza is given as the cause of death (2, 4–7).

To overcome these limitations, approaches have been developed to estimate influenza-related mortality by using routine surveillance data (2, 4–12). Most aim to separate mortality time series into a predictable component of temporal variation (annual periodicity and long-term trends) and, added to this, a variable component. Mortality associated with influenza is expected to be largely explained by the latter. A seminal approach, the Serfling model (9), used a sine wave to model the regular seasonal component of variation and a polynomial in time to account for long-term trends. Mortality exceeding this baseline model in "epidemic months" is termed "excess mortality." Much of this excess, it is argued, is caused by influenza.

Because of several limitations of this model (likely to be particularly severe in tropical and subtropical settings), recent work uses more flexible functional forms (splines) for modeling underlying seasonality and regression models to relate mortality to influenza activity (2, 4, 6, 12). We adopt a similar approach to estimate mortality due to seasonal influenza in Thailand, adjusting for nonlinear associations of mortality with meteorological data. We extend previous approaches by allowing for year-on-year variation in the relationship between subtype-specific influenza activity and mortality.

We use data collected prospectively by the national influenza surveillance system in Thailand. This combines epidemiologic and virological data and was set up by the Thai National Institute of Health at the Ministry of Public Health in 2004 in collaboration with the US Centers for Disease Control and Prevention (13).

METHODS

Data sources

Weekly deaths in Thailand for 2005–2009 were obtained from the Ministry of Public Health and included both all-cause mortality and mortality with codes from the *International Classification of Diseases, Tenth Revision* (ICD-10), for respiratory disease (J00–J99), circulatory disease (I00–I99), cancer (C00–C97), diabetes (E10–E14), renal disease (N00–N07, N17–N19, N25–N27), and liver disease (K70, K73, K74). These have previously been reported to be associated with influenza. We also included 2 control categories that have not been reported to be associated with influenza: septicemia (A40, A41) and unintentional injuries (V01–X59, Y85, Y86) (2).

Influenza data consisted of reports of weekly numbers of patients seeking medical attention with influenza-like illness throughout Thailand and weekly laboratory-confirmed influenza cases from April 2005 to March 2009. These dates were chosen because the influenza surveillance system was not fully operational until 2005 and, following March 2009, health care–seeking behavior for influenza-like illness changed in response to pandemic influenza (13). Visual inspection indicated anomalies in the data in weeks 52, 53, and 1 of each year, and these were excluded from the analysis. Laboratory confirmation data included the number of weekly tests from patients with influenza-like illness and the number positive for influenza A(H3N2), A(H1N1), and B (13). Three meteorological measurements were used: maximum temperature, relative humidity, and rainfall. These were averaged over daily readings from Bangkok obtained from the Thai Meteorological Department. Six out of over 3,000 observations were missing or represented coding errors and were replaced with the last observation carried forward.

Statistical analysis

We defined an influenza activity measure, $B_{j,t}$, as the product of the proportion of laboratory tests positive for influenza type j in week t and the number of patients with influenza-like illness in week t. This is similar to a previously described incidence proxy (2). The number of patients with influenza-like illness due to noninfluenza causes may vary over time, as may the probability that laboratory confirmation for influenza is sought in a patient with influenza-like illness. The activity measure, $B_{j,t}$, will not be affected by such variation and will be proportional to the number of true cases with influenza type j in week t, provided that the probability that a patient with an influenza type j infection seeks medical attention for influenza-like illness and test sensitivity do not vary with time (refer to the Web Appendix, available at http://aje.oxfordjournals.org/).

We estimated mortality due to influenza using regression models that expressed weekly deaths as the sum of a regular seasonal component of variation, a long-term trend, a contribution from each of the influenza types, a component related to meteorological conditions, and an error term. We used separate models for all-cause deaths, deaths in 3 different age groups (≤17, 18–59, ≥60 years), and deaths for specific groupings of ICD-10 codes. Seasonal variation was accounted for by using periodic penalized B-splines (P-splines) (14, 15).

Models considered were of the form

$$D_t = S_t + L_t + \sum\nolimits_{j=1,\ldots,3} \beta_j \times (f \times B_{j,t-1} + (1-f) \times B_{j,t-2}) + W_t + \varepsilon_t, \quad (1)$$

where D_t represents deaths in week t, S_t corresponds to the week t contribution from the periodic seasonal term, L_t corresponds to the week t contribution from the long-term trend term, the β_j terms estimate the contribution to mortality from the 3 influenza types, W_t corresponds to the week t adjustment for other covariates, and ε_t is the residual. We followed previous work in assuming that deaths caused by influenza will lag influenza cases by 1–2 weeks; the f term represents the proportional contribution to deaths of influenza cases 1 week previously (2).

Regression models were developed by using a 2-stage approach where we first performed an exploratory analysis to select the best models and then estimated mortality using the selected model. In an initial exploratory stage, we compared 12 different generalized additive models, accounting for seasonal variation using P-splines, comparing approaches using low-order polynomials and P-splines for modeling the long-term trends, and comparing Gaussian models with Poisson

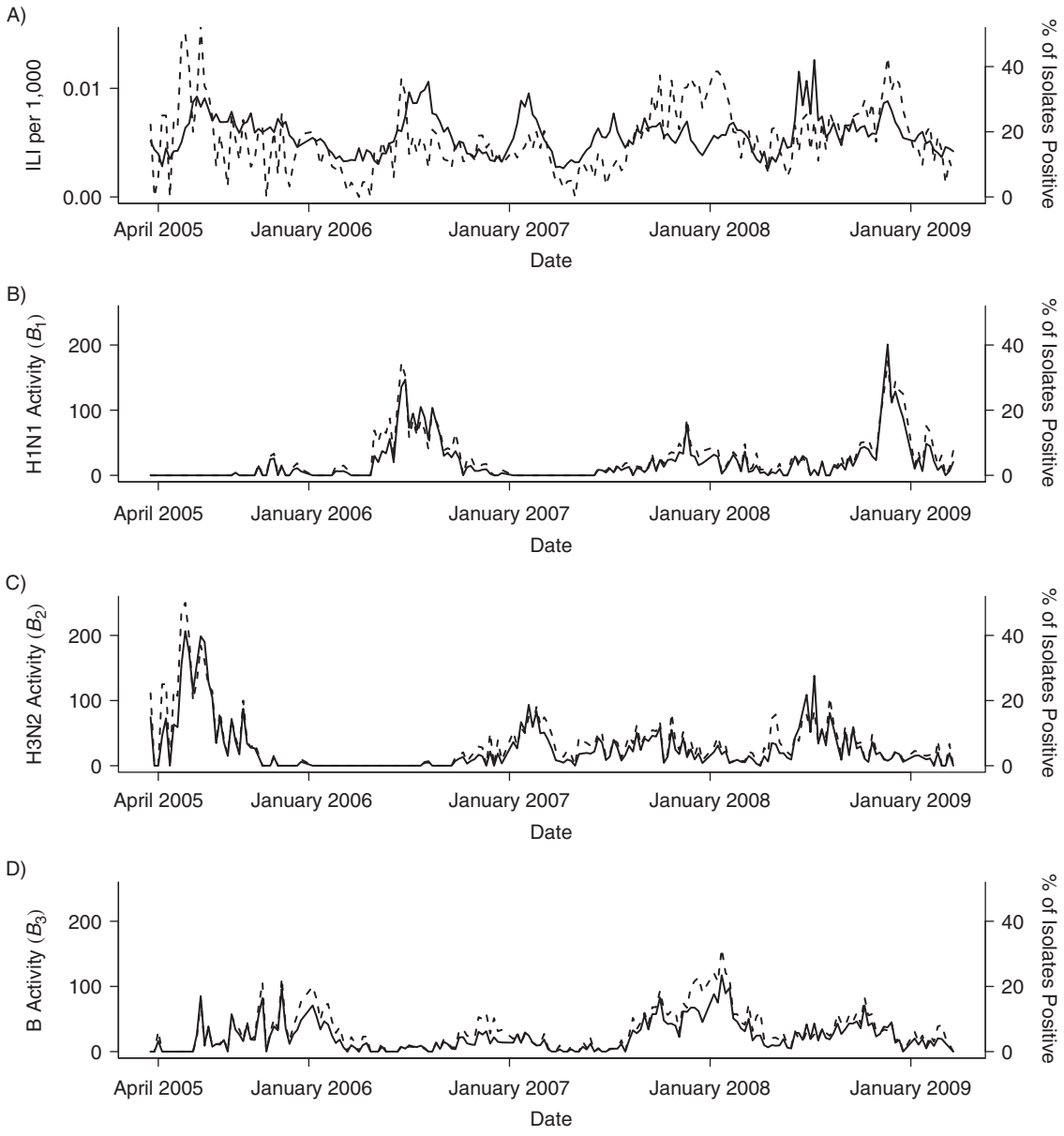

Figure 1. Time series of observed influenza-like illness (ILI) and influenza activity measures (B_1, B_2, B_3) in Thailand, 2005–2009. Influenza activity measures represent the product of influenza-like illness and the percentage of tested isolates positive for a given type in each week. Broken lines show the proportion of tested isolates positive for influenza (A) and positive for specific influenza types (B–D).

models (with an identity link function). We used the Akaike Information Criterion to assess model fit (16). This showed that Gaussian models where long-term trends were modeled by either a P-spline or a quadratic function of the week number gave similar fits (Web Table 1). We used the latter assumption in the second stage, in which we implemented models within a Bayesian framework and estimated parameters using a Markov chain Monte Carlo approach, because it gave greatly improved mixing of the Markov chain (Web Figure 1). This enabled us to estimate the type-specific delay, f, from reported influenza to death, account for temporal autocorrelation between observations by using a second-order random-walk prior, and consider 3 different assumptions about how the coefficients in the regression model relating influenza activity to mortality varied by year. For cause-specific mortality, we report the posterior probability of positive association with influenza (i.e., the posterior probability that influenza-associated mortality is greater than zero). We considered 3 different approaches to adjusting for meteorological variables (no adjustment; adjustment assuming linear relationships; and a semiparametric regression approach with P-splines to allow for nonlinear relationships between meteorological covariates and mortality). Finally, when we found evidence of heteroskedasticity, we extended the best-fitting model by

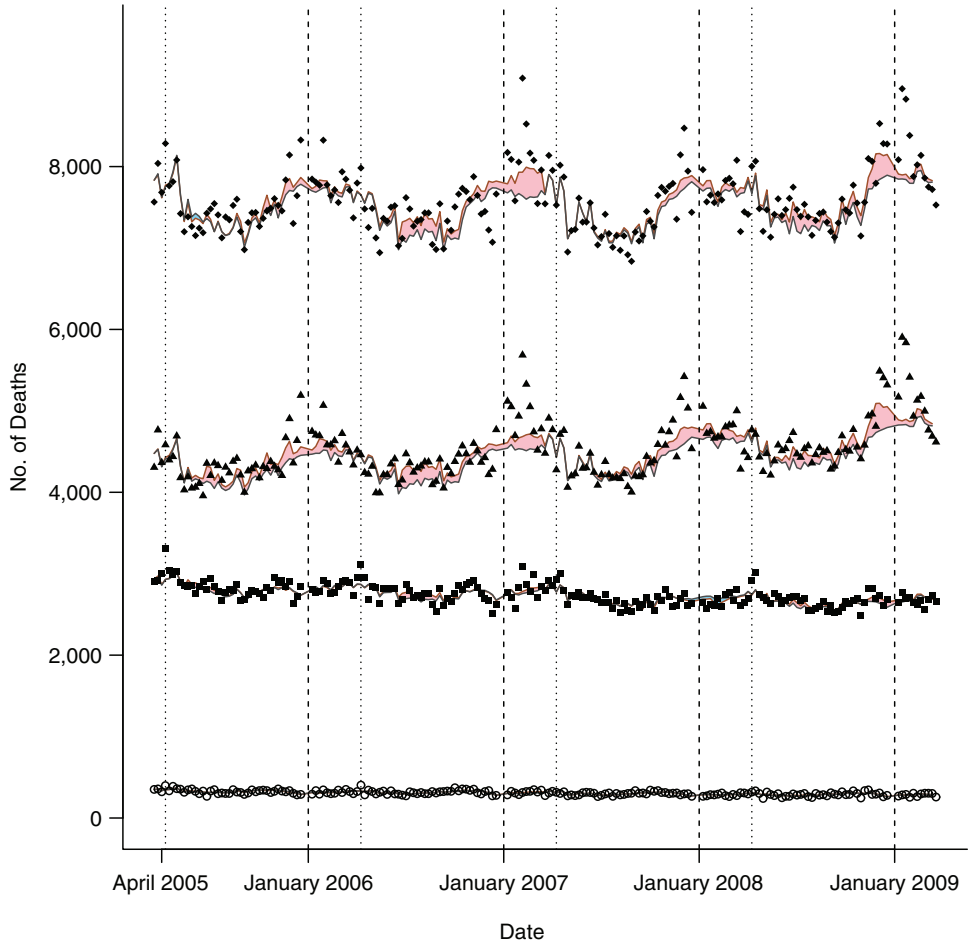

Figure 2. Observed and expected deaths by age group in Thailand, 2005–2009. The figure shows recorded weekly deaths in those aged ≤17 years (open circles), 18–59 years (squares), ≥60 years (triangles), all ages (diamonds), and the expected number of deaths predicted by the full model (red lines) and expected number of deaths excluding those due to influenza (black lines). Shaded areas indicate excess deaths attributed to influenza (pink if positive, blue if negative). Vertical dashed lines indicate the first week of the calendar year, and vertical dotted lines mark the Thai New Year (April 13–15).

allowing the variance to follow a first-order autoregressive conditional heteroskedastic process (17).

Mortality in weeks excluded from the model fitting was estimated by linear interpolation based on estimated mortality in weeks before and after excluded data. The assumed population size of each age group in each year was derived from census data (http://web.nso.go.th/en/census/poph/cen_poph.htm) and World Bank population estimates (http://databank.worldbank.org/). Full-model details are given in the Web Appendix.

Analysis was performed using R, version 2.13.0 (R Foundation for Statistical Computing, Vienna, Austria), with the package *mgcv* for initial model exploration and WinBUGS, version 1.4 (freeware), for the Bayesian analysis (18–20).

RESULTS

Although influenza B was endemic throughout the entire period, there were extended periods when 1 of the 2 influenza A subtypes was absent (Figure 1). No clear seasonal pattern was evident for any influenza type. All-cause mortality data, in contrast, showed a clear seasonal pattern, with peaks close to the end of each calendar year (Figure 2). This seasonal variation was not apparent in those aged <60 years. Combined mortality with classifications previously associated with influenza was elevated close to the end of each calendar year, reflecting annual peaks in mortality from circulatory and respiratory disease (Figure 3). There was also an increasing trend in mortality attributed to influenza-related causes, reflecting increasing mortality from cancer, diabetes, and renal disease. The 2 control causes of mortality also showed seasonal patterns: Septicemia deaths showed troughs close to the end of each calendar year but peaks shortly after the Thai New Year (April 13–15), and unintentional injury deaths showed large peaks during the Thai New Year.

In the models relating influenza activity to all-cause mortality, background seasonal mortality (not explained by influenza) peaked near the start of the calendar year and was at a

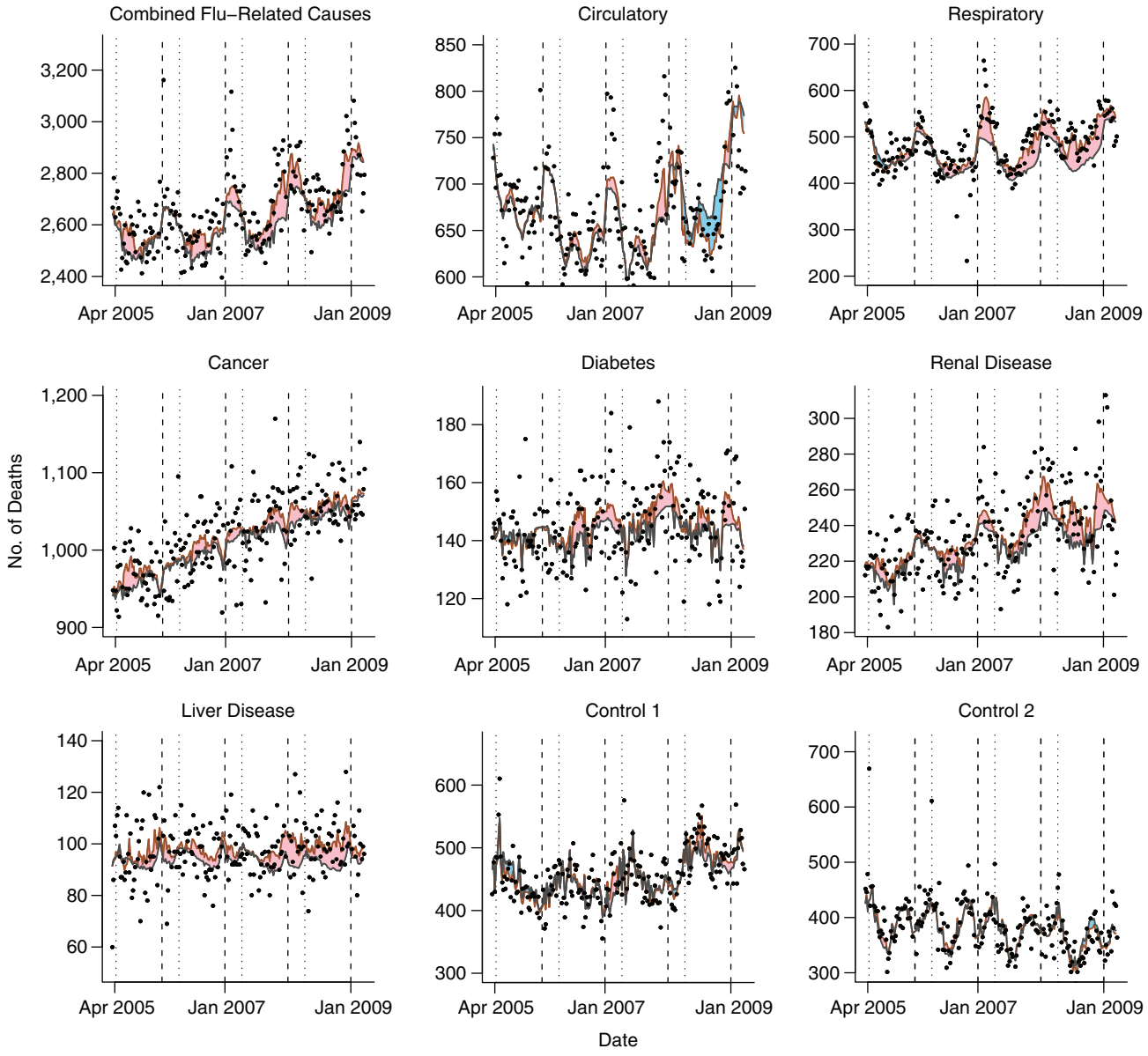

Figure 3. Observed and expected deaths attributed to causes commonly associated with influenza and 2 control causes in Thailand, 2005–2009. Shaded areas indicate excess deaths attributed to influenza (pink if positive, blue if negative). Vertical dashed lines indicate the first week of the calendar year, and vertical dotted lines mark the Thai New Year (April 13–15). Apr, April; Jan, January.

minimum at about week 30 (Web Figure 2). Adjustment for meteorological data substantially improved model fit (Web Table 2). This showed that, superimposed on the regular seasonal variation, all-cause mortality decreased at high levels of relative humidity and increased at high temperatures (Web Figure 3). There was no evidence of any association with rainfall. Allowing for year-to-year variation in the association between influenza activity and mortality also improved model fit. The best model overall accounted for both a nonlinear association between meteorological data and mortality and for year-to-year variation in the association between influenza activity and mortality. We report results for this model allowing for time-dependent variance below. Results obtained by using alternative models are shown in Web Tables 3–9.

The overall posterior mean of 6.1 deaths per 100,000 population per year corresponds to approximately 4,000 annual deaths due to influenza in Thailand (Table 1).

There was considerable variation between the 4 years in both total mortality due to influenza A and the relative importance of H1N1 and H3N2 (Table 2).

H1N1 was associated with only a small increase in mortality in 2005–2006 when H1N1 activity was low but with 2–4 deaths per 100,000 population over the next 3 years. Annual mortality

Table 1. Estimated Number of Influenza-Related Deaths per 100,000 Population, by Age Group, Thailand, 2005–2009[a]

Age Group, years	Influenza A(H1N1)		Influenza A(H3N2)		Influenza B		Total Influenza A		Total Influenza A and B	
	Mean	95% CrI	Mean	95% CrI	Mean	95% CrI	Mean	95% CrI	Mean	95% CrI
All ages	2.6	0.8, 5.1	1.6	−1.7, 5.4	1.9	−3.5, 6.9	4.2	−0.2, 9.2	6.1	0.5, 12.4
≤17	0.0	−0.8, 0.8	0.6	−0.4, 1.6	−0.4	−2.0, 1.3	0.6	−0.8, 2.1	0.1	−0.4, 0.6
18–59	1.4	0.3, 2.7	1.4	−0.4, 3.1	−1.7	−4.0, 0.6	3.0	0.5, 5.6	1.1	−1.7, 4.0
≥60	28.1	11.1, 45.9	13.0	−7.5, 34.5	26.9	−7.7, 62.2	41.0	13.7, 69.2	68.0	27.2, 108.1

Abbreviation: CrI, credible interval.

[a] Estimates were obtained by using the model adjusting for meteorological data and allowing for annual variation in the association between type-specific influenza activity measures and mortality using a random-effects model.

associated with H3N2 was even more variable: In 2005–2006, despite evidence of a large H3N2 epidemic, there was no association with increased mortality, while annual associated mortality subsequently ranged between 0 and 4 deaths per 100,000.

Alternative models gave broadly similar results, although constant-variance models consistently found no evidence that influenza B made any contribution to mortality (Web Tables 3–9). Models that accounted for annual variation in the association between influenza activity and mortality all estimated a larger number of deaths attributed to influenza A than models that did not. In all cases, adjusting for this annual variation led to improved model fit. There was evidence that the relationship between influenza activity and mortality varied over the 4 years for A(H3N2) but not for A(H1N1) (Web Figure 4). In particular, each unit of activity with A(H3N2) in 2006–2007 was associated with a far greater mortality risk than in the other 3 years (Web Table 10). There was no strong correlation between total annual deaths attributed to the 3 different influenza types and at most weak correlation between their year-specific regression coefficients (Web Figure 5).

Almost all influenza-related deaths were estimated to occur in those aged ≥60 years, with an estimated 68 influenza-related deaths annually per 100,000 people in this age group—about 2% of the age group's total mortality rate (Table 1). There was also evidence of an association between influenza A and increased mortality in those aged 18–59 years, with about 3 deaths per 100,000 population per year or 0.3% of the total mortality rate. In those aged <18 years, we estimated less than 1 death per 100,000 per year due to influenza, 0.1% of the total mortality rate. In these age group–specific analyses, influenza B was estimated to account for 40% of the influenza-related mortality in those ≥60 years. There was no evidence of mortality associated with influenza B in other age groups.

Analysis of cause-specific mortality found evidence that influenza was associated with deaths attributed to respiratory disease (probability of positive association, 99.8%, based on adjusted model), cancer (98.6%), diabetes (99.3%), renal disease (98.0%), and liver disease (99.2%). The highest mortality attributed to influenza (1.6 per 100,000 per year) was seen in respiratory disease deaths; about 4% of deaths in this category were attributed to influenza (Table 3). Again, these deaths were mostly in those aged ≥60 years, and in each year apart from 2005–2006, influenza A was estimated to play a dominant role (Table 4). For the 2 control causes of death, we found little evidence of any association with influenza (Table 3; Figure 3). Posterior probabilities for a positive association between influenza and excess mortality were 87.2% for control 1 and 56.5% for control 2 (all prior probabilities were 50%).

Despite the strong seasonal pattern seen in deaths attributed to circulatory causes (Figure 3), the model estimated that influenza made little or no contribution to mortality in this category (probability of positive association, 46.9%). Unplanned analysis of deaths attributed to ischemic heart disease and cerebrovascular disease (subgroups of circulatory disease) (Web Figure 6) showed a similar lack of association between influenza and mortality (Web Table 11). There was, however, some evidence that influenza A was associated with increased mortality for these categories, while influenza B offered protection, with the net influenza association close to zero.

Table 2. Estimated Number of Influenza-Related Deaths per 100,000 Population, by Year, Thailand, 2005–2009[a]

Year	Influenza A(H1N1)		Influenza A(H3N2)		Influenza B		Total Influenza A		Total Influenza A and B	
	Mean	95% CrI	Mean	95% CrI	Mean	95% CrI	Mean	95% CrI	Mean	95% CrI
2005–2006	0.4	−0.1, 0.9	−0.5	−6.1, 5.1	3.3	−2.1, 10.6	−0.1	−5.7, 5.6	3.1	−4.6, 11.9
2006–2007	4.1	0.9, 7.5	3.6	−0.9, 13.2	1.2	−2.9, 6.7	7.7	1.6, 17.8	9.0	2.2, 20.1
2007–2008	2.2	−0.2, 5.8	−0.4	−6.9, 5.6	1.5	−7.2, 8.6	1.8	−5.3, 8.7	3.2	−6.5, 12.3
2008–2009	4.1	0.7, 8.4	3.7	−1.6, 9.4	1.4	−9.0, 8.8	7.8	1.1, 15.5	9.2	−2.3, 19.3

Abbreviation: CrI, credible interval.

[a] Estimates were obtained by using the model adjusting for meteorological data and allowing for annual variation in the association between type-specific influenza activity measures and mortality using a random-effects model.

Table 3. Cause-Specific Mortality[a] Attributable to Influenza for Major ICD-10 Groupings, Thailand, 2005–2009[b]

Recorded Cause of Death	Mean Annual Mortality per 100,000 Population	Mortality per 100,000 Due to Influenza		Cause-Related Deaths Attributed to Influenza, %		f_A[c]		f_B[c]	
		Mean	95% CrI	Mean	95% CrI	Mean	95% CrI	Mean	95% CrI
Circulatory	51.5	0.0	−0.8, 0.8	−0.1	−1.6, 1.5	0.43	0.07, 0.85	0.51	0.16, 0.87
Respiratory	36.8	1.6	0.5, 2.5	4.1	1.4, 7.0	0.49	0.20, 0.80	0.34	0.01, 0.92
Cancer	77.7	0.8	0.0, 1.7	1.2	0.0, 2.2	0.54	0.04, 0.98	0.37	0.01, 0.93
Diabetes	11.0	0.4	0.1, 0.7	3.8	1.1, 6.6	0.44	0.03, 0.94	0.49	0.03, 0.96
Renal disease	17.6	0.4	0.0, 0.8	2.3	0.1, 4.5	0.51	0.05, 0.96	0.46	0.03, 0.96
Liver disease	7.4	0.3	0.1, 0.6	4.4	0.9, 7.7	0.51	0.03, 0.97	0.86	0.46, 1.00
Above causes combined	202.5	3.7	1.4, 6.0	1.8	0.7, 3.0	0.48	0.08, 0.89	0.48	0.02, 0.97
Control 1: septicemia	34.6	0.2	−0.4, 0.8	0.7	−1.2, 2.6	0.58	0.14, 0.96	0.48	0.03, 0.97
Control 2: unintentional injuries	29.3	0.0	−0.8, 0.8	0.2	−2.7, 3.0	0.58	0.06, 0.98	0.52	0.03, 0.97

Abbreviations: CrI, credible interval; ICD-10, *International Classification of Diseases, Tenth Revision*.

[a] "Mortality" was defined as number of deaths.

[b] Estimates were obtained by using the model adjusting for meteorological data and allowing for annual variation in the association between type-specific influenza activity measures and mortality using a random-effects model.

[c] Refer to equation 1.

DISCUSSION

On average, 6 people in every 100,000 were estimated to die each year in Thailand as a result of seasonal influenza, representing 4,000 deaths per year. There was no evidence of a net influenza contribution to circulatory disease deaths.

Strengths of our study include high-quality surveillance data, analytical methods that build on important recent

Table 4. Estimated Number of Influenza-Related Deaths Classified as Due to Respiratory Causes per 100,000 Population, by Year and Age Group, Thailand, 2005–2009[a]

Age Group and Year	Influenza A(H1N1)		Influenza A(H3N2)		Influenza B		Total Influenza A and B	
	Mean	95% CrI	Mean	95% CrI	Mean	95% CrI	Mean	95% CrI
Age ≥60 years								
All years	4.1	1.3, 7.0	5.7	2.4, 9.0	1.8	−2.2, 6.2	11.6	6.1, 17.0
2005–2006	0.2	−1.8, 1.6	−1.8	−6.6, 3.4	2.8	−2.2, 8.3	1.1	−5.5, 8.4
2006–2007	2.3	−1.9, 6.5	8.9	4.6, 13.4	0.1	−6.8, 3.8	11.3	3.8, 18.1
2007–2008	7.0	0.9, 15.4	5.7	−1.1, 12.9	1.6	−5.6, 8.4	14.3	5.8, 23.0
2008–2009	6.2	2.0, 10.0	9.5	3.6, 15.1	2.8	−3.1, 9.3	18.4	9.7, 27.0
Age 18–59 years								
All years	0.3	0.0, 0.6	0.2	−0.2, 0.6	0.2	−0.3, 0.6	0.6	0.0, 1.2
2005–2006	0.1	0.0, 0.3	−0.5	−1.1, 0.1	0.1	−0.6, 0.6	−0.4	−1.2, 0.4
2006–2007	0.2	−0.3, 0.6	0.3	0.0, 0.7	−0.1	−1.0, 0.3	0.4	−0.5, 1.2
2007–2008	0.4	−0.1, 1.1	0.3	−0.4, 1.1	0.3	−0.5, 1.0	1.0	0.1, 1.9
2008–2009	0.6	0.0, 1.3	0.6	0.0, 1.3	0.4	−0.3, 1.4	1.5	0.5, 2.6
Age ≤17 years								
All years	−0.1	−0.3, 0.2	−0.1	−0.4, 0.3	−0.2	−0.7, 0.2	−0.3	−0.9, 0.2
2005–2006	0.0	−0.1, 0.1	0.0	−0.5, 0.5	−0.5	−1.1, 0.0	−0.5	−1.2, 0.16
2006–2007	−0.2	−0.6, 0.2	0.0	−0.3, 0.2	−0.2	−0.8, 0.3	−0.4	−1.1, 0.3
2007–2008	0.0	−0.5, 0.4	−0.1	−0.7, 0.4	−0.7	−1.3, 0	−0.9	−1.6, −0.2
2008–2009	0.0	−0.4, 0.5	0.0	−0.5, 0.5	0.4	−0.5, 1.4	0.4	−0.5, 1.4

Abbreviation: CrI, credible interval.

[a] Estimates were obtained using the model adjusting for meteorological data allowing for annual variation in the association between type-specific influenza activity measures and mortality using a random-effects model.

methodological developments, and thorough sensitivity analyses (2, 12, 13). The credibility of our findings is strengthened by the lack of association between influenza and mortality in the 2 control groups. Although results were generally stable under different model assumptions, estimates of mortality associated with influenza B were close to zero in constant variance models. This might reflect difficulty in identifying contributions to mortality for a pathogen that circulates year round, as is the case for influenza B in Thailand (Figure 1).

Limitations include those of any observational study. Associations between influenza activity and mortality do not necessarily imply a simple chain of causation from infection to death. Additional limitations include the lack of spatial data and information on pathogens other than influenza. Also, because of changes in health care–seeking behavior for influenza-like illness following the 2009 pandemic, it was not possible to estimate mortality associated with the pandemic using the same approach. Accounting for these factors represents an important area for future research. In particular, it will be instructive to see if latitudinal variations in influenza-associated mortality reported elsewhere are also evident in Thailand (21).

Thailand is a developing middle-income tropical country with a predominantly rural population and a nominal per capita gross domestic product close to the world median (22, 23). There is no routine vaccination against *S. pneumoniae* and, in 2008, influenza vaccine sales amounted to only 1.6 per 100 people (24). No national estimates of total mortality caused by seasonal influenza A and B infections are available from any other developing country in the tropics. Our findings may therefore provide an important basis for generalization about the probable burden of seasonal influenza mortality outside high-income countries. Generalizations should, however, be made with caution. In South Africa (which has subtropical and temperate climate zones), influenza has been estimated via a Serfling-type model to cause 340 annual deaths per 100,000 population in those aged over 65 years, 5 times the corresponding rate in the elderly population in Thailand (10). Reasons for this large difference are not clear and need further investigation, but interactions with other pathogens may be one contributory factor (25).

The only previous comparable estimates in a tropical climate zone are from Singapore, a small, completely urbanized, and very high-income country. Using 2004–2006 data, influenza was estimated to account for a mean of 8.3 annual deaths per 100,000 population (5). Also in the tropics, a study in Bangladesh in 2009 (combining seasonal and pandemic influenza) estimated influenza-related mortality to be 11 per 100,000 (26). However, only deaths with influenza-like illness were considered, and influenza-like illness was ascertained retrospectively by interviewing household members the following year.

Seasonal influenza mortality has also been estimated in a number of cities in China with a subtropical climate. In Hong Kong and Guangzhou (both relatively developed populations with gross domestic product per capita 7 and 3 times higher than that of Thailand), estimates were 11.1 and 10.6 per 100,000 population, respectively (4); another study estimated influenza-associated mortality in 5 subtropical Chinese cities to be 11.3 per 100,000 (27). In the United States, annual influenza-related mortality was recently estimated to be 11.9 per 100,000 (2). These results suggest that Thailand experiences a similar or slightly lower influenza-related mortality than these much higher income populations. However, influenza-related mortality is highly age dependent and will be strongly affected by a population's age distribution. For example, the proportion of the population aged >60 years in Hong Kong is 19% (http://www.census2011.gov.hk/en/) but averaged only 11% in Thailand during 2005–2009. Adjusting for differences in age structure and calculating expected mortality for a world-standard age structure give a more informative comparison (28). This gives point estimates for standardized mortality that are very similar in Thailand and Hong Kong (8.8 vs. 8.5 per 100,000 population) (4).

Our findings diverged from those of previous studies in the relative importance of different influenza types. In the United States, influenza A(H1N1) has been estimated to make a small or negative contribution to mortality, while influenza B accounted for about one-fifth of influenza-related deaths (2). In Hong Kong, influenza B and A(H1N1) are estimated to account for about one-third and one-quarter as many deaths as A(H3N2) (4), while another study estimated that types A and B made similar contributions to mortality in northern (temperate) Chinese cities, while in southern (subtropical) cities, type B dominated (27). In contrast, we estimated that A(H1N1) made the largest contribution to mortality, and that type B was associated with roughly half the mortality associated with type A. Some of these differences may reflect chance variation associated with different virus types over the study periods. For example, A(H3N2) mortality appears to have declined following the emergence of the Fujian strain in 2003 (predating our data) (2).

A striking finding was the lack of association of seasonal influenza with circulatory disease mortality. This contrasts with high-income temperate and subtropical settings where influenza is estimated to make a major contribution to circulatory disease hospitalization and death (2, 29, 30). There are several possible explanations. First, "noisy" influenza data or inaccurate ICD-10 coding may prevent a true association from being found. However, although there is clearly potential for improvement in ICD-10 data from Thailand (as elsewhere) (31), the similar seasonal patterns for ischemic heart disease and cerebrovascular disease (Web Figure 6) and the associations between influenza and other ICD-10 codes previously linked with influenza mortality suggest that this explanation is unlikely. Second, because of differences in humidity, aerosol transmission of influenza may be much lower in the tropics than in temperature regions (32). There is evidence that droplet or contact-based spread of influenza is less likely to lead to typical influenza symptoms than is aerosol transmission, and this could conceivably lead to differences in cause-specific mortality (33). Third, associations reported elsewhere between influenza activity and circulatory disease deaths could be mediated by another factor, such as secondary bacterial infections, and such interactions could differ in tropical and temperate zones (34). Fourth, the greater importance of acute rather than chronic circulatory disease in Thailand might be responsible for the different associations with influenza. Finally, it is possible that the high incidence and year-round circulation of influenza B result in more frequent but milder infections that protect against other more severe infections through nonspecific immunity. Interestingly, in

Brazil, the 2009 pandemic was associated with a very large increase in respiratory mortality but no association with circulatory mortality (35).

In summary, we have shown a substantial but previously hidden mortality burden due to influenza in a tropical middle-income country, less than 2% of which is likely to be accounted for by hospitalized cases of influenza pneumonia (36).

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PLOS | ONE

COLLECTION REVIEW

Methodological Variation in Economic Evaluations Conducted in Low- and Middle-Income Countries: Information for Reference Case Development

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Abstract

Information generated from economic evaluation is increasingly being used to inform health resource allocation decisions globally, including in low- and middle- income countries. However, a crucial consideration for users of the information at a policy level, e.g. funding agencies, is whether the studies are comparable, provide sufficient detail to inform policy decision making, and incorporate inputs from data sources that are reliable and relevant to the context. This review was conducted to inform a methodological standardisation workstream at the Bill and Melinda Gates Foundation (BMGF) and assesses BMGF-funded cost-per-DALY economic evaluations in four programme areas (malaria, tuberculosis, HIV/AIDS and vaccines) in terms of variation in methodology, use of evidence, and quality of reporting. The findings suggest that there is room for improvement in the three areas of assessment, and support the case for the introduction of a standardised methodology or reference case by the BMGF. The findings are also instructive for all institutions that fund economic evaluations in LMICs and who have a desire to improve the ability of economic evaluations to inform resource allocation decisions.

Introduction

Increasing demand for health services together with the accelerating developments in health technology place an ever-increasing strain on limited health resources. Health economic evaluation measures resources used against the outcomes of alternative policy options [1]. The ultimate aim of health economic evaluation is to improve resource allocation decisions by addressing efficiency in healthcare. Over the past decade, this method has gained increasing attention from decision makers in both resource-rich and resource-poor countries as well as among global health funders [2–4].

views of the above funding agencies. HITAP's international unit was established with support from the Thai Health-Global Link Initiative Project (TGLIP), the international Decision Support Initiative (funded by the Bill & Melinda Gates Foundation and the Department for International Development, UK), and the Rockefeller Foundation to provide technical assistance on health intervention and technology assessment for governments of low- and middle-income countries. The the Bill & Melinda Gates Foundation had role in study design, data collection and analysis, decision to publish, and preparation of the manuscript.

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Established in 2000, an aim of the Bill & Melinda Gates Foundation (BMGF) is to enhance healthcare through supporting technology development in areas beset by particular health problems, including neglected tropical diseases and vaccine preventable diseases. Since 2004, BMGF has provided cumulative funding in excess of US$200 million for cost-effectiveness analysis and related activities around the world.

To maximise the benefit of economic evaluation information to health policy decisions, it is essential that the studies are comparable both within and across health problems as well as properly performed and reported to effectively assist the health investment decisions that could subsequently have a large impact on the health of target populations. Limited methodological quality is reported to be a significant barrier to the effective use of economic evaluation information [5–7]. This is of particular concern in low- and middle- income countries (LMICs) where research capacity in this field and reliable data sources are insufficient [7,8], and there are few methodological guidelines for performing locally-relevant economic evaluation [9]. As a result, BMGF, being a major funder of this type of research, aims to pioneer the development of a reference case for conducting health economic evaluations in developing countries to be referred to not only by its grantees but also by researchers who receive financial support from other funders.

Prior to this review, there was substantial uncertainty regarding the number, quality, methodology and focus of BMGF-funded economic evaluations as there was no repository or centralised collation mechanism. A key element of the reference case development and the aim of this review was to present a snapshot of the current status of BMGF-funded economic evaluations in focus programme areas.

Methods

Scope

The review included published economic evaluations undertaken in LMICs from 2000 onwards in four focus programme areas for BMGF [10] (vaccine, tuberculosis, HIV/AIDS, and malaria). The initial review identified all types of economic evaluation (cost-minimization; cost-effectiveness analysis; cost-utility analysis; cost-benefit analysis [1]) to provide an indicator of the proportion of economic evaluations that are supported by BMGF. The in-depth analyses included variation in methodology, quality of reporting, and quality of evidence used and was limited to economic evaluations that used the cost per disability adjusted life year (DALY)-averted outcome measure and were funded by BMGF. The review scope was limited to cost-per-DALY studies as i) BMGF sought consistency with the outcome measure of existing programmes that it funds such as the Global Burden of Disease initiative; ii) a cost-utility-study focus was required as the intention of the reference case was to improve the ability of economic evaluation to inform resource allocation decisions in terms of both allocative and technical efficiency, iii) a single study type facilitated meaningful inference from within the time and resources available for the analysis.

Search Strategy

The search aimed initially to identify all economic evaluations in LMIC settings relating to the four programme areas to explore the number of existing studies during the time that BMGF had been established and examine the proportion of studies funded by BMGF. These were then narrowed down further to include only BGMF-funded studies that used cost-per DALY as their most aggregated measure of outcome for the in-depth analysis. To identify these economic evaluations, systematic reviews of this type of studies were firstly retrieved. Since BMGF was established in 2000, the period for the search of published systematic reviews in MEDLINE

and Centre for Reviews and Dissemination databases (CRD) were limited to 2000 to May 2013. Individual economic evaluations were then identified manually through the citations in the relevant systematic reviews. An economic evaluation study was considered relevant if it was a full economic evaluation, i.e. studies that contain comparison of both cost and health outcomes of at least two alternatives [1]; conducted in LMIC settings and published from 2000 onwards. The studies that met criteria were then investigated for their funding sources to identify those which were funded by BMGF.

The search strategies used relevant terms of economic evaluation, including "economic evaluation", "cost-effectiveness", "cost-utility", "cost-benefit", "economic evaluations", "cost effectiveness", "cost utility", and "cost benefit" and the terms of intervention of interest, including vaccine, HIV/AIDS, tuberculosis/TB, and malaria, and the filter 'systematic review' was applied.

Analytical Framework

All economic evaluations which were conducted in LMIC settings and published from 2000 onwards were analysed for their funding source and outcome measures. Most aggregate outcome measure, i.e. the measure that capture the most aspects among the measure used in that study, were considered. Therefore, if a study adopted both death averted and DALY, it would be categorised as using DALY as the aggregate measure.

The analytical frameworks developed by Walker and Fox-Rushby [11] and Teerawattananon et al. [12] for identifying method variations in economic evaluations conducted in LMICs were used on the included BMGF-funded cost-per-DALY studies. The analyses consisted of two parts. First, the manner of reporting, i.e. whether researchers reported adequate details, was explored using a number of variables adapted from Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement [13]. This included i) describing intervention and comparator(s) and the reason of choosing the comparator(s) ii) reporting characteristics of target populations iii) describing the perspective adopted iv) reporting horizon used v) reporting that discounting of costs and outcomes was done where relevant vi) informing unit,i.e. currency, and price date of cost data applied to the study and, if borrowed from other sources, how the cost data was converted to the study currency and price date vii) describing all key model parameter if a model was used viii) reporting Incremental cost-effectiveness ratios (ICERs) ix) discussing generalizability/transferability of the findings x) discussing equity consideration and affordability x) informing role of funders in the design and conduct of the study and xi) describing conflict of interest. Further examination was done to explore variation in methodology for certain variables, i.e. study perspective, analytical approach, uncertainty analysis, methods for currency conversion, methods for DALY calculation, and the threshold used. Second, quality of evidence used was evaluated using an adapted framework for hierarchy of evidence [14] (Table 1). Since the in-depth analysis was done only for cost-per-DALY studies, the hierarchy of the evidence of utilities such as those recommended by Cooper et al. [14] was not considered.

Results

General profiles of the review

Our study identified 56 eligible published systematic reviews of economic evaluations (Fig 1), of which the search period of those identified systematic reviews did not include economic evaluations published in 2012 and 2013. None of the systematic reviews except one (for Tanzania [15]) focused on a particular setting but instead included published literature conducted in low-, middle-, and high-income countries. From those systematic reviews, 204 economic

evaluation articles were found to meet the inclusion criteria. The majority of the economic evaluations focused on vaccines (90 studies), followed by HIV/AIDS (58 studies), malaria (41 studies), and tuberculosis (TB) (15 studies). In total, there were 47 economic evaluations, including 20 cost-per-DALY studies (see S1 List of included cost-per-DALY studies), funded by the BMGF (23% of 204 studies) (Table 2).

Although the majority of studies were funded by non-BMGF organisations, BMGF was most often cited as the funding body compared to any other individual organization, except in area of TB, of which only one study was supported by the foundation. Disease/programme-

Table 1. Hierarchies for data sources, reproduced from Cooper et al., 2005 [14].

Rank	Data components
	Clinical effect sizes/adverse events and complications
1+	Meta-analysis of RCTs with direct comparison between comparator therapies, measuring final outcomes
1	Single RCT with direct comparison between comparator therapies, measuring final outcomes
2+	Meta-analysis of RCTs with direct comparison between comparator therapies, measuring surrogate outcomes. Meta-analysis of placebo-controlled RCTs with similar trial populations, measuring the final outcomes for each individual therapy
2	Single RCT with direct comparison between comparator therapies, measuring the surrogate outcomesSingle placebo-controlled RCTs with similar trial populations, measuring the final outcomes for each individual therapy
3+	Meta-analysis of placebo-controlled RCTs with similar trial populations, measuring the surrogate outcomes
3	Single placebo-controlled RCTs with similar trial populations, measuring the surrogate outcomes for each individual therapy
4	Case control or cohort studies
5	Non-analytic studies (e.g. case reports, case series)
6	Expert opinion
9	Not clearly stated
	Baseline clinical data (if applicable)
1	Case series or analyses of reliable administrative databases specifically conducted for the study covering patients solely from the jurisdiction of interest
2	Recent case series or analyses of reliable administrative databases covering patients solely from the jurisdiction of interest
3	Recent case series or analyses of reliable administrative databases covering patients solely from another jurisdiction
4	Old case series or analyses of reliable administrative databases. Estimates from RCTs
5	Estimates from previously published economic analyses:
6	Expert opinion
9	Not clearly stated
	Costs
1	Cost calculations based on reliable databases or data sources conducted for specific study: same jurisdiction
2	Recently published cost calculations based on reliable databases or data course: same jurisdiction
3	Data source not known: same jurisdiction
4	Using charge (price) rather than cost when societal perspective was adopted
5	Recently published cost calculations based on reliable databases or data sources: different jurisdiction
6	Data source not known: different jurisdiction
9	Not clearly stated
	RCT = randomised control trial.

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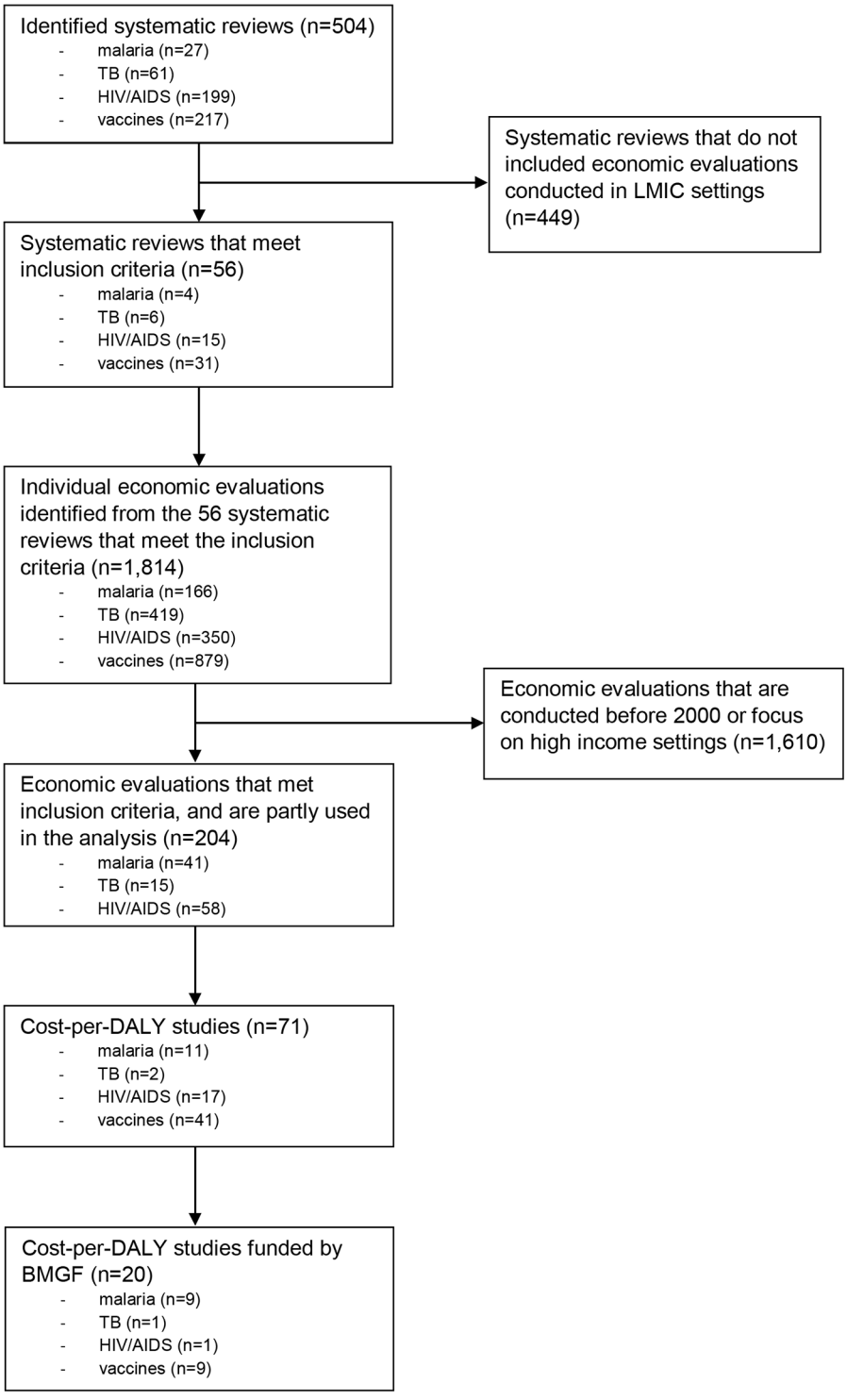

Fig 1. Flow of study selection.

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Table 2. Number of identified economic evaluations by type of funder, country income level of setting where the economic evaluation was conducted, and area of interest.

Programme area	SR abstracts identified	SR matching inclusion criteria	EEs in included SRs	EEs matching inclusion criteria	Included EE funded by BMGF
Malaria	27 (5.4%)	4 (7.1%)	166 (9.1%)	41 (20.1%)	15 (31.9%)
using DALY-averted outcome measure				*17 (23.9%)*	*9 (45.0%)*
TB	61 (12.1%)	6 (10.7%)	419 (22.8%)	15 (7.4%)	1 (2.1%)
using DALY-averted outcome measure				*2 (2.8%)*	*1 (5.0%)*
HIV/AIDS	199 (39.5%)	15 (26.8%)	350 (19.1%)	58 (28.4%)	5 (10.6%)
using DALY-averted outcome measure				*11 (15.5%)*	*1 (5.0%)*
Vaccines	217 (43.1%)	31 (55.4%)	899 (49.0%)	90 (44.1%)	26 (55.3%)
using DALY-averted outcome measure				*41(57.7%)*	*9 (45.0%)*
Total	**504**	**56**	**1,834**	**204**	**47**
using DALY-averted outcome measure				***71***	***20***

SR: systematic review; EE: economic evaluation; BMGF: Bill and Melinda Gates Foundation; DALY: Disability-Adjusted Life Year; TB: tuberculosis

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specific measures such as infection averted were the most common aggregated outcome measures, reported in 39% of studies. Death averted or life year saved were the outcome measured in 11% of studies, while DALY averted and QALY were the most aggregated outcome measures for 38% and 11% of studies respectively. Only two studies (1%) used monetary benefit (cost-benefit analyses) as an outcome measure. (Fig 2).

ICERs derived from each BMGF-funded cost-per-DALY study illustrate that almost all of the interventions in the areas of malaria, TB and HIV/AIDS represented good value for money (as defined by the World Health Organization) as the reported ICERs were below a ceiling threshold equal to Gross National Income per capita (1035 US dollars for low-income countries using World Bank classifications) [16] (Fig 3). It is noteworthy that in the case of vaccines, different settings yielded fairly different ICERs, which may be due to several factors including variation in epidemiology such as disease incidence/prevalence [17]. However, this can also be a consequence of the difference in methodological approaches rather than the true differences in effectiveness or costs of the evaluated interventions.

Manner of reporting and variation in methodology of cost-per-DALY studies funded by the BMGF

The percentage of cost-per-DALY studies funded by the BMGF adhering to a set of reporting requirements is shown in Fig 4. Generalisability/transferability and equity considerations were the attributes most often neglected in the studies, followed by affordability, price date, method of cost adjustment for time difference between price date in source for cost data and price date in the study and method of currency conversion.

Further analyses suggested that there was significant heterogeneity in methodology used in the cost-per-DALY studies funded by the BMGF. Most studies (12 out of 20 studies) were conducted using a societal perspective, followed by healthcare provider (5 studies [18–22]) and health system (1 study [23]) viewpoints, and two studies did not clearly state the perspective used. Regarding the analytical approach, 13 studies were model-based, of which four studies

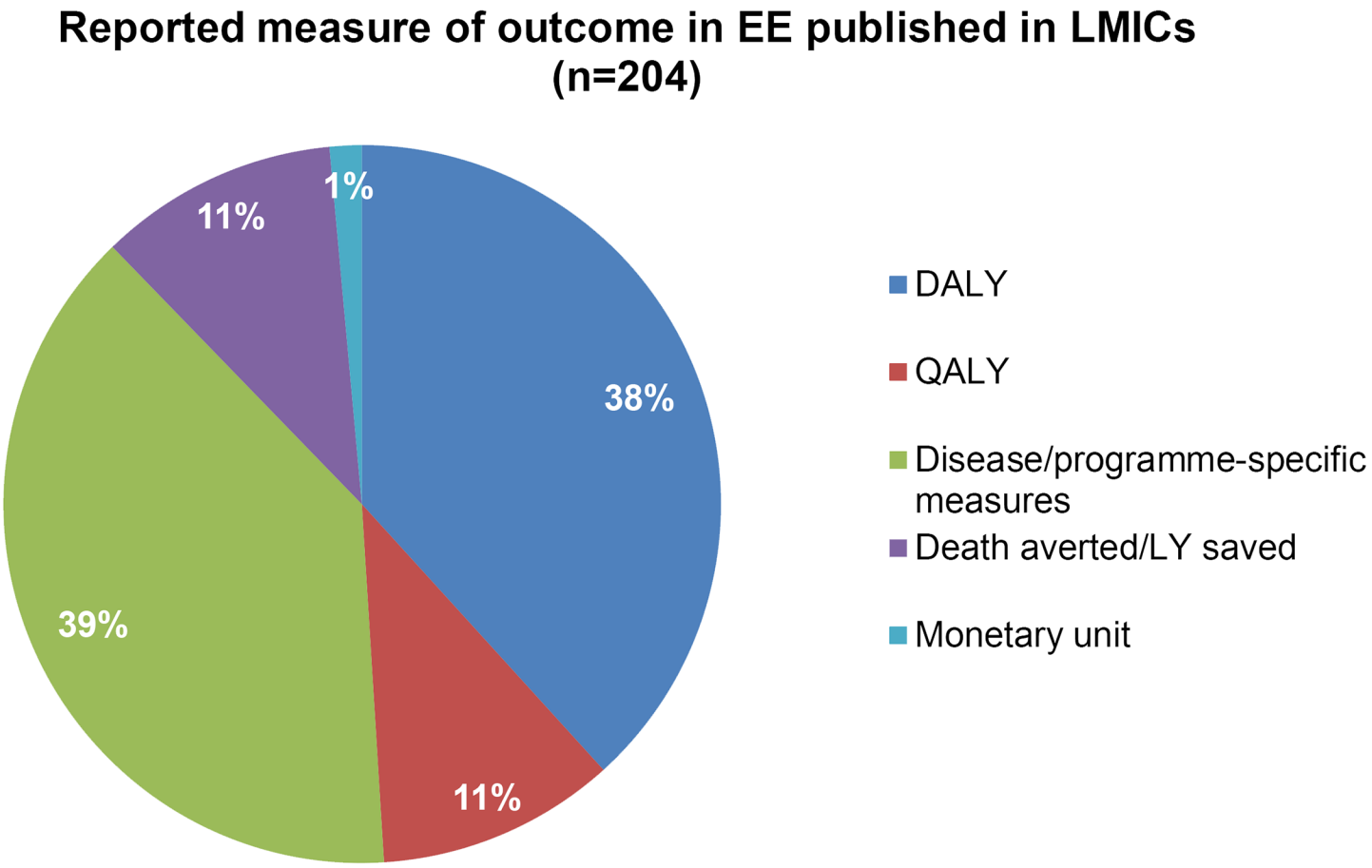

Fig 2. Most aggregated outcome reported in EEs published in LMICs, either funded by BMGF or not (n = 204). DALY: Disability-Adjusted Life Year; QALY: Quality-Adjusted Life Year; LY: life year.

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[20,22,24,25] constructed a decision tree; two studies [26,27] adopted a Markov model; two studies [28,29] applied a dynamic model; one study [21] used a mathematical model; four studies [30–33] did not specify the type of model used. Considering uncertainty analysis, most studies performed univariate or multivariate sensitivity analysis while only two studies [20,23] conducted a probabilistic sensitivity analysis. In some studies [23,25–27,32], a threshold analysis was also carried out along with the sensitivity analyses. More than half of the studies (12 studies) did not describe the method used for converting currencies even though they borrowed cost data from sources outside their study settings. Exchange rates were more frequently used (5 studies [18,19,25,31,34]) rather than purchasing power parity (PPP) (3 studies [17,24,32]) for converting foreign cost data to the local currency of the study setting.

Most studies did not follow the specific methodological recommendations of the Global Burden of Disease Project for the calculation of DALYs [35]. Only the study by Mbonye et al. [36] adhered to all three major methodological specifications, namely using a standard life table, applying age-weighting, and performing discounting for future DALYs. Four studies [21–23,25] used age-weighting and discounting but not standard life table. Thirteen out of the 20 studies discounted future DALYs but did not apply age-weighting and standard life table. Two studies [34,37] did not clearly state whether any of the recommendations were applied.

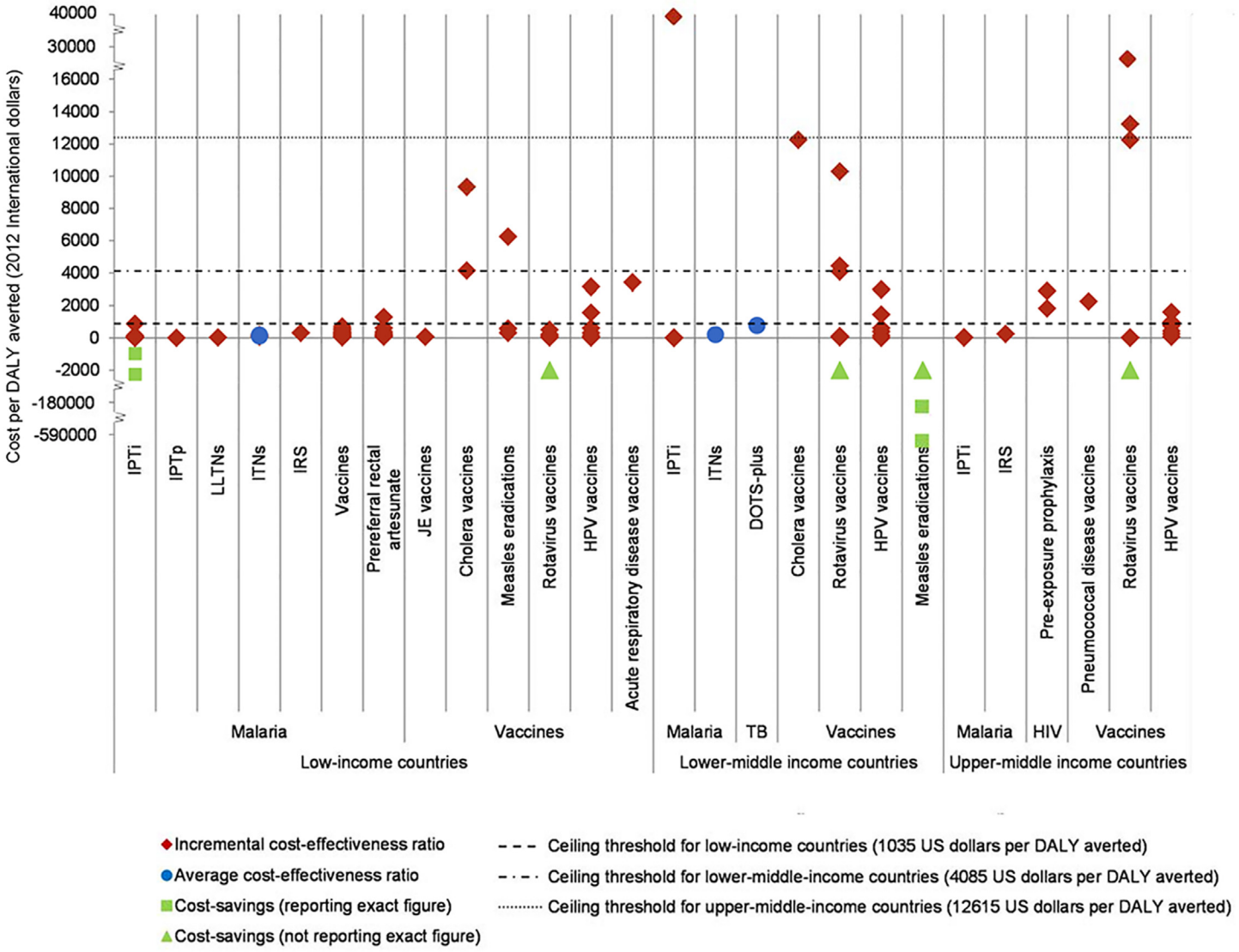

Fig 3. Cost-effectiveness league chart showing ICERs of interventions being evaluated in identified BMGF-funded cost-per-DALY studies (n = 20). IPTi: Intermittent preventive treatment for infants, IPTp: Intermittent preventive treatment for pregnant women, LLTNs: Long-lasting treated nets, ITNs: Insecticide treated nets, IRS: Indoor residual spray, JE: Japanese encephalitis, HPV: Human papilloma virus, DOTS: Directly observed treatment, short course. Source of consumer price index and purchasing power parity: IMF World economic outlook database.

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When discounting was relevant and performed, 3% was the rate used, not only for DALYs but also for cost data. Eleven out of 20 studies described the choice of study comparator(s). Comparators representing current or first-line practice were most commonly adopted (6 studies). Approximately half of the studies referred to a ceiling threshold of 1 to 3 times of capita GDP per DALY gained [38] as the decision rule for determining if a particular technology was good value for money. Seven out of 20 economic evaluations made a recommendation for adopting the technology based on the above decision rule. Lastly, twelve studies clearly informed the role of funders in the study design and conduct.

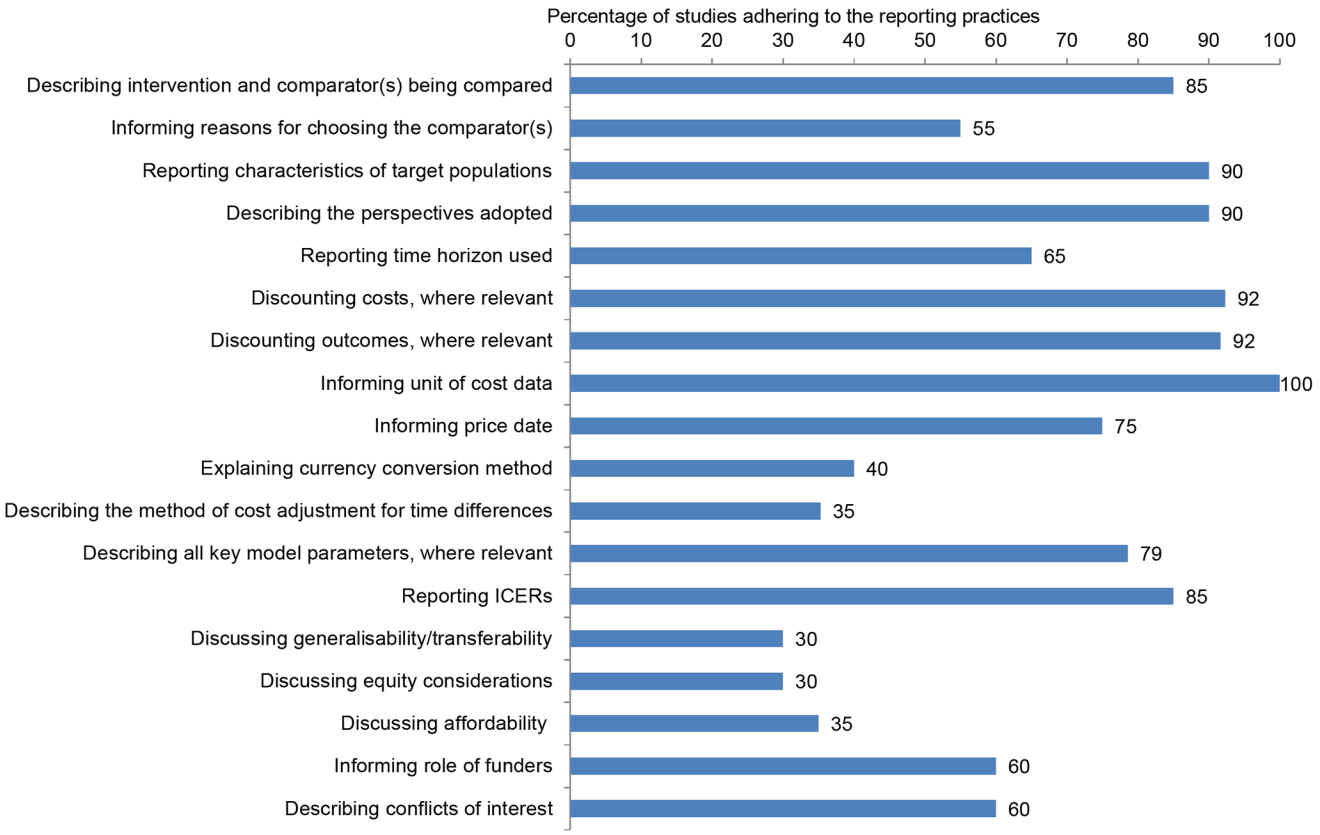

Fig 4. Percentage of BMGF-funded cost-per-DALY studies adhering to good practices for reporting health economic evaluations adapted from CHEERS statement [13] (n = 20).

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Quality of evidence used

Studies generally employed a higher quality of evidence for cost and resource parameters compared to other parameters, with the majority of studies estimating costs based on reliable administrative databases or data sources conducted for specific studies in the same jurisdiction. Baseline clinical data were often derived from relatively low data quality sources, e.g. case series, administrative databases. Similarly, the clinical effect sizes were mostly retrieved from a single RCT (Fig 5).

Discussion

There is an increasing trend of conducting economic evaluations for the purpose of informing resource allocation decision-making in LMICs [39,40], driven largely by increased investment in this kind of policy research by major global health players such as BMGF, GAVI alliance, and the World Health Organization. Although we believe that economic evaluation is a useful priority setting tool, it is far from perfect, especially in a situation where there are no uniform methodological approaches and reporting standards due to numerous methodological controversies and variations, as well as the possibility of biases being introduced in many ways and at various stages of the analysis [41,42]. Also, poor reporting quality is likely to restrict the usefulness of economic assessment in policy decision-making [12,13]. This review summarises key

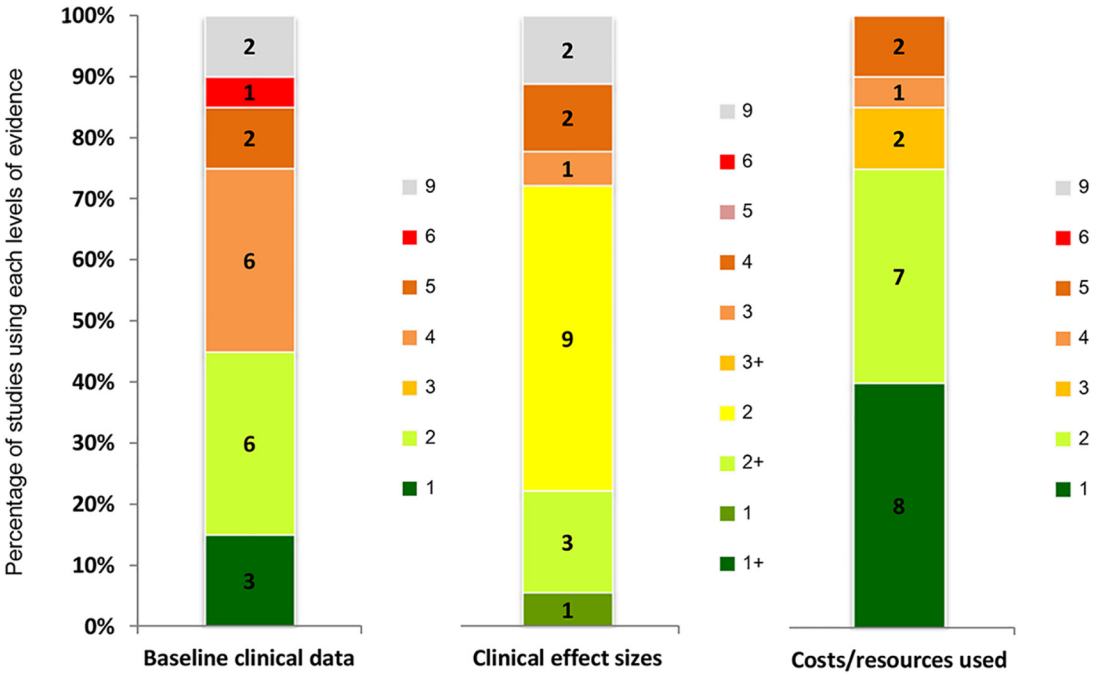

Fig 5. Ranks of evidence used in the included BMGF-funded cost-per-DALY studies (n = 20). Full details of hierarchy of evidence were provided in Table 1 [14].

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issues arising from the review of cost-per-DALY studies published in international journals in selected areas.

The review indicates that

- Methodological variation across economic evaluations is significant in almost every component except for the discount rate used.
- Societal and health care provider's viewpoints are among the most popular study perspectives used. Because household expenditure can be substantial, the use of these different perspectives can easily generate different conclusions even for studies in the same setting, focusing on the same intervention. Difference in perspective adopted among the studies reviewed may be due to the difference in primary audience of the study results, but if the studies aim to inform the same audience, the perspective used should be consistent.
- There is considerable disparity in the costing methods used. A majority of studies do not offer sufficient information about currency conversion and method of cost adjustment for time differences. For those giving adequate information, the exchange rate is often used to convert unit costs borrowed from other settings with more reliable data sources (often resource-rich countries).
- Despite the fact that purchasing power can better reflect opportunity cost of using resources across different settings, PPP was used in only a few studies. This may be explained by the fact that exchange rates are better understood by not only decision makers but also the general public.
- The poor adherence to the three methodological specifications for DALY estimation which were recommended during the period the studies were conducted raises concern—the

eight possible approaches to DALY calculation result in difficulties when making cross-study comparisons. However, it is noteworthy that the latest recommendation from the Global Burden of Disease research program [43] has changed, omitting age-weighting and discounting.

- Only a few (2 out of 20) economic evaluations employed probabilistic sensitivity analysis even though it is widely recommended in resource-rich settings as the most comprehensive method of dealing with various forms of uncertainty in economic evaluation [44].
- The findings of this review are consistent with previous reviews which found better quality of cost and resource data were used for economic evaluations in resource-limited settings compared to baseline clinical data and clinical effect sizes [12]. This may be due to the lack of reliable administrative databases or existing costing studies prompting researchers to conduct primary cost studies.
- Generalisability/transferability of results and equity implication of evaluated interventions are only discussed in less than one-third of all reviewed studies.
- Perhaps the most surprising result is that only 35 percent of the studies discussed the affordability of the interventions being assessed, which is particularly poignant given that these studies were conducted in resource-limited settings.

Implications for the way research is conducted

This review highlights the fact that serious attention needs to be given to the quality of reporting and consistency of the analyses, especially with regard to the following points:

- It is important to adhere to good practice criteria for reporting economic evaluations including providing reasons for choosing the comparator, describing the method of performing currency conversion, and the method of adjustment for time difference between date of cost collection and the analysis.
- As generalisability/transferability of results and equity implications of evaluated interventions are important issues in order to make use of the research finding, they should be discussed.
- Since information on affordability of the evaluated technology is an important input for policy decision-making, it should be emphasised in the discussion.
- The roles of funders and potential conflicts of interest should also be better addressed in future studies.
- There is a need for uniform methodological specifications and reporting standards for conducting health economic evaluations in LMICs for the purpose of improving the quality and reducing the disparity in the methods and reporting used for future studies.

We hope our recommendations will help ensure standards that facilitate value-for-money comparisons of health interventions being considered for introduction in resource-limited settings. Without any standardisation of methods, the differences in a cost-effectiveness ratio may arise from differences in study methodology rather than reflecting true differences between the interventions being evaluated in a given setting.

This review provides an indicator of the variation in methodological approach, use of evidence and quality of reporting in cost-per DALY, BMGF-funded economic evaluations in four programme areas. The findings contribute to the multi-stakeholder and to the production of a

BMGF reference case, not only by identifying key methodological areas that should be addressed within the reference case, but also by providing an indication of priority for methodological research to support the use of a reference case by BMGF-grantees.

Implications for funders and policy makers

This review serves not only to inform the development of a reference case for BMGF, but also to provide insights for local governments, and global, regional and local development partners who wish to make evidence-informed decisions to recognize potential problems in terms of quality and comparability of studies if there is no standard methodological guideline for conducting economic evaluations. Although there are instances of high-quality economic evaluations in LMIC settings, their variability in quality and comparability limits their routine use as a source of evidence for policy formation. This indicates that the reference case would not only be of benefit to BMGF, but also to the wider donor community and local decision makers if it was adopted more widely to enable the improvement of the quality and usefulness of evidence produced by all economic evaluations in LMIC contexts.

Limitations

It is important to point out the limitations of this review. The major limitation was due to the 2-stage search method, i.e. published systematic reviews of health economic evaluations were firstly identified, and then full economic evaluation papers recognised from the citations of those systematic reviews were retrieved. This may result in the omission of individual economic evaluations excluded from the identified systematic reviews. Moreover, this review considers systematic reviews that were published in English only. Thus, the search excluded conference proceedings, master and doctoral theses as well as 'grey literature' such as government reports as well as publications in other languages. However, the results tended to remain valid regardless of the limitations due to the search strategy. As the included studies were published in leading reputable international journals with relatively strong review process, including unpublished material and grey literature works would most likely have resulted in greater variation of methods applied as well as a lower quality of reporting and evidence used. The scope of the quality assessment section of the review limited inclusion of BMGF-funded studies. While this was appropriate to inform a reference case for use by BMGF, this does limit unqualified generalisation of the findings to all economic evaluation regardless of funding source. However, as BMGF was shown to be the largest funder of economic evaluation in LMIC in the included disease areas, we consider that the findings provide a useful indication of the quality of economic evaluations funded by other sources. Moreover, the review focuses on malaria, TB, HIV/AIDS, and vaccines, all of which have received strong support from major global health donors, including Global Fund, the BMGF, and GAVI Alliance. In contrast, other neglected tropical diseases might not have had as many economic evaluation studies of similar quality as those four mentioned areas. Third, it would be of interest to assess the improvement of study quality and reporting over time. However, due to the relatively small number of studies that met our inclusion criteria (use of cost-per DALY as an outcome measure and BMGF funding) this was not possible.

Supporting Information

S1 List. List of included cost-per-DALY studies.
(DOCX)

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Author Contributions

Conceived and designed the experiments: BS VC TW KT WR DW YT. Performed the experiments: BS VC KT WR. Analyzed the data: BS VC TW KT WR. Wrote the paper: BS VC TW KT KC YT. N/A.

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HEALTH AND QUALITY OF LIFE OUTCOMES

RESEARCH Open Access

Measurement properties of the EQ-5D-5L compared to EQ-5D-3L in the Thai diabetes patients

Juntana Pattanaphesaj[1,2] and Montarat Thavorncharoensap[1,2*]

Abstract

Background: The EQ-5D is a health-related quality of life instrument which provides a simple descriptive health profile and a single index value for health status. The latest version, the EQ-5D-5L, has been translated into more than one hundred languages worldwide - including Thai. This study aims to assess the measurement properties of the Thai version of the EQ-5D-5L (the 5L) compared to the EQ-5D-3L (the 3L).

Methods: A total of 117 diabetes patients treated with insulin completed a questionnaire including the 3L and the 5L. The 3L and 5L were compared in terms of distribution, ceiling, convergent validity, discriminative power, test-retest reliability, feasibility, and patient preference. Convergent validity was tested by assessing the relationship between each dimension of the EQ-5D and SF-36v2 using Spearman's rank-order correlation. Discriminative power was determined by the Shannon index (*H'*) and Shannon's Evenness index (*J'*). The test-retest reliability was assessed by examining the intraclass correlation coefficient (ICC) and Cohen's weighted kappa coefficient.

Results: No inconsistent response was found. The 5L trended towards a slightly lower ceiling compared with the 3L (33% versus 29%). Regarding redistribution, 69% to 100% of the patients answering level 2 with the 3L version redistributed their responses to level 2 with the 5L version while about 9% to 22% redistributed their responses to level 3 with the 5L version. The Shannon index (*H'*) improved with the 5L while the Shannon's Evenness index (*J'*) reduced slightly. Convergent validity and test-retest reliability was confirmed for both 3L and 5L.

Conclusions: Evidence supported the convergent validity and test-retest reliability of both the 3L and 5L in diabetes patients. However, the 5L is more promising compared to the 3L in terms of a lower ceiling, more discriminatory power, and higher preference by the respondents. Thus, the 5L should be recommended as a preferred health-related quality of life measure in Thailand.

Keywords: Diabetic, EQ-5D-3L, EQ-5D-5L, Health-related quality of life, Measurement properties, Psychometrics

Background

The EQ-5D - a widely used generic instrument for describing and valuing health outcomes in clinical and economic evaluations - was originally developed in the 1980s [1,2]. Due to its simplicity and brevity, it imposes minimal respondent burden and can be administered using a variety of modalities including self-completion. Many health technology assessment (HTA) organizations including the National Institution for Clinical Excellence (NICE) [3], the US panel on Cost-effectiveness in Health and Medicine [4], and the Thai national guideline of HTA [5] have recommended the EQ-5D as the preferred method for assessing the utility for health technology assessment.

The EQ-5D comprises 2 parts: a simple descriptive profile that can be converted into a single summary index (the EQ-5D index), and a visual analog scale (VAS). At present, the first version of the EQ-5D - known as EQ-5D-3L version (hereafter "the 3L") - has now been translated into more than 140 languages [6]. The 3L

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descriptive system is composed of five dimensions: mobility; self-care; usual activities; pain/discomfort; and anxiety/depression. Each dimension has three levels of impairment, namely no problems (level 1), some/moderate problems (level 2), and extreme problems (level 3). The descriptive response from the EQ-5D can be converted into an index score which is useful for clinical and economic evaluations [2]. For the VAS, a respondent will be asked to rate their health on a 20-centimeter vertical scale. The scale ranges from 0 to 100, where 0 means the worst possible health that the respondent can imagine and 100 indicates the best possible health in the respondent's viewpoint.

Since the 3L is limited to three levels of response categories, a substantial ceiling effect was observed [7-12]. In addition, it has limitations in measuring small changes, especially in mild conditions [13-16]. Previous studies also found that the 3L appeared to be less sensitive when compared to the SF-12 or SF-36 [7,8]. In response to the problems previously mentioned, the 5-level of EQ-5D (EQ-5D-5L, hereafter "the 5L") was developed by a task force within the EuroQol group [13,14]. This version includes five levels of impairment in each of the existing five EQ-5D dimensions. At present, the 5L has now been translated into more than 113 languages [17]. Several studies [15,16,18-24] examining the measurement properties of the 5L have found that it is a valid and reliable instrument. When comparing the 5L with the 3L, it was found that the 5L had a lower ceiling effect [16,18-21,23,24] and greater discriminative power with the potential to better detect the differences between groups [15,16,18,20,21,24]. In addition, it showed better face validity [13,15,25] and test-retest reliability [18,21,23].

Previous studies were conducted in several countries to evaluate the measurement properties of the 3L compared to those of the 5L [15,16,18-24]. However, there is a substantial need to assess the measurement properties of the 5L in different populations and patients. The Thai version of EQ-5D-5L has been available since 2013 but there has been no assessment of its measurement properties in Thailand to our knowledge. Therefore, this study aims to examine this issue and to assess the measurement properties of the 5L in comparison with the 3L among diabetes mellitus patients treated with insulin. The measurement properties will be assessed in terms of distribution; redistribution; ceiling; convergent validity; discriminative power; test-retest reliability; feasibility; and patient preference.

Methods

Subjects and settings

A convenience sample of patients with diabetes mellitus - who received treatment at the outpatient department at Ramathibodi Hospital, Thailand during 7 January and 31 March 2013 - was invited to participate in this study. Patients were eligible if they met the following criteria: aged ≥ 12 years, required regular insulin treatment, and had no complications as determined by the nurse. Pregnant women and disabled persons were excluded from this study.

Procedure and instruments

The questionnaire consisted of 4 parts: 1) one page of the Thai version of the 3L and 5L response scale; 2) the EQ-VAS; 3) two preference questions; and 4) the short-form 36 health survey version 2 (SF-36v2) in Thai. The permission to use the official Thai version of the 3L, 5L, and SF-36v2 was granted by the authoritarians before beginning the data collection process.

The single page of the 3L and 5L response scale contained the 5L version on the left column and the 3L version on the right column. Similar to previous studies [15,18,20], respondents were asked to complete the 5L first, followed by the 3L in order to avoid the tendency to not choose levels 2 and 4 - the "in-between" options - when the 3L was completed first. The index value of the 5L was obtained from an interim mapping generated by the EuroQol group [26] as the valuation study of the 5L in Thailand has not yet been completed. The 3L index value was calculated using the Thai value sets studied by Tongsiri et al. [27].

The preference questions comprised 2 items: 1) Which response scale is easier to use? (the 3L or the 5L or indifferent); and 2) Which response scale best describes your health? [15].

The convergent validity of the 5L and 3L were evaluated by comparing them with the SF-36 as it is a widely-used generic health survey in clinical research and has demonstrated validity among the Thai population [28-30]. The SF-36 contains 8 dimensions, i.e. physical functioning; role limitation due to physical problems; bodily pain; general health perceptions; social functioning; vitality; role limitations due to emotional problems; and general mental health [31]. Since a weighted Likert scale is used as the scoring system, the items for each dimension are summed to provide a score which is then linearly transformed into a value from 0 – 100 (100 indicating the best health level).

This study was approved by the Mahidol University Institutional Review Board (MU-IRB), Thailand and the Institute for the Development of Human Research Protections (IHRP), Ministry of Public Health, Thailand. All participants provided written informed consent and all instruments were self-administered. After completing the questionnaire, the respondents received 3.25 USD for compensation (1 USD = 30.73 Baht). All respondents were also asked to complete a second set of questionnaires after 2 weeks and to return it by mail; the set

consisted of one page of the Thai 3L and 5L response scale and the EQ-VAS. If the second questionnaire did not reach the researcher within 3 days after due date, phone call or short message was made to remind the respondent. The second questionnaires which reached to the researcher later than 21 days were excluded from the analysis.

Statistical analyses

The distribution of the 3L and 5L responses was demonstrated in terms of percentage of each level reported. The redistribution patterns of the responses from the 3L to 5L for each dimension were also reported in terms of percentage. Similar to previous studies [15,21], the response inconsistency and size were determined and are shown in Table 1. To determine the inconsistency, the response of the 3L was converted into the 5L (the $3L_{5L}$) as follows: 1 = 1, 2 = 3, and 3 = 5. Then, the size of inconsistency was calculated as $|3L_{5L}\text{-}5L|\text{-}1$. A size of inconsistency of ≤ 0 indicated consistency, and thus only 7 pairs are considered as consistent responses.

For the ceiling, the proportion of respondents reported 'no problems' for all five dimensions - the proportion of respondents scoring '11111' [16] - was compared for the 3L and 5L. The percentage reduction from the 5L to 3L was calculated as follows: (Ceiling 3L − Ceiling 5L)/ Ceiling 5L. We hypothesized that the ceiling should be lower in the 5L compared with the 3L. Feasibility was assessed by calculating the number of missing values for the 5L and 3L.

Convergent validity was tested by assessing the relationship between each dimension of the 5L and SF-36v2 using Spearman's rank-order correlation (Spearman's rho). We hypothesized that each dimension in the 5L would be more highly correlated to related subscales than to other subscales in the SF-36 compared to the 3L. Specifically, we expect to see strong correlation between these pairs of subscales: mobility and physical functioning; pain and bodily pain; anxiety/depression and mental health. We also expected to identify moderate correlation between these pairs of subscales: self-care and physical functioning or role limitation due to physical problems; usual activity and role limitation due to physical problems. The EQ-5D's responses were recoded to signify that higher scores presented better health statuses. The strength of correlation was determined as follows: absent ($r < 0.20$), weak association ($0.2 \le r < 0.35$), moderate ($0.35 \le r < 0.50$), and strong ($r \ge 0.50$) [32]. Additionally, the relationship between VAS score and index value was reported using the Pearson's correlation coefficient.

Table 1 Size of (in) consistent response

	5L				
3L	**Level 1**	**Level 2**	**Level 3**	**Level 4**	**Level 5**
level 1	-1	0	1	2	3
level 2	1	0	-1	0	1
level 3	3	2	1	0	-1

Adapted from Janssen et al [16]. The size of inconsistency of ≤ 0 indicated consistency.

Discriminative power (or informativity) was determined by the Shannon index (H') and Shannon's Evenness index (J'). H' and J' are often used to reflect the discriminatory power of health state classification [15,16,18,21,33]. H' reflects the absolute information content. The higher the H', the more information is captured by the measure. On the other hand, J' expresses the relative informativity of a system or the evenness of a distribution regardless of the number of categories. In case of an even distribution - when all levels are filled with the same frequency - J' is equal to 1. When comparing the 5L to the 3L, we expect the H' of the 5L to be higher to reflect more discriminatory performance. On the other hand, the J' of the 5L might slightly decrease as the extra level might not be used equally.

The test-retest reliability of both EQ-5D index scores was evaluated using the intraclass correlation coefficient (ICC) and the reliability of each dimension was assessed with Cohen's weighted kappa coefficient. According to Fleiss's standards for the strength of agreement for kappa values [34], Cohen's weighted kappa (k) was determined as follows: poor reproducibility ($k < 0.4$); good reproducibility ($0.4 \le k < 0.75$; excellent reproducibility ($k \ge 0.75$). Regarding intra-rater reliability among each dimension at different times, the data set lacked variance since most respondents responded with level 1 for self-care. The weighted kappa coefficient could not be calculated, thus percentage agreement values was demonstrated also [35,36]. It was calculated as: (a + d)/N, where the values of a and d were obtained from a 2x2 table.

All data were analyzed using SPSS 19. Statistical significance was set a priori as $p < 0.05$.

Results

Characteristics of respondents

A total of 117 patients with diabetes mellitus who met the eligibility criteria were included. The characteristics of the respondents are shown in Table 2. The average age of the respondents was 45 years, with 62.4% being female. Sixty-four (54.7%) respondents had type 2 diabetes. The average diabetes duration of the sample was 9 years and the average BMI was 23.30. Of the 117 respondents who completed the first survey, 101 respondents (86%) returned the second questionnaire set by postal mail.

The health state '11111' was observed in 29.1% in the 5L and 33.3% for the 3L. The second-most frequent health state reported was '11121' which was 14.5% in the 5L and 15.4% in the 3L. Finally, there were no missing

Table 2 Demographic characteristic of respondents

Demographic characteristic	n (%)
Type of diabetes	
Type 1	53 (45.3)
Type 2	64 (54.7)
Gender	
Male	44 (37.6)
Female	73 (62.4)
Marital status	
Single	58 (49.6)
Married	46 (39.3)
Widowed	9 (7.7)
Divorced/Separated	4 (3.4)
Education	
High school	51 (43.6)
Primary school	27 (23.1)
Bachelor's degree	25 (21.4)
Diploma	10 (8.5)
Master's degree or higher	4 (3.4)
Occupation	
Student	50 (42.7)
Government/state enterprise officer	20 (17.1)
Housewife	14 (12.0)
Business owner	11 (9.4)
Unskilled labor	7 (6.0)
Retired	6 (5.1)
Employee	4 (3.4)
Agriculture/fishery	2 (1.7)
Other	3 (2.6)
Health insurance	
Civil Servants Medical Benefits Scheme	58 (49.6)
Out of pocket	32 (27.4)
Universal coverage	20 (17.1)
Social security	7 (6.0)
	Median (IQR)
Age (years)	45.00 (40.0)
Diabetes duration (yr)	9.00 (8.50)
BMI (Kg/M^2)	23.30 (7.37)
Household income per month (Baht)	30,000 (30,000)

values from both the 5L and the 3L, indicating good feasibility for both instruments.

Distribution and ceiling

For all of the dimensions, most respondents reported no problems (level 1) for both the 3L (52-98%) and the 5L (44-97%), as shown in Figure 1. Among responses with health problems, it was clear that the 5L demonstrated better severity level distribution than the 3L except for self-care.

With regards to the ceiling, the 5L showed a slightly decreasing trend for no problem responses compared with the 3L. The percentage of patients reporting the health state '11111' decreased from 33% in the 3L to 29% in the 5L. Nevertheless, no statistically significant difference was found. Self-care reached the highest ceiling (98% for the 3L, 97% for the 5L) and showed the smallest reduction in ceiling (1%) with the 5L. In contrast, pain/discomfort showed the smallest ceiling (52% for the 3L, 44% for the 5L) and also showed statistically significant reduction in ceiling with the 5L. No statistically significant reduction was found for the other dimensions.

Redistribution

Among the answers of no problem (level 1) on the 3L, most of them (85-98%) remained the same (no problem) on the 5L while 2-15% redistributed to slight problems (level 2) on the 5L as shown in Table 3. The majority of the respondents who reported moderate problems (level 2) on the 3L indicated slight problems (level 2) on the 5L (69-100%), while 9-22% shifted to moderate problems (level 3) on the 5L. As such, redistribution occurred the least in self-care. The mean VAS score tended to be lower according to the severity level of the 5L. No inconsistent response was found in this study.

Convergent validity

Table 4 demonstrates the Spearman's correlation coefficients between the EQ-5D and SF-36v2 dimensions. In general, the pattern of correlations between the 2 versions of EQ-5D and SF-36v2 was similar. As expected, stronger correlation between similar dimensions of EQ-5D and SF-36v2 were found: mobility and physical functioning ($r = 0.54$ for the 3L, $r = 0.53$ for the 5L); pain/discomfort and bodily pain ($r = 0.30$ for the 3L, $r = 0.35$ for the 5L); anxiety/depression and mental health ($r = 0.45$ for the 3L, $r = 0.49$ for the 5L). However, self-care and usual activity dimension of the EQ-5D were weakly associated with various dimensions of SF-36v2. Additionally, Pearson's correlation coefficient between the VAS score and index value was also similar between the 3L and 5L (0.36 for the 3L, 0.35 for the 5L with p-value < 0.001).

Discriminative power

The absolute informativity (H') of the 5L was higher than the 3L for all dimensions as shown in Table 5. This reflects that the 5L generated more informativity than the 3L. We also found that the 5L generated similar results compared with the 3L when it came to relative informativity (J').

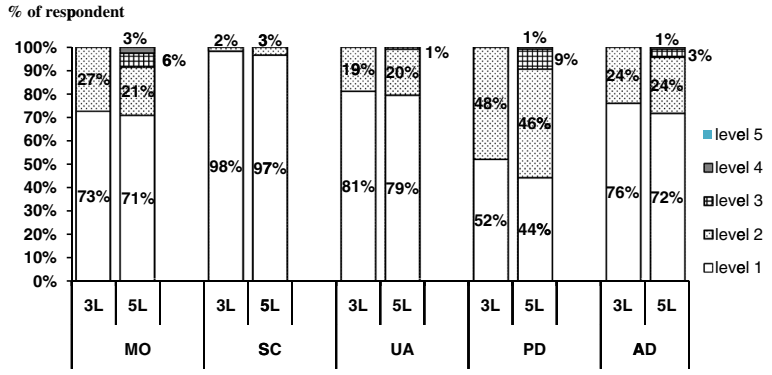

Figure 1 Distribution across severity level of the 3L and 5L dimension.

Test-retest reliability

The time interval between the first and second test was approximately 3 weeks. Overall, the reliability coefficient and percentage agreement of the 5L were slightly lower than the 3L (Table 6). The weighted kappa coefficient for the 3L ranged between 0.39 and 0.70, and between 0.44 and 0.57 for the 5L; this indicated that the 3L had better reproducibility than the 5L. The percentage agreement returned higher values than the weighted kappa coefficient; it was between 0.78 and 0.98 for the 3L and 0.67 and 0.97 for the 5L. The ICCs of the 3L and 5L indexes were 0.64 and 0.70, respectively, which indicated excellent reproducibility for both instruments.

Table 3 Redistribution pattern of response from 3L to 5L

Dimension	3L	5L	n (%)	Mean VAS	Size of inconsistent response*
Mobility	1	1	83 (98%)	81.02	−1
		2	2 (2%)	85.00	0
	2	2	22 (69%)	72.38	0
		3	7 (22%)	71.43	−1
		4	3 (9%)	72.67	0
Self-care	1	1	113 (98%)	79.19	−1
		2	2 (2%)	70.00	0
	2	2	2 (100%)	60.00	0
Usual activities	1	1	93 (98%)	80.82	−1
		2	2 (2%)	80.00	0
	2	2	20 (91%)	71.85	0
		3	2 (9%)	50.00	−1
Pain/discomfort	1	1	52 (85%)	81.54	−1
		2	9 (15%)	86.33	0
	2	2	45 (80%)	77.77	0
		3	10 (18%)	64.50	−1
		4	1 (2%)	50.00	0
Anxiety/depression	1	1	84 (94%)	81.38	−1
		2	5 (6%)	71.80	0
	2	2	23 (82%)	73.48	0
		3	4 (14%)	67.50	−1
		4	1 (4%)	60.00	0

*The size of inconsistency of ≤ 0 indicated consistency.

Patient preferences

Thirty-six percent of respondents indicated that the 5L was easier to answer than the 3L while 33% of respondents indicated that there was no difference between the 5L and the 3L. In terms of reflecting health status, most respondents (63%) agreed that the 5L was better in

Table 4 Correlation coefficients between EQ-5D and SF-36v2 dimensions

Dimension	PF	RP	BP	GH	VT	SF	RE	MH
3L								
Mobility	.54**	.28**	.41**	.42**	.25**	−0.07	0.11	0.14
Self-care	0.16	0.05	.19*	0.12	0.14	0.16	0.06	0.18
Usual activities	.25**	.21*	.30**	.19*	.27**	0.18	0.13	.28**
Pain/discomfort	.19*	0.17	.30**	.24**	.18*	0.11	.21*	.22*
Anxiety/depression	0.05	0.09	.23*	.22*	.21*	.32**	.29**	.45**
5L								
Mobility	.53**	.29**	.44**	.44**	.23*	−0.08	0.09	0.11
Self-care	.24**	.20*	.23*	0.18	0.16	.24**	.21*	.22*
Usual activities	.30**	.23*	.29**	.22*	.24*	0.16	0.14	.24**
Pain/discomfort	.24**	.23*	.35**	.28**	.22*	0.08	0.16	0.18
Anxiety/depression	0.08	0.12	.19*	.21*	.28**	.35**	.29**	.49**

PF (physical functioning), RP (role limitation due to physical problems), BP (bodily pain), GH (general health perceptions), SF (social functioning), VT (vitality), RE (role limitations due to emotional problems), MH (general mental health).
*Correlation is significant at the 0.05 level (2-tailed).
**Correlation is significant at the 0.01 level (2-tailed).

Table 5 Shannon's index (*H'*) and Shannon's Evenness index (*J'*) of 3L and 5L

Dimension	*H'*		*J'*	
	3L	5L	3L	5L
Mobility	0.85	1.20	0.53	0.52
Self-care	0.12	0.21	0.08	0.09
Usual activities	0.70	0.78	0.44	0.34
Pain/discomfort	1.00	1.40	0.63	0.60
Anxiety/depression	0.79	1.06	0.50	0.46

describing their health states while 29% indicated that both versions were similar.

Discussion

This report is the first study in Thailand that assesses the measurement properties of the 5L and compares it with the 3L. Similar to previous studies [16,18,20,21,23,24], self-care showed the highest percentage of ceiling effect in both the 3L and 5L. On the other hand, the lowest ceiling was found in pain/discomfort (44%) [18,21,23]. Similar to the previous studies [16,18-21,23,24], the proportion of the ceiling in our study was lower in the 5L (29%) compared with the 3L (33%). However, in the previous studies that involved patients with a variety of severity higher reduction in ceiling of the 5L (3-17%) was identified [16,18,21,23]. The smaller reduction in ceiling found in our study is probably due to the fact that our respondents were likely to perceive that they were healthy, which was consistent with their median VAS score of 0.78. In fact, our finding is similar to those of the previous study [20], which found a slight reduction in ceiling effect among participants; whose median VAS score was 80.

In each dimension, more than half of the responses were in level 1 (no problem) for both the 3L and 5L. In addition, we found that the majority of level 1 in the 3L still remained at level 1 in the 5L (85-98%) while only 2% (self-care) to 15% (in pain/discomfort) were upgraded to level 2 in the 5L. The redistribution from 3L-level 2 (some problems) to 5L-level 2 (slight problems) was also high, ranging from 69% for mobility to 100% for self-care. On the other hand, redistribution from 3L-level 2 to 5L-level 3, ranging only from 9% for usual activities to 22% for mobility. This is probably due to the fact that most respondents in our study perceived that they were healthy and have no problem. In addition, for those who indicated having some problems in the 3L they are more likely to have slight problems rather than moderate problems. This finding supports that the 5L can present more details of severity than the 3L and that the inclusion of the slight problems (level 2) in the 5L is essential, especially when the respondents were in mild condition. However, no supportive evidence of the inclusion of severe problems (level 4) in the 5L was found in our study as no 3L-level 3 responses were reported. Again, this may also be due to the fact that our respondents were likely to perceive that they were healthy.

No inconsistent responses were found in our study. This indicates that our respondents were able to consistently answer both the 3L and 5L. This is similar to previous studies [15,18,20,21,23,24] which showed that inconsistency was quite low, ranging from 0.5% to 3.5%. However, the consistent responses may be due to the low number of the sample size and the characteristics of our sample - educated and healthy diabetic patients. In addition, even when the respondents completed the questionnaires themselves, they were well-advised by trained staff. However, it should be noted that the single page of the 3L and 5L response scale used in this study was against the standards for the EQ-5D which should be used separately in one page A4 format. As the result, the answers from the 3L and the 5L may not be totally independent and might generate less reliable results.

The measurement of reliability and agreement is important in health classification as it reveals the amount of errors of the measurement. The concept of 'reliability' differs from 'agreement' in that reliability is a relative measure which is the ratio of variability between subjects to the total variability of all measurement in the sample [36]. Thus, it reflects the ability of an instrument

Table 6 Test-retest reliability of the 3L and the 5L

Dimension	Weighted kappa coefficient (95% CI)		Percentage agreement	
	3L	5L	3L	5L
Mobility	0.70 (0.53-0.86)	0.57 (0.40-0.74)	0.89	0.83
Self-care	n/a*	n/a	0.98	0.97
Usual activities	0.39 (0.16-0.62)	0.45 (0.25-0.65)	0.82	0.81
Pain/discomfort	0.56 (0.39-0.72)	0.44 (0.29-0.58)	0.78	0.67
Anxiety/depression	0.50 (0.31-0.70)	0.49 (0.33-0.65)	0.82	0.77
	Intraclass correlation coefficient (ICC)**			
EQ-5D index	0.64 (0.51-0.74)	0.70 (0.57-0.79)		

*Not enough information to calculate kappa coefficient for self-care dimension.
**ICC was 2-way random, single measures, and absolute agreement.

to differentiate between subjects. In contrast, an agreement is an absolute measure which is the degree to which responses are identical. Cohen's weighted kappa is often used in assessing test-retest reliability of ordinal instruments as it takes the chance agreement into account. However, the lack of variance in the data set meant that the kappa could not be calculated so it was necessary to rely on the percentage agreement values. However, it should be cautioned that the percentage agreement may give higher reproducibility figures than the kappa coefficient [35].

Unlike previous studies [21,23,24], our results of the test-retest reliability/agreement showed that the 5L was slightly less reproducible than the 3L in all dimensions. This is probably due to the fact that the average time interval between the two tests was too long (approximately 14–21 days) so the condition of the patients might have changed [36]. If this is the case there is a higher chance of distorting the 5L results as the 5L is better than the 3L in capturing small changes in health status. In fact, a simple question such as "Has your health changed significantly since last time you filled in the questionnaire?" should be added and only patients whose conditions were stable should be included in the test-retest analysis. Since there is no check whether health status of the patients was changed or remained the same the result of test-retest reliability should be interpreted with cautions.

Convergent validity was evaluated by correlations between the EQ-5D and SF-36v2 dimensions. Both the 3L and 5L presented an acceptable degree of association and similar correlation pattern with the SF-36v2 in some pairs of dimension, i.e. mobility versus physical functioning; pain/discomfort versus bodily pain; and anxiety/depression versus mental health. The findings were similar to the study by Kimman et al. [28] that assessed the relationship of the 3L with the SF-36v2 among the occupational population in Thailand.

Similar to previous studies [15,16,20], absolute informativity (H') increased in all dimensions for the 5L while in terms of the evenness of distribution evaluated by Shannon's Evenness index (J'), the 5L was comparable to the 3L. While the maximum value of H' for the 5L is 2.32, our H' values ranged from 0.21 to 1.40 which was lower than the findings from Pickard et al. [16] (0.84-2.00) and Janssen et al. [15] (2.05-2.26). With the maximum value of J' set at 1.00, our J' values ranged from 0.09 to 0.60 which was also lower than Pickard et al. [16] (0.36-0.86) and Janssen et al. [15] (0.88-0.97). The lower H' and J' values found in our study may have risen from the mild characteristic of our sample since the extreme problems (3L-level 3 and 5L-level 5) were not reported. As the result, the levels of responses of the EQ-5D were used ineffectively, resulting in low H' and J' values.

In our study, diabetic mellitus was chosen as it is a common chronic disease that substantial affects quality of life [37,38]. Additionally, diabetes was ranked as third and eighth in terms of Disability Adjusted Life Year (DALY) loss in Thai women and men, respectively [39]. We included patients with no complications in our study to ensure that the health status will be stable enough in order to test the test-retest reliability/agreement. However, given the mild condition of our sample, we were unable to assess the redistribution of answers from the 3L-level 3 to the 5L.

Further studies should be conducted for patients with a variety of severe health problems. In addition, it should be noted that the generalizing of the findings to different groups of patients should be made with caution as the pattern of responses may differ by disease characteristics [8]. One further limitation is that the 5L index values were obtained from the interim mapping generated by the EuroQol group since the valuation study for the 5L in Thailand has not been completed yet. Although the calculation was based on the Thai 3L value sets, the results of the mapping may deviate compared to the actual responses [40]. In addition, it is also worth noting that about 20% of our respondents were in the age 12–15 years old. Although the use of adult version may be allowed among this age group of respondents there is very limited evidence on the suitable of the use of adult version especially in term of validity and reliability among this group of respondents.

Conclusions

In summary, this study suggests that the 5L was greater than the 3L in terms of distribution, ceiling, informativity, discriminatory power, and patient preferences. The 5L also showed reasonable convergent validity and test-retest reliability. Thus, the 5L should be recommended for use in research or clinical practice and can also be used as a preferred health-related quality of life questionnaire in Thailand.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

All named authors contributed jointly to the conception, study design, interpretation and writing of the report. JP was involved in the data collection and analysis. Both authors read and approved the final manuscript.

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Is diabetes and hypertension screening worthwhile in resource-limited settings? An economic evaluation based on a pilot of a Package of Essential Non-communicable disease interventions in Bhutan

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In response to a lack of cost-effective data on screening and early treatment of diabetes and hypertension in resource-limited settings, a model-based economic evaluation was performed on the World Health Organization (WHO)'s Package of Essential Non-communicable (PEN) disease interventions for primary health care in Bhutan. Both local and international data were applied in the model in order to derive lifetime costs and outcomes resulting from the early treatment of diabetes and hypertension. The results indicate that the current screening option (where people who are overweight, obese or aged 40 years or older who visit primary care facilities are screened for diabetes and hypertension) represents good value for money compared to 'no screening'. The study findings also indicate that expanding opportunistic screening (70% coverage of the target population) to universal screening (where 100% of the target population are screened), is likely to be even more cost-effective. From the sensitivity analysis, the value of the screening options remains the same when disease prevalence varies. Therefore, applying this model to other healthcare settings is warranted, since disease prevalence is one of the major factors in affecting the cost-effectiveness results of screening programs.

Keywords Bhutan, cost-effectiveness analysis, diabetes mellitus, hypertension, non-communicable diseases, Package of Essential Non-communicable disease interventions (PEN)

KEY MESSAGES

- An assessment of the entire intervention pathway of screening for hypertension and diabetes in patients who are overweight, obese or over 40 years visiting primary health services in Bhutan found that the current screening recommendations outlined in the WHO's PEN offered value for money.
- While opportunistic screening resulted in 70% coverage, it is likely that universal screening may even yield better value for money. Universal screening should be considered as a priority option in Bhutan and other resource-limited settings, if financially and technically feasible.

Introduction

In recent years, there has been increasing global recognition of the significant negative health and economic consequences of non-communicable diseases (NCDs) such as cardiovascular disease (CVD), diabetes, cancer and respiratory tract disease. According to one recent analysis of the global burden of disease, the last 10 years has seen an unprecedented rise in the levels of NCD-related morbidity and mortality (Lozano *et al.* 2012; Murray *et al.* 2012), with the majority of NCD-related deaths now occurring in low- and middle-income countries (LMIC) (World Health Organization 2008). Because NCDs disproportionately affect working age adults, this rise in NCD-related morbidity and mortality has particularly significant economic implications for LMICs.

Significant evidence has emerged on the benefits of early intervention and proper management for certain NCDs, such as CVD and diabetes (Chobanian *et al.* 2003; Furie *et al.* 2011; Qaseem *et al.* 2012). However, most of this evidence relies on data from randomized controlled trials (RCTs), and thus has limited generalizability (The World Bank 2011) for application in everyday clinical practice, particularly in low-resource settings. Very little research has yet been conducted into the cost-effectiveness of comprehensive programs for managing NCDs in LMICs. The World Health Organization (WHO) responded to the need for increased prevention and control of NCDs in LMICs by initiating the Package of Essential Non-communicable (PEN) disease interventions for primary health care in low-resource settings. The WHO PEN uses an integrated approach to assess and manage cardiovascular risk using hypertension and diabetes as entry points (World Health Organization 2010; Mendis and Chestnov 2013). In addition, PEN aims to strengthen primary health-care systems' ability to respond to the rise in NCDs by offering a set of cost-effective interventions for prevention and control that are feasible for implementation in resource-limited settings (World Health Organization 2010).

Bhutan is one of the LMICs where rising NCD rates have become a particularly challenging health problem. The NCDs account for 60% of the total burden of disease in terms of Disability-Adjusted Life Years (DALYs) lost (The World Bank 2011). Although there are few quality health statistics for NCDs, a study conducted by the Ministry of Health in the capital city, Thimpu, identified alarming data that 93% of the respondents were exposed to at least one of the common NCD risk factors, including unhealthy diet, physical inactivity, and consumption of alcohol and/or tobacco, more than 50% of the respondents were exposed to at least two of the risk factors, and more than 38% were exposed to at least three risk factors (Non-Communicable Diseases Division 2013). As a result, in 2009, the Ministry of Health of the Royal Government of Bhutan introduced several of the PEN interventions in two selected districts—Paro and Bumthang (Wangchuk *et al.* 2013). The interventions focused on diabetes and hypertension because implementation of screenings and treatments/lifestyle modifications for these diseases were deemed feasible within the primary health-care context of Bhutan.

Due to resource restrictions in LMIC health systems, there is often a gap between the planning and implementation of interventions. Given this, the PEN framework for implementation recommends that all programs begin with an evaluation of the likely impact and efficiency of the intervention program, emphasizing the importance of evidence-based implementation and program monitoring and evaluation (World Health Organization 2010). Given that most LMIC governments work within a context of multiple, often competing, health priorities, economic intervention evaluations can also help policymakers make evidence-based decisions about appropriate resource allocation. However, to date, very few evaluations of this kind been conducted on NCD prevention and control programs, particularly in resource-limited settings (Mulligan *et al.* 2006).

This article hopes to go some way to address this lack by assessing the cost-effectiveness of the PEN project implemented in Bhutan and analysing the costs and health consequences of the program in both the short and long term. A number of recommendations are made for the use of economic modelling to inform policy. The results of this study should be of use not only to the Bhutanese government but also to decision-makers in other resource-limited settings who are involved with the prevention and control of NCDs.

Methods

Overview of PEN interventions and policy options

Bhutan's PEN protocol informed the public about the criteria for blood glucose and blood pressure screenings. This includes patients who are aged 40 years or older, or overweight or obese [body mass index (BMI) 23+], or had a high waist circumference (WC) (WC >80 cm in females and >90 cm in males). Therefore, in order for the population to visit a health facility, they must perceive that their physical status matches the eligibility criteria. This recommendation is in line with recent findings that obesity is the best predictor of undiagnosed diabetes (odds ratio 3.2) (Junrungsee *et al.* 2011). Those diagnosed with diabetes and/or hypertension were treated according to Bhutan's PEN protocol, which focuses on lifestyle modification and medicine (Non-Communicable Diseases

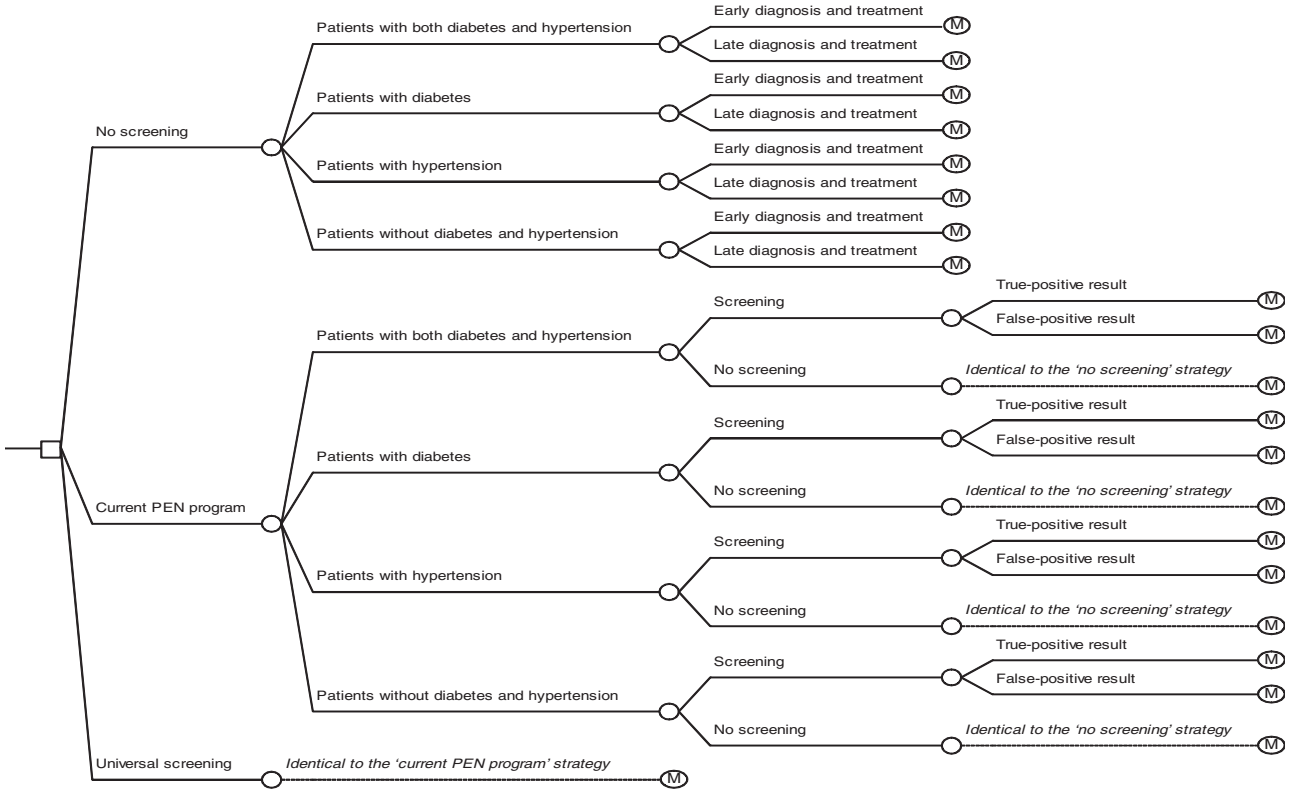

Figure 1 Decision tree model showing the three strategies for prevention and control of diabetes and hypertension.

Division 2013). Evidence from this pilot study found that screening coverage reached the program target at approximately 70% of the eligible population in the two districts studied. Another policy option is to scale up the screening program to cover the remaining 30% of the eligible population who did not perceive the risk or were not willing to visit a health facility for diabetes and hypertension screening. This strategy includes inviting the whole population aged 40 years or older or those who are younger but with perceived health risks by initiating more proactive public communication and invitations. The counterfactual scenario was set as no screening program, with most patients consequently receiving treatment at a later stage in the progression of either diabetes and/or hypertension.

Analysis and model

A model-based economic evaluation was performed to capture all of the costs and consequences of the entire pathway resulting from diabetic and hypertension screenings (from screening to death). The model consisted of a decision tree and a Markov model and was constructed using Microsoft Office Excel 2007 (Microsoft Corp., Redmond, WA). The lifetime costs and DALY averted were calculated for three possible strategies: 'no screening', 'current PEN program', and 'universal screening'. The decision tree diagram illustrating these three strategies can be found in Figure 1. In the two screening scenarios ('current PEN program' and 'universal screening'), all eligible patients underwent blood glucose and blood pressure testing. Patients who tested positive for diabetes and hypertension were then treated. In the 'no screening' option, the effect of medical treatments for diabetes and hypertension differs among the early- and late-stage of diagnosis.

For each strategy, three separate Markov models—one for diabetes, one for hypertension and one for diabetes with hypertension—were employed simultaneously to forecast the costs, complications and health outcomes associated with the diseases. The diabetes model contained the following seven health states: diabetes without complications, coronary artery disease, stroke, nephropathy, retinopathy, neuropathy and death (Figure 2a–f). The hypertension model contained the following health states: uncontrolled hypertension, controlled hypertension, stroke and death (Figure 3).

A cost-effectiveness analysis was conducted from the societal perspective. The lifetime time horizon for the adult cohort was 40 years or older, and the cycle length was set to 1 year. The main outcome measures were lifetime costs, DALY averted and the incremental cost-effectiveness ratio (ICER) per DALY averted. DALYs were calculated using WHO standard methods (World Health Organization 2003) without age weighting. In addition, the Monte Carlo simulation was performed to estimate costs and outcomes over a patient's lifetime. In accordance with the WHO's guideline (World Health Organization 2003), future costs and DALYs were discounted at a rate of 3%.

Model parameters

The model input parameters are presented in Table 1.

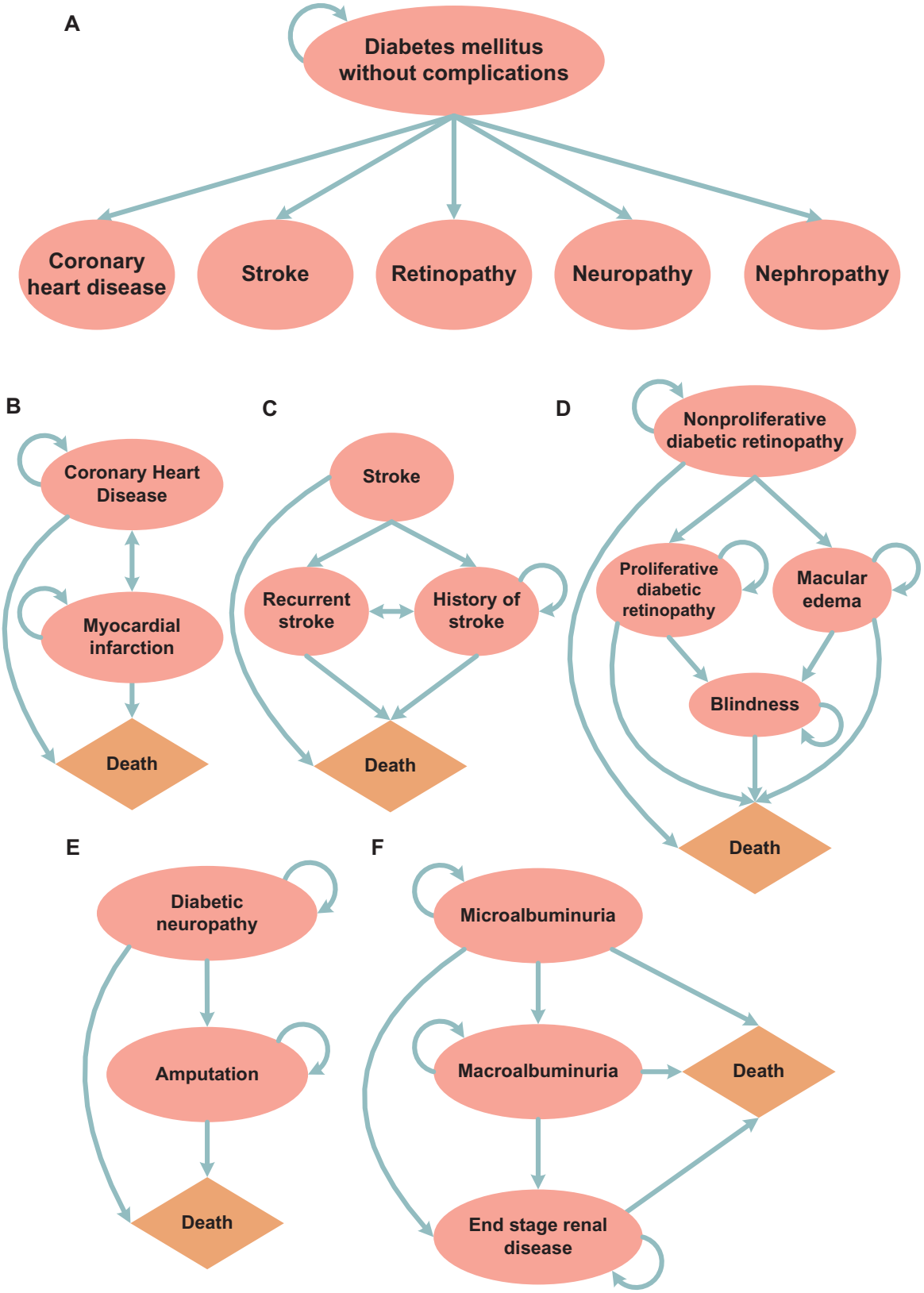

Figure 2 Markov model representing the possible events for (a) patients with diabetes without complications, (b) coronary artery disease, (c) stroke, (d) retinopathy, (e) neuropathy, (f) nephropathy and death.

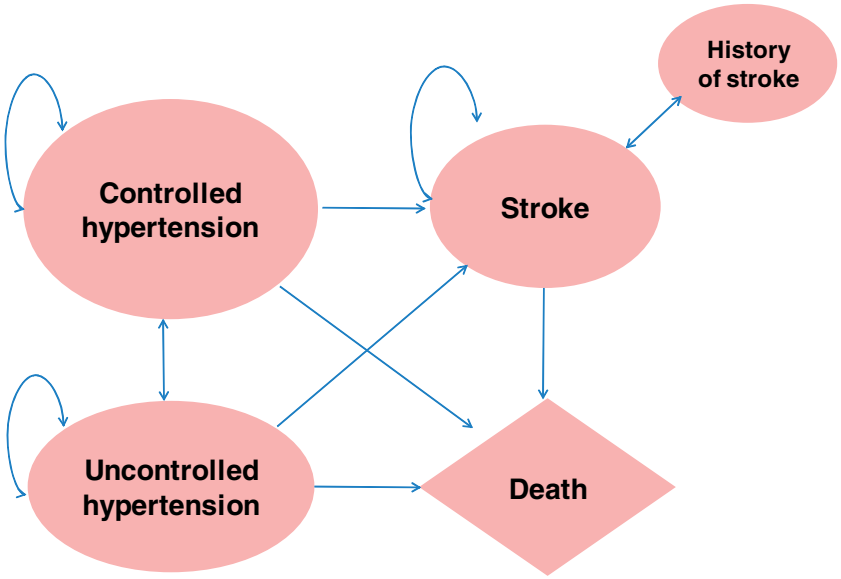

Figure 3 Markov model representing the events that could occur for patients with hypertension and its complications.

Table 1 Model input parameters

Parameters	Distribution	Mean	Standard error	Reference
Epidemiological parameter				
Proportion of hypertension in diabetes mellitus patients	Beta	54.1%	0.00122	Giri *et al.* (2013)
Prevalence of DM in Bhutan population aged 25–74	Beta	8.2%	0.00561	Giri *et al.* (2013)
Prevalence of hypertension	Beta	26%	0.0092	Giri *et al.* (2013)
Transitional probabilities				
Probability of death due to diabetes	Beta	0.0044	0.000001	Pratipanawatr *et al.* (2010)
Coronary artery disease				
Probability of patients developing coronary artery disease	Beta	0.0091	0.00001	Leelawattana *et al.* (2006)
Probability of patients developing myocardial infarction	Beta	0.0305	0.0004	World Health Organization (2010)
Probability of death due to myocardial infarction	Beta	0.1622	0.02	Srimahachota *et al.* (2012)
Probability of death due to coronary artery disease	Beta	0.0695	0.0003	Pratipanawatr *et al.* (2010)
Risk ratio of developing coronary artery disease	Normal	0.85	0.09	World Health Organization (2013)
Risk ratio of developing myocardial infarction	Normal	0.90	0.06	World Health Organization (2013)
Risk ratio of death due to coronary artery disease	Normal	1.11	0.13	World Health Organization (2013)
Stroke				
Probability of patients developing stroke	Beta	0.0055	0.0001	Leelawattana *et al.* (2006)
Probability of diabetic patients developing stroke	Beta	0.0095	0.0001	World Health Organization (2010)
Probability of death due to stroke	Beta	0.0013	0.0000004	Pratipanawatr *et al.* (2010)
Probability of death due to recurrent stroke	Beta	0.0024	0.0000004	Pratipanawatr *et al.* (2010)
Risk ratio of developing stroke	Normal	0.96	0.08	World Health Organization (2013)
Risk ratio of developing previous stroke	Normal	0.96	0.08	World Health Organization (2013)

(continued)

Table 1 Continued

Parameters	Distribution	Mean	Standard error	Reference
Risk ratio of death due to stroke	Normal	1.11	0.13	World Health Organization (2013)
Retinopathy				
Probability of patients developing diabetic retinopathy	Beta	0.0388	0.00003	Leelawattana *et al.* (2006)
Probability of progression from non-proliferative diabetic retinopathy to proliferative diabetic retinopathy	Beta	0.08	0.0102	Vijan *et al.* (2000)
Probability of progression from non-proliferative diabetic retinopathy to macular oedema	Beta	0.03	0.0102	Vijan *et al.* (2000)
Probability of progression from diabetic retinopathy to blindness	Beta	0.09	0.0102	Vijan *et al.* (2000)
Probability of progression from macular oedema to blindness	Beta	0.05	0.0102	Vijan *et al.* (2000)
Mortality multipliers for non-proliferative diabetic retinopathy	Normal	1.49	0.08	Vijan *et al.* (2000)
Mortality multipliers for proliferative diabetic retinopathy	Normal	1.76	0.03	Vijan *et al.* (2000)
Mortality multipliers for macular oedema	Normal	1.76	0.03	Vijan *et al.* (2000)
Mortality multipliers for blindness	Normal	2.34	0.03	Vijan *et al.* (2000)
Risk ratio of patients developing diabetic retinopathy	Normal	0.85	0.09	Coca *et al.* (2012)
Risk ratio of blindness	Normal	1.0	0.02	Coca *et al.* (2012)
Neuropathy				
Probability of patients developing amputation	Beta	0.0013	0.000001	Leelawattana *et al.* (2006)
Probability of patients developing foot ulcer	Beta	0.0069	0.00001	Leelawattana *et al.* (2006)
Probability of patients developing peripheral artery disease	Beta	0.0041	0.000004	Leelawattana *et al.* (2006)
Probability of progression from neuropathy to amputation	Beta	0.0015	0.000002	Krittiyawong *et al.* (2006)
Probability of death due to neuropathy	Beta	0	0	Pratipanawatr *et al.* (2010)
Probability of death due to amputation	Beta	0.1001	0.0045	Junrungsee *et al.* (2011)
Risk ratio of developing neuropathy	Normal	0.99	0.02	World Health Organization (2013)
Risk ratio of developing amputation	Normal	0.84	0.22	World Health Organization (2013)
Risk ratio of death due to amputation	Normal	0.84	0.22	World Health Organization (2013)
Nephropathy				
Probability of patients developing diabetic nephropathy	Beta	0.0835	0.00004	Leelawattana *et al.* (2006)
Probability of progression from microalbuminuria to macroalbuminuria	Beta	0.028	0.0018	Adler *et al.* (2003)
Probability of progression from macroalbuminuria to end stage renal disease	Beta	0.023	0.0038	Adler *et al.* (2003)
Probability of progression from microalbuminuria to end stage renal disease	Beta	0.003	0.0008	Adler *et al.* (2003)
Probability of death due to microalbuminuria	Beta	0.030	0.002	Adler *et al.* (2003)
Probability of death due to macroalbuminuria	Beta	0.046	0.0054	Adler *et al.* (2003)
Probability of death due to end stage renal disease	Beta	0.192	0.0265	Adler *et al.* (2003)
Risk ratio of developing microalbuminuria	Normal	0.86	0.06	Coca *et al.* (2012)
Risk ratio of developing macroalbuminuria	Normal	0.74	0.07	Coca *et al.* (2012)

(continued)

Table 1 Continued

Parameters	Distribution	Mean	Standard error	Reference
Risk ratio of developing end stage renal disease	Normal	0.69	0.21	Coca *et al.* (2012)
Risk ratio of death due to renal disease	Normal	0.99	0.30	Coca *et al.* (2012)
Hypertension				
Probability of progression from uncontrolled hypertension to controlled hypertension	Normal	0.7258	0.0006	a
Probability of progression from controlled hypertension to uncontrolled hypertension	Beta	0.05		Assumption
Probability of patients with controlled hypertension developing stroke	Beta	0.0070	0.0001	a
Probability of patients with uncontrolled hypertension developing stroke	Beta	0.0146	0.0004	a
Probability of death due to controlled hypertension	Beta	0.0285	0.00002	Blood Pressure Lowering Treatment Trialists' Collaboration (2000)
Probability of death due to uncontrolled hypertension	Beta	0.0239	0.00001	Blood Pressure Lowering Treatment Trialists' Collaboration (2000)
Probability of death due to stroke	Normal	2.72	0.02	Lovibond *et al.* (2011)
Intervention effectiveness				
Sensitivity of screening for diabetes (capillary blood glucose)	Beta	84%		Rolka *et al.* (2001)
Specificity of screening for diabetes (capillary blood glucose)	Beta	88%		Rolka *et al.* (2001)
Sensitivity of screening for hypertension (ambulatory blood pressure monitoring)	Beta	100%		Lovibond *et al.* (2011)
Specificity of screening for hypertension (ambulatory blood pressure monitoring)	Beta	100%		Lovibond *et al.* (2011)
Risk reduction of intensive glycaemic and hypertension control	Normal	0.46	0.046	CDC Diabetes Cost-effectiveness Group. (2002)
Relative risk of intensive hypertension control	Normal	0.70	0.1	Blood Pressure Lowering Treatment Trialists' Collaboration (2000)
Costs (BNT per year)				
Screening				
Diabetes (capillary blood glucose)	Gamma	1966		
Hypertension (ambulatory blood pressure monitoring)	Gamma	1721		
PEN program (per patient)	Gamma	28		a
Costs of treating diabetes and follow up				
Direct medical cost				
No complication	Gamma	24 100	13 427	
Coronary artery disease	Gamma	1 904 000	311 542	
Stroke	Gamma	337 500	73 299	
Nephropathy	Gamma	261 314	35 942	
Retinopathy	Gamma	25 107	14 309	
Neuropathy	Gamma	83 807	16 477	
Direct non-medical cost				a
No complication	Gamma	531	173	
Coronary artery disease	Gamma	2214	536	
Stroke	Gamma	2214	536	
Nephropathy	Gamma	2214	536	
Retinopathy	Gamma	531	173	
Neuropathy	Gamma	531	173	

(continued)

Table 1 Continued

Parameters	Distribution	Mean	Standard error	Reference
Costs of treating hypertension and follow up				
Direct medical cost				
No complication	Gamma	25 371	13 500	
Stroke	Gamma	337 500	73 299	
Direct non-medical cost				a
No complication	Gamma	531	173	
Stroke	Gamma	2214	536	
Disability weight				
Diabetes	Beta	0.015	0.002	World Health Organization (2004)
Coronary artery disease	Beta	0.246	0.025	
Stroke	Beta	0.920	0.092	
Previous stroke	Beta	0.266	0.017	
Nephropathy	Beta	0.091	0.006	
Neuropathy	Beta	0.072	0.003	
Blindness	Beta	0.552	0.021	
Myocardial infarction	Beta	0.439	0.018	
End stage renal disease	Beta	0.098	0.005	
Amputation	Beta	0.102	0.017	

[a]Analysis of primary data collected by the authors.

Epidemiological data

Prevalence was calculated using data provided by Giri *et al.* (2013). The prevalence of diabetes, hypertension and diabetes and hypertension was 2.08, 26 and 6.12%, respectively.

Health state transitional probabilities

Transitional probabilities between health states were obtained from published studies, as shown in Table 1. This contains the probabilities of disease occurrence, the probabilities of developing complications and the probabilities of death. In the model analysis, data on relative risk reduction of complication or death events from patients with diabetes and hypertension who were receiving medication was also taken into consideration. For example, patients taking angiotensin-converting enzyme (ACE) inhibitors had a stroke risk 30% lower compared with those taking a placebo [four trials, 12 124 patients: relative risk (RR) 0.7, 95% confidence interval (CI) 0.57 to 0.85] (Blood Pressure Lowering Treatment Trialists' Collaboration 2000).

Intervention effectiveness

The sensitivity and specificity of the screening for diabetes and hypertension were derived from the international literature. In the model, sensitivity was set to 84% and specificity to 88% for the capillary blood glucose tests (Rolka *et al.* 2001); sensitivity and specificity were both set to 100% for the sphygmomanometer due to its extremely high levels of accuracy and it is considered to be a gold standard diagnosis (Lovibond *et al.* 2011).

Because no local information was available, baseline probabilities of developing complications due to diabetes were derived from the Thai Diabetic Registry, which contains historical data of more than 5000 Thai diabetic patients (Krittiyawong *et al.* 2006). Local data from approximately 1000 hypertensive patients in Paro and Bumthang, some whom underwent screening and subsequent treatment, and some of whom did not, was used to estimate outcomes in terms of controlled vs uncontrolled hypertensions. According to the PEN protocol, the controlled hypertension defines as having a blood pressure of less than 140/90 mmHg, and otherwise for the uncontrolled hypertension ($\geq$140/90 mmHg). Baseline probabilities for patients with uncontrolled hypertension suffering a stroke and death were derived from a model developed by Lovibond *et al.* (2011).

The effectiveness of early- and late treatment for diabetes was from two large systematic reviews and meta-analyses—Boussageon *et al.*'s. on microvascular complications (World Health Organization 2013) and Coca *et al.*'s (2012) on macrovascular complications. It was found that intensive treatment reduces the risk of complications significantly more for microvascular complications than it does for macrovascular complications. The model assumed the results from the intensive treatment would be equivalent to the early treatment of diabetes. A systematic review and meta-analysis comparing the risks associated with uncontrolled (which was assumed to be the same as a placebo scenario) and controlled hypertension conducted by the Blood Pressure Lowering Treatment Trialists' Collaboration found that controlled hypertension reduced stroke incidence by 30% (95% CI, 0.57–0.85) (Blood Pressure Lowering Treatment Trialists' Collaboration 2000). For those with co-morbidities, diabetes with hypertension, we assumed similar outcomes to those for diabetes treatment, because the majority of diabetes patients in trials also had hypertension.

Cost and disability weights

Costing data was garnered using a standard questionnaire which was used to survey 16 key informants including

Table 2 Lifetime costs and health outcomes of each strategy using a societal perspective

Options	Costs (BTN)	Incremental LYs	Incremental DALYs averted	ICER (BTN per DALY averted)
No screening	210 023	–	–	–
Current PEN program	205 735	0.018	0.038	−112 906
Universal screening	203 897	0.008	0.016	−112 906

BTN, Bhutanese Ngultrum (value as of 2013); DALYs, disability adjusted life years; ICER, incremental cost-effectiveness ratio; LYs, life years.

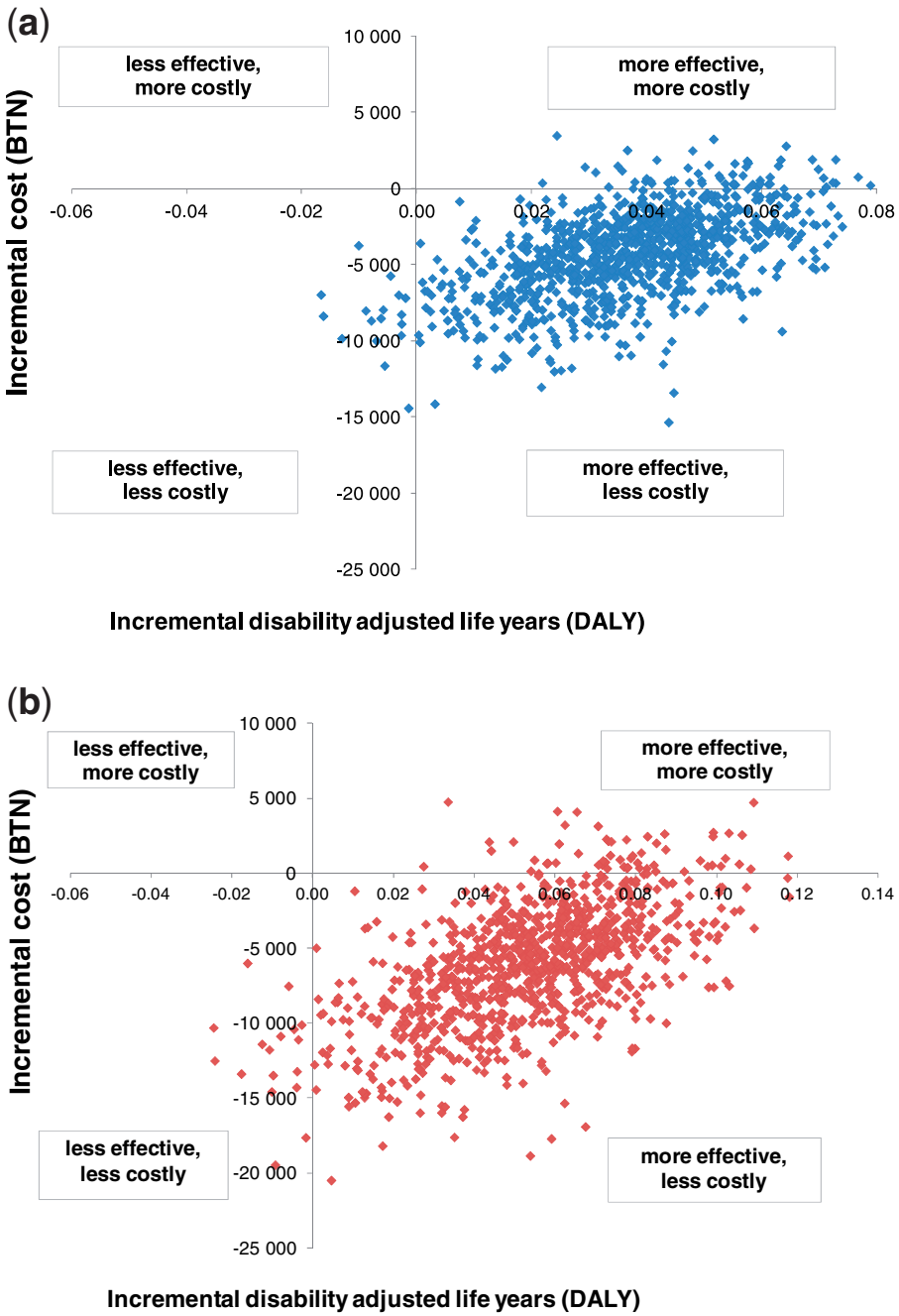

Figure 4 (a) Cost-effectiveness plane demonstrating the incremental costs and incremental disability-adjusted life years (DALYs) of 'current PEN program' compared with 'no screening. (b) Cost-effectiveness plane demonstrating the incremental costs and incremental disability-adjusted life years (DALYs) of 'universal screening' compared with 'no screening'.

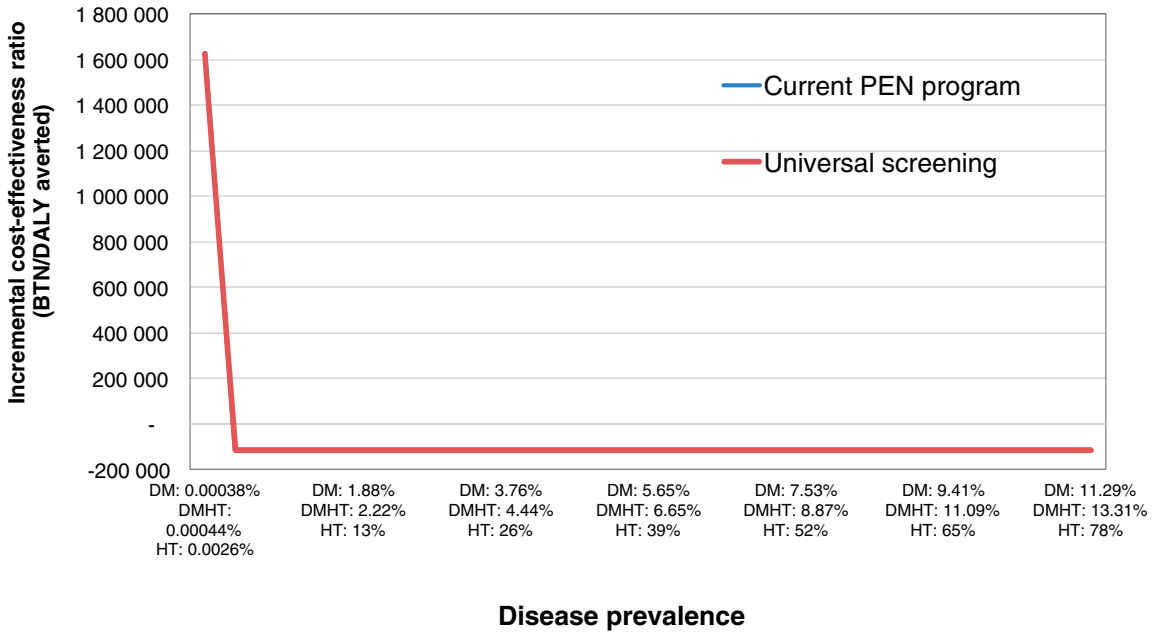

Figure 5 One-way sensitivity analysis on the prevalence of diabetes, co-morbidity of diabetes and hypertension, and hypertension, resulting in different incremental cost-effectiveness ratios of 'current PEN program' and 'universal screening' compared with 'no screening'. DM, diabetes; DMHT, diabetes with hypertension; HT, hypertension.

clinicians, pharmacists and public health experts in Bhutan. A societal perspective was adopted; as a result, both direct medical costs and direct non-medical costs are included in the model. Direct medical costs refer to the screening costs, the annual cost of treating the diseases and its complications, while direct non-medical costs refer to travel and food costs, personal facilities and opportunity costs incurred by patients. All costs were derived from 2013 values and presented in Bhutanese Ngultrum (BTN), as summarized in Table 2. For international comparison, costs can be converted into international dollars using the purchasing power parity (PPP) conversion rate. A PPP 2013 dollar is worth 22.144 BTN (The International Monetary Fund 2013).

The number of DALYs was based on the Years of Life Lost (YLL) due to premature mortality and the Years Lost due to Disability (YLD) of patients with diabetes, hypertension and resulting complications. YLDs are calculated using a disability weight for each health condition. The weight reflects the severity of the disease ranging from 0 (perfect health) to 1 (death). The disability weights of diabetes, hypertension and resulting complications were identified by the Global Burden of Disease Project (World Health Organization 2004). A standard life table with a life expectancy of 82.5 years was applied. Detailed information on the disability weights exploited in the model is presented in Table 2.

Uncertainty analyses

A probabilistic sensitivity analysis (PSA) was undertaken to explore the impact of parameter uncertainty. A cost-effectiveness analysis was also undertaken using a range of input parameters, depending on their distribution. In each simulation, one value from each variable was sampled to estimate the costs and DALYs. The model was run through 1000 simulations. The results were presented as a cost-effectiveness acceptability curve, and compared to the willingness-to-pay of 159 168-477 504 BTN/DALY averted (The International Monetary Fund 2013). In addition, a one-way sensitivity analysis was conducted where the lower and upper limits (95% confidence interval) of certain input parameters were analysed to examine the effect of that parameter on the cost-effectiveness so that the main influential parameters could be identified.

Results

Table 2 displays the probabilistic results of life-time costs, life-years gained, DALY averted and ICERs of all scenarios. Both the current PEN program and universal screening had lower life-time costs and higher health gains than no screening, and both screening scenarios had negative ICERs, showing they were cost-saving interventions. Figure 4 illustrates the cost-effectiveness planes generated from 1000 model simulations. Each dot shows how the possible costs and health gains compare between the current PEN program and no screening (Figure 4a), and universal screening and no screening (Figure 4b). Results confirm that the current PEN program and universal screening are certainly cost-effective and, most likely, cost-saving options in Bhutan.

Figure 4 depicts the cost-effectiveness acceptability curves for all options and demonstrates that both the current PEN program and universal screening are superior to no screening, at any willingness-to-pay threshold. Figure 5 shows the cost-effectiveness data from selected levels of diabetic and hypertension prevalence (threshold analysis). The current PEN program is shown to be a cost-saving intervention, as long as the prevalence of diabetes and hypertension is higher than 0.3 per 1000 people in the population. This is significantly lower

than the current prevalence of diabetes and hypertension in Bhutan, which is 342 per 1000 people in the population (2 per 1000 for diabetes, 6.12 per 1000 for diabetes and hypertension, and 26 per 1000 populations for hypertension alone).

Discussion

The WHO PEN is an innovative and action-oriented way for LMICs to reduce the burden of NCDs. By focusing on primary care interventions in low-resource settings, the program can help LMICs to ensure efficient resource use, sustainable health financing, and equitable access to basic essential health services. This is the first economic evaluation of PEN and the first economic evaluation of a joint diabetes and hypertension screening program in a resource-limited setting. The findings clearly illustrate that the current policy in Bhutan, i.e. opportunistic screening for diabetes and hypertension using the PEN approach, represents good value for money. The findings also suggest that expansion of this to a universal screening program may be even more cost-efficient. The results support the WHO's standpoint, which indicates that the WHO PEN is very cost-effective and feasible to implement in all countries (World Health Organization 2013). The findings are in line with those from previous studies that assessed the cost-effectiveness of diabetic screening (although all of these have been conducted in resource-rich settings) (Mendis and Chestnov 2013).

Furthermore, our results are consistent with those from the previous clinical studies that show the substantial benefit of the effective management of diabetes compared to hypertension. Indeed, the results of this study may somewhat overestimate the clinical benefit of screenings because similar health outcomes were assumed for both ambulatory screening visits and community screenings initiated on the basis of age. In addition, due to data limitation, this study did not assess the—potentially larger—impact of lifestyle modification in preventing diabetes and hypertension among those with negative screenings. As a result, we believe that the results of the analysis are likely to be conservative and the scaling-up of diabetic and hypertension screenings to a national-wide program should be a priority in Bhutan. Moreover, this study further recommends universal screening instead of opportunistic screening at primary care facilities because of the relatively high prevalence of diabetes in the Bhutanese population. If financially and technically feasible, universal screening though community-based programs should be introduced.

As with any study, particularly in a new and relatively unexplored area, our analysis contains certain limitations. First, the results apply only to one particular setting—Bhutan. Nevertheless, the inclusion of a sensitivity analysis allows different disease prevalence to be inputted into the model, enabling the study results to be used in other settings with similar health and economic infrastructures. Second, this study examines one-off, rather than sequential, screening options. Although PEN does not state how often diabetes screening should be performed, the American Diabetes Association recommends repeated screenings at least every 3 years for those who have received a negative screening result. The value for money of repeated screenings in Bhutan and other resource-limited settings is, as yet, unclear. Third, without availability of local data, the long-term treatment effectiveness was derived from the international literature rather than assessment of pilot districts—a limitation that may affect the results of this study. However, an evaluation of the short-term outcomes in the pilot districts did indicate a significant reduction of CVD risk and increased healthy lifestyle of the target population (Wangchuk *et al.* 2013), suggesting that this limitation is unlikely to be a factor that will affect the results. Fourth, costs were obtained from local experts rather than from costing data collected from local health providers. Although, some costs were validated with previous study data and found to be consistent, indicating that this limitation is also unlikely to result in a different study conclusion. Furthermore, we assumed a large standard error (equal to the mean) for each cost parameter and extensively assessed the impact of this in the PSA. A prospective costing study should be conducted in the future to complement our findings. Fifth, we assume that the unit cost per person screened, which includes community engagement, training staff, and providing services, of the target 30% that are not covered by the program is equivalent to the unit cost of the current policy. This is a linear assumption, which may not be true because the 30% of the population may be a marginal group that requires higher unit cost. However, due to a lack of data about the cost of access to the 30% and because we found that the PEN program is very cost-effective, scaling up the program to coverage at the highest level should be worthwhile. This is also to send the message to decision makers that although the previous target of 70% of the population has been reached, the country should aim for a coverage that is as high as possible. Lastly, this study did not include data on primary NCD prevention interventions either at a population level (such as laws or taxation aimed at reducing consumption of tobacco, alcohol or high-fat food) or at an individual level (such as increased physical activity or following a lower fat diet). Because these kinds of interventions are likely to be even more cost-effective than screenings and treatments of diabetes and hypertension, Bhutan and other countries that use this study as a resource should consider integrating these kinds of interventions alongside PEN screening and treatment options.

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SCHWERPUNKT

The use of economic evaluation for guiding the pharmaceutical reimbursement list in Thailand

Kosten-Nutzen-Bewertungen als Instrument zur Festlegung der Liste von zu erstattenden Arzneimitteln in Thailand

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KEYWORDS
Health economic evaluation;
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Summary Medicines expenditure consumes a significant proportion of public health expenditure in Thailand, where Universal Health Coverage has been in place since 2002. The National List of Essential Medicines has been successfully used as a pharmaceutical benefits package for all public health plans. All patients are eligible for all medicines included in the list free of charge by law. Health economic evaluation has been employed as a tool for the development of this list, including price negotiation of medicines before inclusion, especially of high-cost medicines or medicines with high budget implications. This paper illustrates the current process, mechanisms, and impact and informs of seven success factors that have contributed to the successful use of health economic evaluation in Thailand. These include strong political commitment, development of individual and institutional capacity, participation of all relevant stakeholders, establishment of standard methodological and process guidelines, consideration of several elements in the decision-making process, using evidence as a starting point rather than a deciding factor, and strong enforcement. The lessons learned from this study are likely to be applicable to other settings committed to evidence-based decision making.

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SCHLÜSSELWÖRTER
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Erstattung;
Entscheidungsfindung

Zusammenfassung Ausgaben für Arzneimittel machen einen großen Anteil der öffentlichen Gesundheitsausgaben in Thailand aus, wo seit 2002 eine umfassende Gesundheitsversorgung besteht. Die sogenannte National List of Essential Medicines wurde erfolgreich genutzt, um damit ein Paket von erstattungsfähigen Arzneimitteln für alle öffentlichen Krankenversicherungssysteme zu schnüren. Allen Patienten werden die darin gelisteten Arzneimittel ohne weitere Zuzahlung gesetzlich garantiert. Dabei dienen Kosten-Nutzen-Bewertungen als Instrument für die Erstellung dieser Liste und liefern Informationen für Preisverhandlungen, insbesondere für sehr teure Arzneimittel und Arzneimittel mit hoher Ausgabenwirkung.

Im vorliegenden Beitrag werden der derzeitige Prozess, die Mechanismen und der Effekt von Kosten-Nutzen-Bewertung in Thailand dargestellt. Aus Sicht der Autoren haben sieben Faktoren dazu beigetragen, dass die Kosten-Nutzen-Bewertung so effektiv in der Entscheidungsfindung genutzt werden kann: politischer Wille und Einsatz, Entwicklung der personellen und institutionellen Ressourcen und Expertise, Beteiligung aller relevanten Akteure, Einführung methodischer und prozessualer Standards, Berücksichtigung mehrerer Kriterien in der Entscheidungsfindung, Evidenz als Ausgangspunkt und nicht als einziges Entscheidungskriterium und eine klare Umsetzung. Die Autoren gehen davon aus, dass diese Erfahrungen und Erkenntnisse auch auf andere Länder übertragbar sind, die sich der Entscheidungsfindung auf Grundlagen der evidenzbasierten Medizin verpflichtet fühlen.

Introduction

Since 2002, Thailand has been recognized as one of the few lower-middle income countries that has introduced Universal Health Coverage (UHC) [1]. Although UHC was achieved, Thailand has a pluralistic healthcare system in which three public health insurance schemes exist. These are the Civil Servants Medical Benefits Scheme (CSMBS) for government employees and their dependents, the Social Security Scheme (SSS) for private employees, and the Universal Health Coverage Scheme (UHCS) for the remaining population [2]. These three schemes apply different provider payment mechanisms and invest differently in terms of per capita health expenditures (Table 1).

Economic Evaluation for Universal Health Coverage

Between 2000 and 2007, the Thai government almost doubled its health investments, good quality health service became a right, and even more so, it was viewed as an inherent right by all Thai people. An increase in health investments, however, requires careful consideration of a long-term budget impact and a sustainable UHC. As a result, the introduction of UHC was coupled with an increasing pressure to consider the value for money of health investments.

During this period, the capacity for using health economic evaluations for health resource allocation had not yet reached the level at which it could make a significant contribution to public policy. A systematic review found an increasing trend in economic evaluation studies conducted from the year 1982, when the first study was published in an international journal, and 2005 [3]. However, there were a number of serious problems in terms of the quality of the studies conducted and the irrelevancy of the topic with regard to policy. For example, studies applied different methods and used inconsistent quality of data, resulting in an incomparability of studies to inform allocative efficiency. Furthermore, many of the studies were conducted based on personal interest of the researchers, without any stakeholder consultation, or initiated by funders who were mainly international organizations or the industry. These practices led to a call for a standardized method and systematic identification of topic priorities for health economic evaluation studies.

An Initiative for Economic Evaluation Reform

In 2007, the Health Intervention and Technology Assessment Program (HITAP) was established with the aim of promoting evidence-based resource allocation focusing on the use of health technology assessment (HTA), of which economic evaluation plays a major role. HITAP is not only mandated to generate evidence for policymaking, but it also builds up human capacity, develops health technology assessment infrastructure, and communicates and disseminates HTA results to all stakeholders [4]. The decision makers who use HITAP's evidence to inform their policy decisions include the Ministry of Public Health, the National Health Security Office (which manages the UHC scheme), the National Science Technology and Innovation Policy Office, and the National Research Council of Thailand.

In 2008, HITAP issued the first method guidelines for conducting health economic evaluation to help develop HTA infrastructure in Thailand [5]. The aim of this guideline was to create a standard for all economic evaluation studies in order to facilitate minimal variations in methodology and support the use of high quality data. A number of decision-making bodies endorsed the guidelines, leading to the release of a second version in 2013. Apart from the guidelines, HITAP also conducted a study on the willingness to pay per quality-adjusted life year (QALY) among Thai households and its results were adopted by multiple decision-making bodies as the appropriate threshold for health investment in the Thai setting, which is around 1-1.5 times of Gross National Income (GNI) per capita [6].

To ensure that the evidence generated by HITAP is pivotal to the decision-making process, two-way communication

Table 1 Characteristics of three public health insurances in Thailand.

Scheme (year of establishment)	Beneficiaries	Coverage	Source of fund	Payment method
Civil Servant Medical Benefit Scheme (1963)	Government employees, retirees and dependents	6 millions, 10%	General tax, non contributory	Fee for service reimbursement model
Social Security Scheme (1990)	Private sector employees	8 million, 13%	Payroll tax tripartite contribution	Capitation inclusive for all ambulatory and inpatient care
Universal Coverage Scheme (2002)	Population not eligible for the above two schemes	47 million, 74%	General tax, non contributory	Capitation for ambulatory care and case mix for inpatient care

with relevant stakeholders is a key factor. HITAP managed this by conducting a capacity gap survey for both decision-makers and researchers to understand their level of understanding of health economic evaluation and the need for further learning [7]. The survey results were used to design the first two-day basic health economic evaluation workshop given to decision makers and three-day advanced economic evaluation modeling workshop for researchers, both of which now run annually. These workshops have continued to run for the last ten years, making it one of the longest running health economic evaluation training workshops in Asia. It has expanded to occasionally include training for international scholars from Vietnam, the Philippines, Myanmar, India, and Bhutan. By keeping an open channel of information exchange between stakeholders, the workshops have consequently benefitted over 1,200 participants.

National List of Essential Medicines

In addition to HITAP's role in advising the benefits package for UHC, which includes applying health economic evaluation for medical devices, vaccines, and public health interventions [8,9], the research unit has also successfully employed HTA to inform the National List of Essential Medicines (NLEM). Thailand spends around 3.9% of GDP on health and the public sector contributes to approximately 76% of the total health expenditure [10]. A majority of this expenditure is spent on medicines, which accounted for approximately 134 billion Baht in 2010 (45 Baht = 1 Euro as of March 14, 2014). This vast expenditure signifies the extent to which medicines play a significant part in the Thai health system. However, Thailand relies heavily on imported medicines and around 74% of the total medicines expenditure is accounted for by imports from multinational companies. In order to ensure equitable access to medicines across public health programs, the government requires all three public insurance schemes to provide a list of medicines issued by the NLEM at all public health facilities. Therefore, only medicines on the NLEM are reimbursable pharmaceuticals in Thailand. Although it is unlikely that patients under the UHCS and SSS can have drugs reimbursed outside the NLEM, the CSMBS allows patients to have drugs reimbursed outside the NLEM if there are at least three physicians who confirm the need for the drug.

The concept of Thailand's NLEM differs from the World Health Organization's (WHO) Model List of Essential Medicines in that, whereas the WHO list is a minimum requirement list, Thailand's NLEM is an optimum list. At the moment, the NLEM has more than 700 items of active ingredients and 1000 dosage forms [11]. When the NLEM was first introduced in 1981, only cost, safety, and efficacy were considered as criteria for inclusion whereas effectiveness was added to the list of criteria in 2004. Since 2008, cost-effectiveness has also been added as a criterion for the consideration of including new medicines. As of 2009, the NLEM can be divided into six categories, which are A, B, C, D, E1, and E2 (see Table 2).

High-cost medicines or medicines with high budget impact are unlikely to be available for patients under the SSS and UHCS unless they are included in the E2 category. The E2 medicines are purchased by the government at the central level (as opposed to purchase at hospital level for category A-D medicines) and are supplied to the hospitals that dispense them. It requires a pre-authorization and auditing system for review in order to ensure appropriate use of these high-cost or high budget impact medicines. For the CSMBS with fee for service payments, the medicines are purchased by hospitals so it is often at a higher cost than purchases made centrally by the government. For the medicines on the E2 list, economic evaluation and budget impact analysis (BIA) information is required for the Sub-committee for the development of the National List of Essential Medicines to consider in decision-making.

Table 2 Categorization of Medicines on the NLEM.

Category	Type of Medicine
A	Basic medicines that every health facility must make available
B	Alternative, second-line medicines of those in category A
C	Medicines prescribed only by specialists
D	Medicines used only for particular indications and diseases
E1	Medicines used for special or vertical programs
E2	Medicines that are of high cost but are important for particular groups of patients.

Table 3 Thai guidelines for pharmacoeconomic research.

Guideline item	Explanation of the requirement for pharmacoeconomic research
Study perspective	The economic evaluation should be conducted using a societal perspective.
Comparator	The drug should be compared to the standard intervention that is currently offered by the public health insurance. If there is no publicly funded intervention available, the common practice is recommended.
Analysis technique	Cost utility analysis is highly recommended in order to support allocative efficiency. In particular cases, cost-effectiveness analysis or cost-benefit analysis can be used with good justification.
Time horizon	A time horizon is sufficient in order to capture potential costs and consequences of all interventions being considered.
Costing methods	A standard costing menu, which is a standard list of unit costs of direct medical, direct non-medical and indirect costs in Thailand, is recommended. This is to ensure compatibility of costing inputs across studies and to overcome resource and time constraints for health technology assessment. Primary data collection on costs, using both macro- and micro-costing approaches, is also acceptable with good justification.
Quality of life methods	EQ5D with the Thai preference score is the most preferable option. Other standard health-related quality of life measures, such as HUI or SF36 as well as TTO and SG, are also acceptable.
Modeling techniques	Epidemiological modeling is acceptable in order to capture long-term consequences of interventions. The model should be conducted in a transparent manner and based on high-quality input data, such as systematic reviews or national databases.
Incremental methods	Incremental costs and incremental outcome should be reported alongside incremental cost-effectiveness ratio.
Discounting	All costs and outcome beyond 1 year should be discounted with a 3% discount rate.
Sensitivity analysis	A probabilistic uncertainty analysis is recommended, although a one-way sensitivity analysis and threshold analysis is accepted.
Expert panels	Expert panels should be used to verify the model and study results, including fine-tuning policy recommendations. It is also acceptable that the expert panel provides input parameters in the case of a lack of primary data.

Health Economic Working Group

In order to monitor the high-cost and budget implications of the medicines, a health economic working group (HEWG), which functions under a Sub-committee for the development of the NLEM, operates to develop processes and mechanisms, generates evidence to support decision-making, and assures quality [12]. To ensure a multidisciplinary approach, the working group consists of health economists, representatives from the Sub-committee, academics, representatives from the three health insurance schemes, and the secretariat, which is a joint position occupied by the Thai Food and Drug Administration (FDA) and HITAP. The working group enforced the standard method guidelines to ensure quality and compatibility of studies; it also endorsed process guidelines for conducting health economic evaluation (see Table 3).

After expansive consultation with all stakeholders, including the private sector, the process guidelines were adopted in 2010. These guidelines inform researchers and scholars about how to conduct a health economic evaluation, starting with fine-tuning the topic. The process guidelines also delineate a very clear timeframe and channel for involvement of each stakeholder taking part in the health economic evaluation study. These, for example, are decisions on the length of the evaluation process itself (twenty four weeks from the start of the process until completion) as well as when and how stakeholders can provide input to the studies. The guidelines also stipulate that researchers must organize a stakeholder consultation meeting prior to completing the study.

During the first few years after the establishment of HITAP, most of the requests for HTA by decision makers were made on an ad hoc basis; however, due to an increase in demand for health economic evaluation and evidence from the Sub-committee, the health economic working group proposed a program framework which was also endorsed by the Sub-committee in 2010 (see Figure 1). The framework acts as a guide for (the topic for) health economic evaluation studies in support of the development of the NLEM. At the outset, seventeen groups of experts informed on the topic and in 2013 the number of groups increased to twenty. The groups of experts include, for example, cardiologists, neurologists, psychiatrists, infectious disease specialists, nephrologists, ophthalmologists, etc. Once these groups identify the topic, they collect information about efficacy, safety, and costs. If the costs are likely to be high, they pass the topic onward to the Sub-committee, which considers the information and decides whether a health economic evaluation should be conducted. Although cost-effectiveness is a key factor in the decision-making process, the Sub-committee has the opportunity to consider both the results presented by the working group as well as other social aspects.

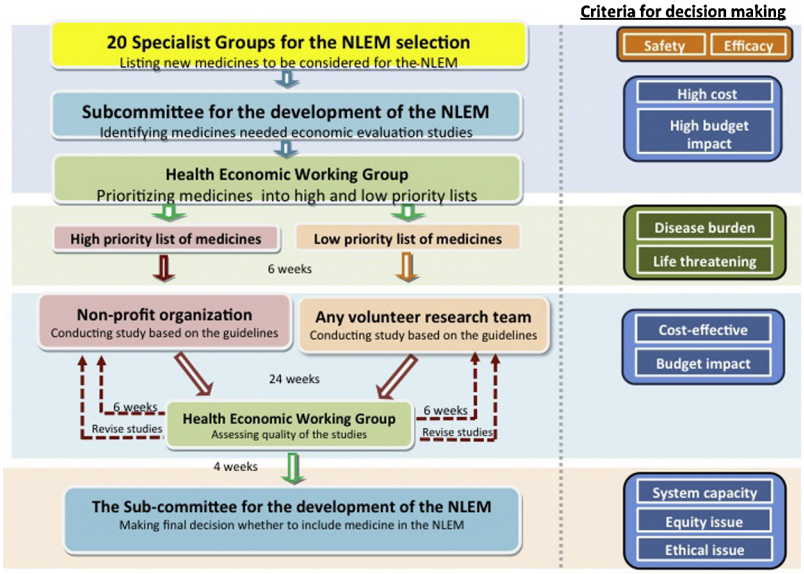

Figure 1 Framework in incorporating health economic evidence into pharmaceutical reimbursement list.

Before requesting the HEWG to conduct an economic evaluation, the Sub-committee first prioritizes the list of topics according to the burden of disease and the degree to which the condition is considered life threatening. For the final list of priorities, the Sub-committee will request non-profit organizations that are part of the HEWG, such as HITAP and most university research centers, to conduct a study with a timeline of twenty-four weeks with financial support from the public health insurance schemes. The study includes quality assessment through internal (HEWG members) and external (experts outside the HEWG) review, and if approved, the HEWG presents the results to the Sub-committee. On the other hand, low priority topics that are not within the capacity of the HEWG, which normally conducts only (approximately) 12 to 15 studies per year, will be announced for those who are interested in submitting a proposal to conduct the study voluntarily without payment. These can be non-profit organizations outside the working group as well as for-profit organizations such as pharmaceutical companies. Nevertheless, these organizations are required to follow the method and process guidelines that are first reviewed by the HEWG.

To date, thirty-two studies have been conducted by the HEWG, while private companies have conducted four studies (see Table 4 for selected studies). As seen in Table 4, health economic evaluation information plays a significant role in adopting new high-cost medications for inclusion in the NLEM. Although many medicines are now included, it is not always the case that all medicines with an ICER less than 1.2 GNI per capita per QALY (160,000 Baht per QALY), which is the current threshold, are included. For example, imiglucerase, for the treatment of gaucher disease type 1, yields more than 6 million Baht per QALY, but the medicine is still included in the NLEM for two reasons. First, the medicine treats a very rare disease and the health economic evaluation study estimated that there would be no more than five people who require treatment per year. In addition, gaucher disease type 1 is terminal but curable through bone marrow transplantation (the patient who undertakes bone marrow transplant needs to take imiglucerase for one to two years before undergoing transplant). Second, if imiglucerase were not included in the list, the bone marrow transplant, which is currently under the UHC benefits package, would mainly be available for the rich who are able to pay for imiglucerase before undertaking bone marrow transplantation. For these two reasons, the Sub-committee decided to approve inclusion of imiglucerase despite its ICER being well above the threshold.

Economic evidence generated by private companies also plays a role in determining the NLEM. Table 4 shows that the economic evaluation study on ustekinumab conducted by for-profit organizations turns out not to be cost-effective under Thailand's healthcare setting. As a result, private companies are less likely to recommend the inclusion of the non-cost-effective medicines in the NLEM given that they are responsible for conducting the research on cost-effectiveness of the drug. The procedure of passing on the low priority topics to non-working group organizations is an advantage because, as a result, private companies decide to decrease the price of their drugs in the private market accordingly.

Additionally, health economic evaluation also informs the exclusion of medicines that may be of interest to particular physicians. For example, the treatment of mild to moderate Alzheimer's disease and the treatment of osteoporosis are two groups of medicines that have been vehemently proposed by health professionals for inclusion in the list. However, the first economic evaluation conducted in 2008 for both medicines found that good value for money was not represented, resulting in exclusion. After the exclusion, the medicines' prices dropped significantly and the HEWG revisited the study, finding that the medicines were cost-effective but produced a very large budget impact. For that reason, both medicines are currently still excluded from the list.

Table 4 Cost-effectiveness league table of economic evaluations supporting the development of the National List of Essential Medicines in Thailand.

Medicines	Comparator	Indications	Incremental cost-effectiveness ratio (Baht/QALY)	Coverage decisions	Year
Peg-interferon alpha 2b plus ribavirin	treatment of cirrhosis and hepatoma	chronic hepatitis C subtype 2, 3	cost-saving	Yes*	2011
Peg-interferon alpha 2a plus ribavirin	treatment of cirrhosis and hepatoma	chronic hepatitis C subtype 2, 3	cost-saving	Yes*	2011
lamivudine or tenofovir	treatment of cirrhosis and hepatoma	chronic hepatitis B	cost-saving	Yes	2011
bevacizumab	ranibizumab	Age-related macular degeneration, diabetic macular edema	cost-saving	Yes	2012
intravenous immunoglobulin (IVIG)	intravenous steroid and immunosuppressant	Dermatomyositis	cost-saving	Yes	2013
intravenous immunoglobulin (IVIG)	intravenous steroid and immunosuppressant	chronic inflammatory demyelinating polyneuropathy (CIDP)	57,000	Yes	2013
intravenous immunoglobulin (IVIG)	intravenous steroid	idiopathic thrombocytopenic purpura (ITP)	87,000	Yes	2013
dasatinib, nilotinib	high-dose imatinib	chronic myeloid leukemia	92,000	Under price negotiation	2013
oxaliplatin (FOLFOX)	5-fluorouracil/leucovorin	advance colorectal cancer	126,000	Yes*	2012
sidenafil	digoxin, diuretic, anticoagulant and oxygen therapy	pulmonary arterial hypertension	168,000	Yes	2013
Galantamine, donepezil or rivastigmine	palliative care	mild-to-moderate Alzheimer's disease	157,000-240,000	No	2010
alendronate, risedronate, raloxifene	vitamin D and calcium	osteoporosis	300,000-800,000	No	2008
rituximab + CHOP regimen	CHOP regimen (cyclophosphamide, hydroxydaunorubicin, oncovin, and prednisone)	diffused large B-cell lymphoma	600,000	No	2013
bosentan or iloprost	digoxin, diuretic, anticoagulant and oxygen therapy	pulmonary arterial hypertension after failing sidenafil	1,023,000-4,462,000	No	2013
sunitinib	palliative care	metastasis renal cell carcinoma	2,400,000	No	2013
rituximab	sequential DMARDs	rheumatoid arthritis	1,100,000	No	2013
gefitinib or erlotinib	docetaxel	Second-line treatment for non-small cell lung cancer	1,500,000-2,000,000	No	2013
ustekinumab	palliative care	chronic plaque psoriasis	3,500,000	No	2013
imiglucerase	palliative care	Gaucher disease type 1	6,300,000	Yes*	2012
Atorvastatin**, fluvastatin or pravastatin	simvastatin	High risk for acute coronary syndrome	negative dominant	No	2008
recombinant human erythropoietin	blood trasfusion	chemotherapy-induced anemia	negative dominant	No	2008
adefovir, entecavir, telbivudine and peg-interferon alpha 2a	lamivudine or tenofovir	treatment of chronic hepatitis B	negative dominant	No	2011

* inclusion in the NLEM after price negotiation.
** withdraw from the NLEM as a result of health economic evaluation.

Table 5 Results from price negotiation (unit in Baht: 30 Baht = $1).

Medicines	Original price	Reduced price	Potential saving
tenofovir (per tablet)	43	12	375 million
Oxaliplatin (injection 50 mg/25 ml)	8,000	2,500	152 million
pegylate interferon alpha-2a (180 mcg)	9,241	3,150	600 million

Table 5 also shows the results of price negotiation using health economic evaluation and BIA data. In 2010, the Sub-committee established a price negotiation working group within which information on cost-effectiveness is used to engage in price negotiations with companies. As a result of price negotiation through the work of this working group, more than 1 billion Baht of the health budget is being saved annually. An example of this would be the price negotiation of oxaliplatin for the treatment of advanced colorectal cancer. The original health economic evaluation study indicated that at that time the current price was not cost-effective and the price would need to be lowered by at least 20% in order for the medicine and regimen to become cost-effective. The working group effectively negotiated with the pharmaceutical companies and secured a discount of 30%, resulting in the inclusion of oxaliplatin in the list.

Conclusion

Based on Thailand's experience, the use of health economic evaluation to inform policy on medicines is feasible and useful. It not only helps to make fair and evidence-based decisions on prioritization of medicines, but it also fosters efficient use of resources. However, this will not happen overnight since a number of supporting factors are needed, seven of which have been essential to Thailand's health system.

First, strong political commitment from the Chair of the Sub-committee has been crucial: During the past six years, two Chairs have had very strong support regarding the use of health economic evaluation as part of the development of the NLEM. Both also helped develop clearer mechanisms to make effective use of economic evaluation (as seen in Figure 1).

Second, the development not only of the individual capacity, but also the institutional capacity is critical: in Thailand, HITAP plays a coordinating role in developing infrastructure and networking. Through training it also enables other academic institutes and individuals to generate high quality and policy relevant evidence.

Third, similar to the policy process of the NLEM Sub-committee, the HEWG encourages wide participation of all relevant stakeholders in its process, for example, by allowing an involvement of private companies in conducting economic evaluation for medicines in the low-priority list.

Fourth, the establishment of standard methodologies and the adoption of process guidelines are important in order to ensure high academic integrity of studies as well as transparent and participatory processes of the studies: this allows all stakeholders to contribute to the process, irrespective of the outcome.

Fifth, the versatility of the health economic working group on the types of information used is a key element in the decision-making process. In addition to the use of health economic evaluation, other factors such as social values as in the case of imiglucerase come into play, which raised the legitimacy of the decision-making process as well as reduced resistance from stakeholders, especially patients and physicians.

Sixth, health economic evaluation of medicines is not the deciding factor of inclusion or exclusion in the list: Evidence is used as a starting point for policy development of medicines. Medicines that are not cost-effective may still be included in the list if there are other strong supporting factors, as is the case with imiglucerase. Also, the NLEM development process in Thailand allows the use of economic evaluation for price negotiation. The process in Thailand has worked very well because evidence is justification for sound negotiations, which is a powerful tool in engaging the public and private sectors constructively, especially when private companies take part in the research, as was the case with ustekinumab.

Lastly, strong enforcement of the availability of the NLEM to all patients who need those medicines is fundamental to its purpose: by law, providers and health facilities cannot refuse to prescribe the medicines on the list if the patient meets the medical criteria. If done, there are serious consequences in the form of lawsuits and public criticism (bad press). Therefore, medicines on the NLEM are always available to patients, making the development of the NLEM a very solid process. This is in contrast to the experience in some other countries, where a NLEM exists but where no mechanisms to enforce its implementation prevail. Without enforcement, medicines become available only on paper and patients do not receive the essential treatment that is much needed, rendering the whole process meaningless.

Conflict of Interest

Yot Teerawattananon and Netnapis Suchonwanich are members of the Sub-committee for the development of the National List of Essential Medicines. Yot Teerawattananon is a vice-chair of the Health Economic Working Group. Netnaphis Suchonwanich is a chair of the Price Negotiation Working Group. Pritaporn Kingkaew is the secretariat of the Health Economic Working Group. Nattha Tritasavit has no conflict of interest.

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A Cost-Utility Analysis Comparing Standard Axillary Lymph Node Dissection with Sentinel Lymph Node Biopsy in Patients with Early Stage Breast Cancer in Thailand

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ABSTRACT

Objectives: In Thailand, axillary lymph node dissection (ALND) is the dominant form of treatment for breast cancer, even though the treatment often leaves patients with some degree of arm morbidity. Sentinel lymph node biopsy (SNB) is widely accepted globally as a preferable alternative procedure because of its lower rates of associated morbidity. This study compared the cost-utility of SNB and ALND in patients with early stage breast cancer in Thailand. **Methods:** A decision tree with a 5-year time horizon was developed. Outcomes that were relevant to SNB and ALND were included, along with locoregional recurrence of cancer and lymphedema scenarios. The model parameters were derived from a meta-analysis of international clinical trials and other relevant literature. The resources and cost data were derived from the medical records of tertiary hospitals. Health utilities were measured by using the standard gamble technique. A sensitivity analysis was performed using a set of plausible parameters. **Results:** The incremental cost-effectiveness ratio (ICER) in the base-case analysis showed that SNB was more cost-effective than ALND. ICERs were −275,140 and −470,600 Thailand baht/quality-adjusted life-year gained from the provider perspective and the societal perspective, respectively. The most sensitive parameter was the utility score of patients with early stage breast cancer who had received breast-conserving therapy with lymphedema; the sensitivity and specificity of SNB had no impact on the ICER. **Conclusions:** The study confirmed that SNB was an economically viable alternative treatment to ALND. In developing countries, where resources are limited, nationwide implementation of SNB warrants widespread support from relevant stakeholders, including medical personnel and policymakers.

Keywords: axillary lymph node dissection, breast cancer, cost-utility analysis, sentinel lymph node biopsy.

Introduction

Over the last 10 years, the incidence of breast cancer in Thailand has increased significantly. The age-standardized rate for breast cancer has risen from 20.4 per 100,000 in 2003 to 25.6 per 100,000 in 2006. Today, 29,167 cases are diagnosed each year [1], making it the leading cancer in women in Thailand. Advancements in cancer care that have occurred over the last 10 years, particularly the multidisciplinary approach that has resulted from collaboration between surgeons, oncologists, and radiologists, has resulted in a dramatic improvement in both the survival rate and the quality of life of patients with breast cancer. Although advanced adjuvant chemo-radiation plays an important role in cancer care, surgery is still the main treatment option for local control of disease. Because the breast lymphatic system is drained through axillary lymph nodes, axillary lymph node dissection (ALND) has become a standard treatment for both cancer staging and the controlling of local recurrence (LR). Axillary recurrence decreases the 5-year survival rate of patients with breast cancer by approximately 28% to 40% [2,3]. However, ALND causes arm morbidity in around 20% of the patients, including symptoms such as frozen shoulder, armedema, and lymphagitis [4]. Following the introduction of screening mammograms, the number of stage breast cancer cases that exhibit axillary metastasis has decreased significantly because of earlier detection [5]. Many studies [6,7] report that as many as 70% to 80% of patients with early stage breast cancer show no axillary lymph nodes metastasis. For patients who show no palpable axillary lymph node, sentinel lymph node biopsy (SNB) is conducted to identify the first drainage lymph node, which can prevent the need for ALND. SNB has been widely accepted worldwide [8] as a comparative procedure to ALND that can identify early metastasis in patients with early stage breast cancer who have a tumor smaller than 5 cm and a clinically nonpalpable axillary lymph node. The procedure has

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been shown to reduce the risk of many short- and long-term complications associated with ALND, including long hospital stays, infection, lymphedema, and frozen shoulder. For instance, Kell et al. [9] reported a 70% reduction in the rate of lymphedema and a 75% reduction in the rate of arm numbness for patients who underwent SNB as opposed to ALND. Veronesi et al. [10] also found that SNB and ALND resulted in a similar 10-year survival, LR, and metastasis rates.

Although ALND causes higher levels of morbidity than does SNB, ALND is still the standard procedure for patients with breast cancer in Thailand, due to a lack of both trained personnel and facilities that are necessary to implement SNB nationwide. No economic evaluation has yet been undertaken in any developing country setting to compare the cost-effectiveness of ALND and SNB in terms of cost, treatment outcome, and complications. This study aimed to address this gap in the data by evaluating the cost-utility of SNB compared with ALND in patients with early stage breast cancer in Thailand. The results will help health care providers and policymakers decide whether to put SNB into clinical practice throughout the country.

Methods

Overview

In Thailand, all patients who are diagnosed with early stage breast cancer and who have no palpable axillary lymph nodes undergo either a mastectomy or breast-conserving therapy (BCT); these surgical treatment options are conducted with either SNB or ALND, depending on the surgeon's preference. ALND is far more common in standard treatment than is SNB, which is currently performed only in a few university and tertiary hospitals throughout Thailand. Following SNB or ALNB, chemo-radiation is usually provided, followed by a 5-year hormonal treatment.

To compare the economic value of SNB with ALND, we conducted an evaluation using a hypothetical cohort of women aged 50 years who were diagnosed with early stage breast cancer and had clinically nonpalpable axillary lymph nodes. We chose to focus on postmenopausal women aged 50 years because this is the age at which breast cancer incidence peaks in Thai women [1]. All costs and outcomes after the first year were discounted at a rate of 3% per annum, as recommended by Thailand's health technology assessment guidelines [11].

Design of analysis model

The study was based on a decision analytic model that compared the cost and utility of ALND with those of SNB in patients with early stage breast cancer in Thailand from societal and provider perspectives. We generated a decision tree with a 5-year time horizon (Fig. 1) that covered all relevant outcomes, including lymphedema and locoregional recurrence rates. All patients were postmenopausal and underwent BCT and either axillary dissection or SNB. For each procedure, the pathology results may be positive (true positive, false negative) or negative (true negative, false positive). Some patients who undergo SNB may later undergo ALND as well, in cases in which the axillary lymph nodes were found to have metastasized. There are two main techniques used to identify the sentinel lymph node in SNB—either a blue dye or a radioactive substance is injected near to the tumor site. In this study, only the blue dye technique was included in the analysis because this is the procedure that is commonly used in the Thai setting. Given the lack of frozen section data in Thailand, we assumed the frozen section data from the diagnosis stage of SNB, which is conducted intraoperationally, to be 100% accurate. Although sensitivity and specificity of SNB were reported from the final histopathology examination, we conducted sensitivity analysis on these two parameters to minimize these parameters and frozen section uncertainty. Another model assumption was that all SNBs were performed by experienced surgeons who had passed the "learning curve" period. After both SNB and ALND, there is a risk that patients may experience lymphedema in the second and third years after treatment. In the fourth and fifth years, patients experience one of three possible outcomes—LR, regional recurrence (RR), or no locoregional recurrence. For those who experience LR, a mastectomy is usually conducted, either with or without axillary dissection; for those who experience RR, axillary clearance is usually conducted. In both recurrence groups, there is a risk that patients might experience lymphedema after the second surgery. All patients received chemotherapy and radiation after treatment, as per standard guidelines.

Final health states represent the outcomes measurement in most clinical trials, which use the presence of lymphedema, LR, and RR in the arm (or absence thereof). The distance metastasis rate in patients with early stage breast cancer is predominantly dependent on initial staging, which is usually similar in both arms; therefore, we did not assess this in the analysis.

Model parameters

Clinical parameters were decided on the basis of an extensive search of the published data. They are summarized in Table 1. The prevalence of axillary lymph node metastasis in 2-cm tumors was 31.5%, which increased in-line with tumor size. The sensitivity and specificity of SNB were derived from a meta-analysis of six randomized controlled trials (RCTs) [15–20], which compared SNB and ALND in patients with early stage breast cancer. The locoregional recurrences of SNB were derived from a meta-analysis of five RCTs [10,15,22,23], while the recurrence rate for ALND was derived from a single RCT [24] because no other published data were available. Because many of the clinical trials that examine lymphedema measurements use many different methods, we used data only from one RCT (NSABP B-32) to avoid confusion. The NSABP B-32 trial measured the lymphedema rates for both SNB and ALND patients using the water displacement method, which is recognized as the most reliable method for assessing lymphedema rates [26]. We analyzed the lymphedema rate as part of our sensitivity analysis.

Utility

Quality-adjusted life-years (QALYs) were derived from the patients' life-years and utility scores. Utility was measured using the standard gamble technique in 110 healthy Thai women aged 26 to 60 years because women in these ages can develop breast cancer. All hypothetical health states were developed on the basis of evidence from the literature review and expert opinions. Patient-reported outcomes [28,29] related to health quality of life in patients with breast cancer were reviewed and modified so that they were appropriate for the Thai context. Although the cognitive interview included questions related to sexual well-being, these responses were excluded from health state description because they were deemed irrelevant. Content validation was conducted by three medical professionals who specialized in caring for patients with breast cancer and five patients with breast cancer. The construct validity was proven by the statistical difference between better health states and worse health states (such as early stage breast cancer and recurrence of breast cancer). The six health states were as follows: 1) early stage breast cancer treated with BCT, with no recurrence, but with lymphedema; 2) early stage breast cancer treated with BCT, with no recurrence and without lymphedema; 3) LR of breast cancer, with lymphedema; 4) LR of breast cancer without lymphedema; 5) RR of breast cancer, with lymphedema; and 6) RR of breast cancer without lymphedema. Patients who experienced LR were treated with a mastectomy with axillary dissection, whereas those experiencing RR were treated with only additional axillary dissection. We assumed that the outcomes of

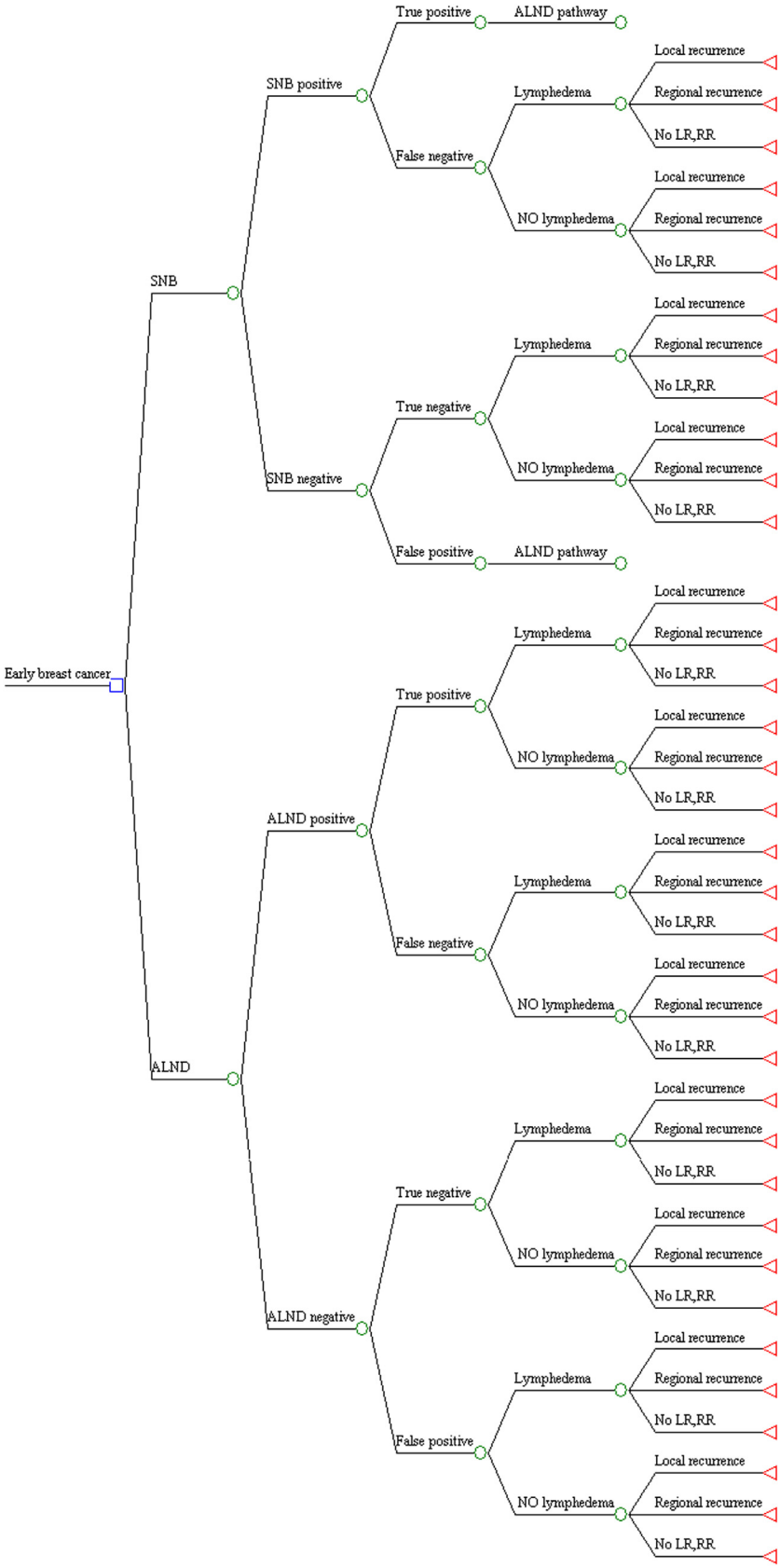

Fig. 1 – Decision tree. ALND, axillary lymph node biopsy; LR, local recurrence; RR regional recurrence; SNB, sentinel lymph node biopsy.

Table 1 – Model parameters and data sources.

Parameter	Distribution	Mean	Standard error	Data source
Probability of axillary metastasis in 2-cm tumors	Beta	0.315	0.018	[12–14]
SNB				
Sensitivity	Beta	0.902	0.017	[15–20]
Specificity	Beta	1.0	0	[15–20]
ALND				
Sensitivity	Beta	0.304	0.038	[21]
Specificity	Beta	0.988	0.004	[21]
Probability of local recurrence				
SNB negative and no metastasis lymph node (true negative)	Beta	0.022	0.003	[10,15,22,23]
SNB negative and metastasis lymph node (false negative)	Beta	0.019	0.006	[24]
ALND with no metastasis lymph node	Beta	0.014	0.006	[10,15,22,23]
ALND with metastasis lymph node	Beta	0.036	0.009	[24]
Probability of regional recurrence				
SNB negative and no metastasis lymph node (true negative)	Beta	0.004	0.002	[10,15,22,23,25]
SNB negative and metastasis lymph node (false negative)	Beta	0.009	0.005	[24]
ALND with no metastasis lymph node	Beta	0.004	0.001	[10,15,22,23,25]
ALND with metastasis lymph node	Beta	0.005	0.003	[24]
Probability of lymphedema				
SNB	Beta	0.117	0.011	[26]
ALND	Beta	0.276	0.013	[26]
Utilities for health states*				
Early stage breast cancer status after BCT	Beta	0.76	0.04	
Early stage breast cancer status after BCT with lymphedema	Beta	0.59	0.04	
Advanced stage breast cancer with regional recurrence	Dirichlet	0.60	0.04	
Advanced stage breast cancer with regional recurrence and lymphedema	Dirichlet	0.45	0.03	
Advanced stage breast cancer with local recurrence	Dirichlet	0.61	0.03	
Advanced stage breast cancer with local recurrence and lymphedema	Dirichlet	0.39	0.03	
Cost				
Direct medical cost†				
First-year cost of SNB	Gamma	39,673.80	2,561.30	
First-year cost of SNB and ALND	Gamma	61,100.37	14,947.61	
First-year cost of ALND	Gamma	47,737.25	3,794.58	
Cost of follow-up of SNB per year	Gamma	3,207.51	47.99	
Cost of follow-up of SNB and ALND per year	Gamma	5,013.62	210.05	
Cost of follow-up of ALND per year	Gamma	7,954.54	325.54	
Operation after local recurrence (2 y)	Gamma	44,022.99	44,022.99	
Operation after regional recurrence (2 y)	Gamma	3,9254.19	3,9254.19	
Radiation cost in early stage breast cancer (5 y)	Gamma	51,126.51	51,126.51	
Chemo-radiation cost for recurring breast cancer (3 y)	Gamma	11,7285.6	11,7285.6	
Lymphedema care cost (4 y)	Gamma	102,084.95	102,084.95	
Lymphedema care cost (2 y)	Gamma	82,966.29	82,966.29	
Direct nonmedical cost				
Cost of travel	Gamma	142.55	11.60	[27]
Cost of food	Gamma	52.51	5.35	[27]
Indirect cost				
Cost of productivity loss of patient per day	Gamma	80.29	11.34	[27]
Cost of productivity loss of one relative per day	Gamma	95.51	35.41	[27]

ALND, axillary lymph node dissection; BCT, breast-conserving therapy; SNB, sentinel lymph node biopsy.
* Data source: Interview (standard gamble technique).
† Data source: Hospital databases

both the SNB group and the ALND group would show similar clinical presentation and would share the same health states given the similar clinical progression of both procedures but would differ in the occurrence rate. The utility data are presented in Table 1.

Cost

Both the societal and health care provider perspectives were examined in this analysis. The cost used in the societal perspective was composed of direct medical costs and direct nonmedical costs, whereas the cost used in the provider perspective included only direct medical costs. Direct medical costs were grouped into three categories—surgical procedures, lymphedema care, and radiation and chemotherapy. Direct medical costs of each procedure comprised operation costs, anesthesia care costs, hospitalization costs, and related investigation and medication costs. Lymphedema care costs comprised physiotherapy care costs and medication costs. Radiation costs comprised

radiation therapy costs and medication and investigation costs. Number of resources used for all cost items and their charge were derived from the financial databases of the university hospital and the national cancer center. All charges were converted to costs using the cost to charge ratio reported by Riewpaiboon [27]. Chemotherapy costs were taken from Supakul et al. [31]. Direct nonmedical costs, which comprised patient expenses for food, transportation, and costs arising from relative productivity loss during hospitalization and outpatient visits, were derived from standard cost lists for health technology assessment [27]. Follow-up schedules and investigations were in line with those outlined in international guidelines [32]. Costs of lymphedema comprised first-year procedure costs and follow-up costs per year for 4 or 5 years of radiation treatment. For patients who experienced arm lymphedema in the second year, additional lymphedema care costs were calculated for 4 years. If patients had LR or RR, costs included the operation in the first year plus costs associated with two follow-up years and costs of the second operation and chemo-radiation. For patients undergoing a second procedure and who experienced lymphedema, costs included lymphedema care for 2 years. We excluded the cost of chemotherapy and hormonal therapy after the first treatment because we assumed that all patients received the same treatment and so the cost would not affect the results. All costs were adjusted for inflation to the year 2012 by applying the Thai consumer price index [30].

Uncertainty Analysis

A one-way sensitivity analysis was performed on all relevant parameters, including the prevalence of axillary metastasis, sensitivity and specificity of SNB, cost of each procedure, and utility score. The value of each parameter was tested within a plausible range of 95% confidence interval (CI) or 10th and 90th percentile. A threshold analysis was undertaken on relevant parameters at a willingness-to-pay (WTP) value of 120,000 Thai baht (THB) per QALY gained, as recommended by the Health Economic Working Group under the Subcommittee for Development of the National List of Essential Drugs. A probabilistic sensitivity analysis using the Monte-Carlo stimulation with 1000 iterations was undertaken to test the uncertainty of the model. A gamma distribution was used for cost, while the beta distribution and the dirichlet distribution was used for probability and utility parameters, respectively. Because cost of operation after recurrence, lymphedema care cost, and radiation cost came from the reimbursement list, values for standard error for these were not available. We used standard error equal to mean in sensitivity analysis. A cost-effectiveness acceptability curve was also presented.

Results

The base-case analysis of the cost utility of SNB and ALND in patients with early stage breast cancer found that SNB cost less than ALND but resulted in higher QALYs. The incremental cost-effectiveness ratios (ICERs) of SNB compared with those of ALND were −275,140 THB/QALY gained from the provider perspective and −470,600 THB/QALY gained from the societal perspective (see Table 2).

One-Way Sensitivity Analysis

Our one-way sensitivity analysis (Fig. 2) showed that the utility score of early stage breast cancer, post-BCT patients with lymphedema was the most sensitive parameter, in which a range of 95% CI in the parameter resulted in an ICER range of −145% to 316%. In contrast, the probability of a true positive outcome (sensitivity) had a minimal effect on ICER for both ALND and SNB. Tumor mass determines the prevalence of axillary metastasis; given that, a threshold analysis was performed to explore the effect of the axillary metastasis rate on the value for money of SNB. The results showed that at a WTP value of 120,000 THB/QALY gained, SNB was superior to ALND, even when the rate of axillary metastasis changed from 0% to 85%. The axillary metastasis rate in early stage breast cancer cases, in which the tumor is smaller than 5 cm, was found to be approximately 49% to 58% [12–14]. This means that SNB is statistically more cost-effective than ALND for early stage breast cancer treatment. Given that some model parameters obtained from international studies are generally more accurate than parameters garnered from clinical practice, the sensitivity and specificity of SNB were also tested. The results from the one-way sensitivity analysis showed that both parameters were less sensitive to ICER change and that SNB was still more cost-effective even when the sensitivity and specificity of the test decreased. The lymphedema rate after ALND was tested because the severity of lymphedema in post-ALND patients can vary widely, and many patients with a mild form of lymphedema may not require treatment. We found that ALND was the more cost-effective treatment option, when fewer than 10% of the patients developed lymphedema; however, this was not verifiable in the clinical setting, in which more than 10% of the patients who had ALND develop lymphedema. Moreover, direct medical cost applied in this study did not include the cost that occurred during the learning curve of SNB; however, in one-way sensitivity analysis, ICER showed minimal change when the direct medical cost of SNB in the first year varied between 10th and 90th percentile.

Probabilistic Sensitivity Analysis

The probabilistic sensitivity analysis showed that SNB is more cost-effective than ALND for all WTP values (Fig. 3). At a WTP value of 120,000 THB, the probability of SNB being cost-effective was 77.5% while the probability of ALND being cost-effective was 22.5%.

Discussion

Our cost-utility analysis was based on a 5-year decision tree model that compared the cost-effectiveness of ALND with SNB treatments for patients with early stage breast cancer in Thailand from both the provider and societal perspectives. SNB was found to be cost saving from both perspectives, giving an ICER of −275,140 THB/QALY gained from the provider perspective and −470,600 THB/QALY gained from the societal perspective. At Thailand's ceiling threshold of 120,000 THB/QALY gained, the probability that SNB would be cost-effective in patients with early stage breast cancer was found to be 77.5%. Some model parameters were derived from international studies, in which breast cancer tends to be diagnosed at an earlier stage than in Thailand, and so tumors tend to be smaller and the risk of axillary metastasis is correspondingly lower. Despite this, our threshold analysis still confirmed SNB to be the most cost-effective option, despite the significantly high risk of axillary metastasis (85%). In clinical practice, however, SNB was not recommended for patients with a tumor larger than 5 cm because of its high false-negative rate with tumors of that size.

In Thailand, most patients with breast cancer undergo a mastectomy, in contrast to most international contexts that have been studied, in which BCT is the most common surgical treatment. Many studies [33,34] have shown that the outcomes of mastectomy are comparable with those of BCT in terms of LR and survival rate. However, because of criteria and follow-up period limitations in previous studies, no definitive evidence has yet

Table 2 – Cost-effectiveness of SNB and ALND in provider and societal perspective.

Treatment	QALYs	Cost (THB)		ICER	
		Provider	Societal	Provider	Societal
ALND*	3.385	152,212	215,473		
SNB*	3.431	139,552	193,820	−275,140	−470,600

ALND, axillary lymph node dissection; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; SNB, sentinel lymph node biopsy; THB, Thai baht.
* Excluding cost of first chemotherapy and hormonal treatment.

been established [35–37] on how the lymphedema rate differs for each procedure. However, the one-way sensitivity analysis that was conducted as part of this study on the probability of developing lymphedema revealed a range of 95% CI. The results showed a minimal change in ICER as a result of developing lymphedema, and SNB was still considered more cost-effective. The one-way sensitivity analysis of the sensitivity and specificity of SNB demonstrated that SNB was still more cost-effective than ALND.

In 2012, Verry et al. [38] compared the cost-effectiveness of SNB with that of ALND from the provider perspective using a Markov model over a 20-year period. The study parameters were mainly garnered from the Sentinel Node versus Axillary Clearance trial [18], and the utility was derived from Kanis et al. [39]. The study showed that SNB was marginally more cost-effective than ALND and indicated several sensitive parameters that affected the outcomes. The researchers highlighted the need for more reliable information on the specificity of SNB and the risk of axillary recurrence after SNB; we did not identify this need in our study. Although no relevant clinical trials have yet been conducted in Thailand from which we could derive our parameters, we ensured that the parameters were appropriate for the Thai context by deriving the utility from healthy Thai women and testing sensitive parameters through a sensitivity analysis. The most sensitive parameter that we identified in our analysis was the utility of early stage breast cancer post-BCT patients with lymphedema. Although SNB had the additional cost of pathological examination, there were studies [40,41], which compared direct medical costs between SNB and ALND in the early postoperative period, that found that SNB was cost saving and hospital stay cost was the most significant parameter. In our study, the duration of hospital stay between both groups was not much different because the patients were discharged early and had follow-up at the outpatient clinic. Because most breast cancer treatments are undertaken in outpatient clinics, we included direct nonmedical costs and examined the data from both the provider and societal perspectives. The ICER from the societal perspective was found to be nearly twice that from the provider perspective, and the cost of travel was one of the most sensitive parameters. After conducting the probabilistic sensitivity analysis with 1000 iterations in a range of probable values of total cost, health outcomes, and ICERs, the results showed that the probability of SNB being more cost-effective than ALND at different WTP values was more than 70%.

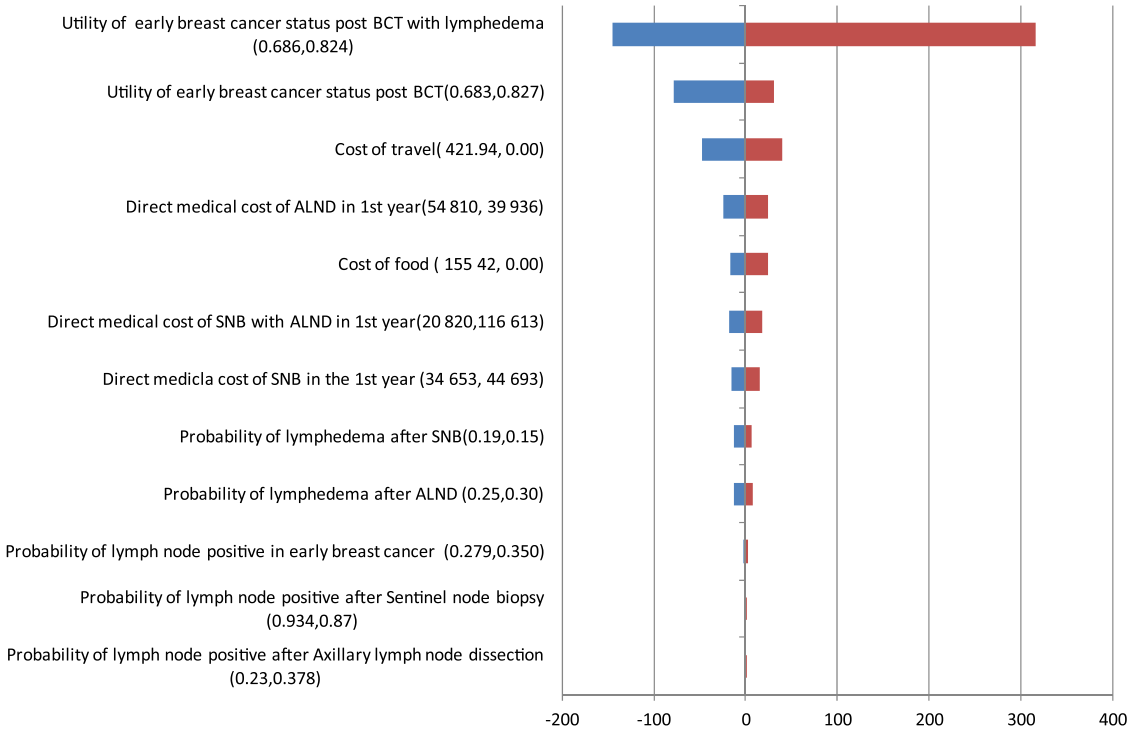

Fig. 2 – The percentage change in ICER compared with the mean ICER for each parameter. Mean ICER = −470,602.22 THB/QALY gained. ALND, axillary lymph node dissection; BCT, breast-conserving therapy; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; SNB, sentinel lymph node biopsy; THB, Thai baht.

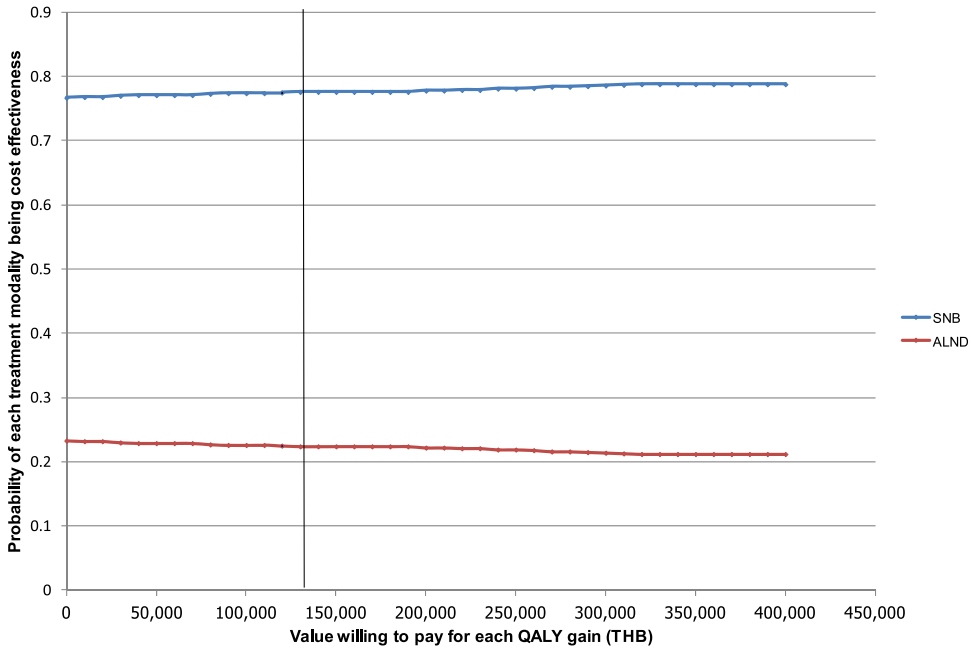

Fig. 3 – Cost-effectiveness acceptability curve. ALND, axillary lymph node dissection; QALY, quality-adjusted life-year; SNB, sentinel lymph node biopsy.

Because we used a 5-year model, our study had insufficient data to interpret the cost-utility between SNB and ALND over a lifetime. Our model aimed to evaluate the efficacy of SNB in reducing lymphedema while also giving similar LR and RR rates to ALND. Recurrence almost always occurs within 5 years after treatment, and so this model is deemed to be a good model for predicting recurrence rates. We did not include survival as an outcome because this fell outside the timescale of our model. Our assumption was in line with the data from Veronesi et al. [10], the longest follow-up clinical trial, results of which showed that mortality in early stage breast cancer was strongly predicated by initial staging and treatment and that after 10-year follow up there was no statistically significant difference in the mortality rate between SNB and ALND groups.

Conclusions

Our study demonstrated that SNB gives patients with early stage breast cancer a better quality of life and is a more cost-effective option than ALND. The results are generalizable to other Southeast-Asian countries because these countries share broadly similar living costs, cultural norms, and lifestyles to those examined in our study. Moreover, our findings make a clear case for clinicians and policymakers to provide SNB treatment nationwide to improve the standard of care for Thai patients with breast cancer.

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EXPERT REVIEWS

Cost-utility analysis of adjuvant chemotherapy in patients with stage III colon cancer in Thailand

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Background: In Thailand, there has been no economic evaluation study of adjuvant chemotherapy for stage III colon cancer patients after resection. Objective: This study aims to evaluate the cost-utility of all chemotherapy regimens currently used in Thailand compared with the adjuvant 5-fluorouracil/leucovorin (5-FU/LV) plus capecitabine as the first-line therapy for metastatic disease in patients with stage III colon cancer after resection. Methods: A cost-utility analysis was performed to estimate the relevant lifetime costs and health outcomes of chemotherapy regimens based on a societal perspective using a Markov model. Results: The results suggested that the adjuvant 5-FU/LV plus capecitabine as the first-line therapy for metastatic disease would be the most cost–effective chemotherapy. Conclusions: The adjuvant FOLFOX and FOLFIRI as the first-line treatment for metastatic disease would be cost–effective with an incremental cost–effectiveness ratio of 299,365 Thai baht per QALY gained based on a societal perspective if both prices of FOLFOX and FOLFIRI were decreased by 40%.

Keywords: adjuvant chemotherapy • cost-utility analysis • oxaliplatin • stage III colon cancer • Thailand

Nowadays, colorectal cancer is a major public health issue. It is the third most common type of cancer with one million new cases worldwide and was the fourth leading cause of death in 2004 [1]. In Thailand, colorectal cancer was the third most frequent malignancy in males and the fifth in females with age-standardized incidence rates of 11.3 and 7.9 per 100,000 for males and females during 2001–2003, respectively [2]. Surgical resection is the mainstay initial treatment for stage III colon cancer. Almost 50% of patients who undergo curative surgery alone finally relapse and die due to microscopic metastases, which are present but undetected at the time of surgery [3]. The role of chemotherapy for colon cancer after curative resection has been used as adjuvant chemotherapy, which has anti-tumor activity that helps decreasing relapse and death. It has been proven that the benefits of adjuvant chemotherapy (i.e., 5-fluorouracil combined with leucovorin [5-FU/LV]) are to reduce relapse rates and improve overall survival by 33% in patients with node-positive colon cancer (stage III or Dukes' stage C), but not in those with stage II or Dukes' stage B [4,5].

At present, 6 months of 5-FU/LV treatment is considered the standard approach for stage III colon cancer [6]. Although several regimens of 5-FU/LV exist, some regimens can lead to a difference in toxicity [6]. Moreover, capecitabine and oxaliplatin in combination with 5-FU/LV have been evaluated as the adjuvant treatments for patients with stage III colon cancer [7]. Capecitabine is an oral dosage form of chemotherapy with convenience, favorable safety and better-tolerated toxicity [7]. The addition of oxaliplatin to the 5-FU/LV has demonstrated a synergistic activity, which leads to a significant improvement in disease-free survival and overall survival in the adjuvant setting [8–10].

In Thailand, only 5-FU/LV and capecitabine are currently included in the National List of Essential Medicines (NLEM), the reimbursement drug list for patients enrolled under the Civil Servant Medical Benefit Scheme (9% of the Thai population), the Social Security Scheme (11% of the population) and the Universal Coverage (UC) scheme (80% of the Thai population). However, oxaliplatin is still costly and has not yet been included in the NLEM.

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Table 1. All compared interventions in this study.

Adjuvant chemotherapy regimen	First-line chemotherapy regimen for metastatic disease
5-FU/LV	Capecitabine
5-FU/LV	FOLFOX
5-FU/LV	XELOX
5-FU/LV	FOLFIRI
Capecitabine	FOLFOX
Capecitabine	XELOX
Capecitabine	FOLFIRI
FOLFOX	FOLFIRI
XELOX	FOLFIRI

FOLFOX: Fluorouracil/leucovorin/oxaliplatin; FOLFIRI: Irinotecan plus 5-FU/LV; 5-FU/LV: 5-Fluorouracil and leucovorin; XELOX: Capecitabine/oxaliplatin.

Prior to this study, there have not been any economic evaluation studies of adjuvant chemotherapy for stage III colon cancer patients after resection in Thailand. Therefore, in 2010, the Thai Subcommittee for Development of the NLEM requested economic evaluation information of an adjuvant chemotherapy regimen, particularly an oxaliplatin-added regimen in stage III colon cancer, to determine whether oxaliplatin should be included in the NLEM. The objective of this study is to evaluate and compare lifetime costs and health outcomes of chemotherapy regimens with the standard treatment available in Thailand (i.e., the adjuvant 5-FU/LV and the first-line capecitabine for metastatic disease) for patients with stage III colon cancer. The results from this study would be very beneficial for the NLEM subcommittees for decision-making regarding whether oxaliplatin should be included into the list.

Methods

A cost-utility analysis using a Markov model was performed to evaluate and compare lifetime costs and outcomes of stage III colon cancer patients aged 50 years who required the adjuvant chemotherapy after resection. This study was conducted based on a societal perspective as recommended by Thailand's health technology assessment guidelines, since it is the most comprehensive viewpoint which incorporates all costs and benefits regardless of who incurs the costs or gains the benefits [11]. Studied interventions included the adjuvant chemotherapy followed by the first-line chemotherapy for metastatic disease. The adjuvant chemotherapy regimens were as follows: 5-FU/LV, capecitabine monotherapy, 5-FU/LV/oxaliplatin (FOLFOX) and capecitabine/oxaliplatin (XELOX). Based on the current clinical practice guidelines for the management of disease recurrence, the first-line chemotherapy regimens for metastatic disease were as follows: capecitabine monotherapy, fluorouracil/leucovorin/oxaliplatin (FOLFOX), capecitabine/oxaliplatin (XELOX) and irinotecan plus 5-FU/LV (FOLFIRI). Table 1 demonstrates the set of eight interventions compared with the adjuvant 5-FU/LV and capecitabine as the first-line chemotherapy for metastatic disease (i.e., a standard treatment).

All future costs and health outcomes were discounted to present values at the rate of 3% per year as recommended by Thailand's health technology assessment guidelines [12]. The primary outcomes were life year (LY) gained, quality-adjusted life year (QALY) gained and the incremental cost–effectiveness ratio (ICER) in Thai baht (THB) per LY and QALY gained. The results of ICER values obtained from this study were used to determine the cost–effectiveness of each alternative intervention when compared with the societal willingness-to-pay (WTP) threshold, the amount of money which the Thai society is willing to pay for 1 year of life adjusted for its quality of life (i.e., QALY) gained for the adoption of health technologies and interventions. The societal WTP threshold announced by the Subcommittee for Development of the NLEM and the Subcommittee for Development of the Health Benefit Package and Service Delivery, National Health Security Office (NHSO) is between one- to three-times the Thai Gross Domestic Product (GDP), or approximately 100,000 THB (6000 purchasing power parity [PPP]$) to 300,000 THB (18,000 PPP$) [13]. If health technologies with ICERs below the per capita GDP are considered very cost-effective, those between one- and three-times per capita GDP being cost-effective, while ICERs above three-times per capita GDP indicate that a health technology is not cost-effective. These threshold values are in line with those suggested by the Commission on Macroeconomics and Health, WHO [14].

Economic model

Figure 1 illustrates the Markov model structure used to estimate the relevant costs and health outcomes during a lifetime horizon with a cycle length of 1 year. The model simulation was used to estimate the costs and health outcomes over a 99-year period to cover the maximum expected lifetime horizon. The study compared eight mutually exclusive treatment options with the adjuvant 5-FU/LV followed by capecitabine as the first-line therapy for metastatic disease as stated in Table 1. The Markov model consisted of three health states: alive without relapse or pre-relapse, alive with relapse and death. All stage III colon cancer patients aged 50 years who required the adjuvant chemotherapy after resection start at the 'alive without relapse' state. If cancer metastasis, either local or distant, was detected, the patients would move to the 'alive with relapse' state and require the first-line treatment for metastatic disease. Patients in all states could stay in the same state or move to the 'death' state. An arrow represents the probability of moving from one state to another, known as the transitional probability.

Based on clinical information and practice, the assumptions of the analytical model were addressed. First, patients completing resection of histological stage III colon cancer were treated by adjuvant chemotherapy for 6 months. Second, all recurrences were assumed to occur within 5 years after resection of the primary tumor. Third, the survival of patients with relapse was equal to that of patients diagnosed with stage IV colon cancer depending on the efficacy of the chemotherapy regimen given over a lifetime period. Fourth, the survival of patients

who were disease-free was estimated from the overall survival of stage III colon cancer depending on the efficacy of the adjuvant chemotherapy regimen given. Finally, it was assumed that utility scores of patients receiving intravenous chemotherapy regimens (i.e., 5-FU/LV, FOLFOX, XELOX and FOLFIRI) were the same, but different from those of patients receiving oral chemotherapy (i.e., capecitabine).

Cost variables

Both direct (i.e., medical and non-medical) and indirect costs were included based on a societal perspective. All costs were converted and reported in 2010 THB using the consumer price index [15]. The average annual exchange rate of THB to one US dollar was 30 THB in 2010 [16]. For international comparison, costs were converted to international dollars using the PPP$ exchange rate of 1 PPP$ (2010) per 17.8 THB [17]. Table 2 illustrates the cost and resource use parameters used in this study.

Direct medical costs

Direct medical costs covered all treatment costs (i.e., chemotherapy cost and other healthcare costs) obtained from two data sources (Table 2). Costs of chemotherapy were calculated from chemotherapy dosage based on body surface area which was defined as 1.60 m^2 multiplied by the price per dosage retrieved from the reference price database of the Drugs and Medical Supplies Information Centre (DMSIC), the Ministry of Public Health [18]. Other healthcare costs except the chemotherapy cost of stage III colon cancer patients were retrieved from the hospital database at the National Cancer Institute (NCI). Direct medical costs were classified into two states (i.e., 'alive without relapse' and 'alive patients with relapse'). Data included demographic characteristics (e.g., age, gender), principal diagnosis (i.e., ICD-10), health insurance type and total cost of treatment. All 114 patients with a principal diagnosis related to colon cancer stage III and IV receiving treatment at the NCI from January 2005 to December 2010 were selected. Based on demographic characteristic results of these patients, mean age was 60 years and 51% were female. About 61% were patients with stage III colon cancer receiving adjuvant chemotherapy, while 39% were those with stage IV colon cancer receiving the treatment. The charges per patient per year were adjusted to costs using the cost-to-charge ratio of 0.8 [19].

In the first year, direct medical costs of patients without relapse included chemotherapy costs and other healthcare costs without chemotherapy. Direct medical costs in the first year were higher than those at subsequent years due to the cost of chemotherapy regimens given for 6 months. As such, the average chemotherapy costs during the first year of patients receiving XELOX were 344,094 THB (standard error [SE] = 344,094) followed by FOLFOX (298,375 THB, SE = 298,375), capecitabine monotherapy (124,146 THB, SE = 124,146) and 5-FU/LV (10,680 THB, SE = 10,680). In addition, other healthcare costs included the cost of central line, the cost of complications of line infections, the cost of thrombosis for all interventions, the cost of other medications without chemotherapy, cost of pre-treatment medications, cost of management of adverse events and toxicities,

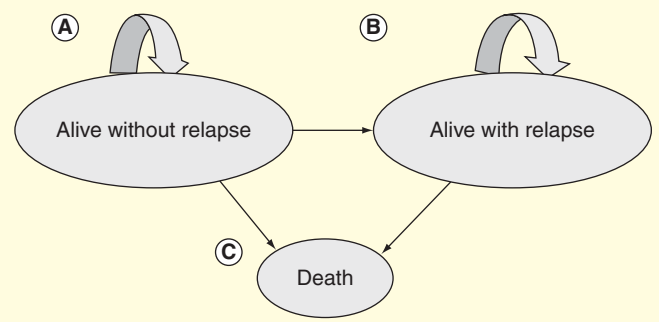

Figure 1. Schematic diagram of the Markov model. Markov model consists of three health states as follows: **(A)** alive without relapse or pre-relapse, **(B)** alive with relapse and **(C)** death. An arrow represents the probability of moving from one state to another known as transitional probability. The cycle length is one year with a 99-year time horizon. All stage III colon cancer patients after resection who required the first-line adjuvant chemotherapy would start at 'alive without relapse' state. If cancer either local or distant metastasis were detected, the patients would move to 'alive with relapse' state and required the second-line treatment. Patients in all states could stay in the same state or move to death state.

cost of laboratory and diagnostic tests (e.g., staging CT scan), cost of procedures, cost of outpatient visits and cost of hospitalizations. The average other healthcare costs of patients receiving FOLFOX, XELOX, capecitabine and 5-FU/LV were estimated to be the same in the first year (27,597 THB, SE = 26,666). Direct medical costs of patients without relapse in subsequent years were the costs of follow-up and other medication prescribed after the first year of chemotherapy. The average costs per year were estimated to be 28,228 THB (SE = 28,228).

Direct medical costs of patients with relapse in the first year were estimated from the cost of treatment for stage III colon cancer patients with disease recurrence and patients diagnosed with stage IV colon cancer. The annual cost of chemotherapy in the first year was the same as that in subsequent years, since it was assumed that patients with relapse would receive a chemotherapy regimen over a lifetime period. The average chemotherapy costs of patients with relapse receiving FOLFOX, XELOX, capecitabine and FOLFIRI were estimated to be 596,749 THB (SE = 596,749), 688,188 THB (SE = 688,188), 248,293 THB (SE = 248,293) and 878,359 THB (SE = 878,359), respectively. Moreover, other healthcare costs of patients with relapse in the first year and subsequent years included the cost of other medications without chemotherapy drugs, cost of laboratory and diagnostic tests, cost of pre-treatment medications and cost of management of adverse events and toxicities. The average other healthcare costs of patients with relapse treated with FOLFOX, XELOX, capecitabine and FOLFIRI were assumed to be the same (i.e., 70,133 THB, SE = 70,133).

Direct non-medical & indirect costs

Direct non-medical costs included the costs of food, accommodation and transportation due to receiving the treatment as well as direct medical costs incurred outside hospitals (e.g., at

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Table 2. Input parameters used in economic model.

Parameter	Distribution	Mean	SE	Ref.
Yearly discount rate (%)				
Costs (range)		3 (0–6)		[1]
Outcomes (range)		3 (0–6)		[1]
Transitional probability parameters				
Annual probability of moving from without relapse to relapse				
Patients receiving FOLFOX	Beta	0.133	0.0092	Meta-analysis
Patients receiving XELOX	Beta	0.140	0.0097	Meta-analysis
Patients receiving capecitabine	Beta	0.149	0.0102	Meta-analysis
Patients receiving 5-FU/LV	Beta	0.175	0.0121	[2]
Annual probability of death at without relapse state				
Patients receiving FOLFOX in the 1st year	Beta	0.040	0.0076	[3]
Patients receiving FOLFOX in the 2nd year	Beta	0.063	0.0095	[3]
Patients receiving FOLFOX in the 3rd year	Beta	0.056	0.0093	[3]
Patients receiving FOLFOX in subsequent years	Beta	0.035	0.0077	[3]
Patients receiving XELOX in the 1st year	Beta	0.030	0.0054	[4]
Patients receiving XELOX in the 2nd year	Beta	0.072	0.0083	[4]
Patients receiving XELOX in the 3rd year	Beta	0.044	0.0069	[4]
Patients receiving XELOX in subsequent years	Beta	0.047	0.0072	[4]
Patients receiving capecitabine in the 1st year	Beta	0.020	0.0044	[2]
Patients receiving capecitabine in the 2nd year	Beta	0.082	0.0087	[2]
Patients receiving capecitabine in the 3rd year	Beta	0.100	0.0099	[2]
Patients receiving capecitabine in subsequent years	Beta	0.074	0.0092	[2]
Patients receiving 5-FU/LV in the 1st year	Beta	0.020	0.0045	[2]
Patients receiving 5-FU/LV in the 2nd year	Beta	0.112	0.010	[2]
Patients receiving 5-FU/LV in the 3rd year	Beta	0.103	0.0104	[2]
Patients receiving 5-FU/LV in subsequent years	Beta	0.090	0.0103	[2]
Annual probability of death at relapse state				
Patients receiving FOLFOX in the 1st year	Beta	0.287	0.0189	Meta-analysis
Patients receiving FOLFOX in the 2nd year	Beta	0.489	0.0277	Meta-analysis
Patients receiving FOLFOX in subsequent years	Beta	0.490	0.0343	Meta-analysis
Patients receiving XELOX in the 1st year	Beta	0.344	0.0228	Meta-analysis
Patients receiving XELOX in the 2nd year	Beta	0.538	0.0305	Meta-analysis
Patients receiving XELOX in subsequent years	Beta	0.705	0.0493	Meta-analysis
Patients receiving capecitabine in the 1st year	Beta	0.386	0.0256	Meta-analysis
Patients receiving capecitabine in the 2nd year	Beta	0.571	0.0324	Meta-analysis
Patients receiving capecitabine in subsequent years	Beta	0.800	0.0560	Meta-analysis
Patients receiving FOLFIRI in the 1st year	Beta	0.350	0.0232	Meta-analysis

DMISC: Drugs and medical supplies information center; FOLFOX: Oxaliplatin/5-fluorouracil/leucovorin; 5-FU/LV: 5-Fluorouracil/leucovorin; NCI: National Cancer Institute; SE: Standard error; XELOX: Capecitabine/oxaliplatin.

Table 2. Input parameters used in economic model (cont.).

Parameter	Distribution	Mean	SE	Ref.
Transitional probability parameters (cont.)				
Annual probability of death at relapse state (cont.)				
Patients receiving FOLFIRI in the 2nd year	Beta	0.515	0.0292	Meta-analysis
Patients receiving FOLFIRI in subsequent years	Beta	0.573	0.0401	Meta-analysis
Patients receiving 5-FU/LV in the 1st year	Beta	0.386	0.0256	[5]
Patients receiving 5-FU/LV in the 2nd year	Beta	0.571	0.0323	[5]
Patients receiving 5-FU/LV in subsequent years	Beta	0.800	0.0560	[6]
Annual direct medical cost				
At without relapse state				
Cost of FOLFOX	Gamma	298,375	298,375	DMSIC
Cost of XELOX	Gamma	344,094	344,094	DMSIC
Cost of capecitabine	Gamma	124,146	124,146	DMSIC
Cost of 5-FU/LV	Gamma	10,680	10,680	DMSIC
Cost of other healthcare without FOLFOX in the 1st year	Gamma	49,844	49,844	NCI
Cost of other healthcare without XELOX in the 1st year	Gamma	49,844	49,844	NCI
Cost of other healthcare without capecitabine in the 1st year	Gamma	49,844	49,844	NCI
Cost of other healthcare without 5-FU/LV in the 1st year	Gamma	49,844	49,844	NCI
Cost of follow-up in the following years	Gamma	28,228	28,228	NCI
At relapse state				
Cost of FOLFOX	Gamma	596,749	596,749	DMSIC
Cost of XELOX	Gamma	688,188	688,188	DMSIC
Cost of capecitabine	Gamma	248,293	248,293	DMSIC
Cost of FOLFIRI	Gamma	878,359	878,359	DMSIC
Cost of other healthcare without FOLFOX in the 1st year	Gamma	70,133	70,133	NCI
Cost of other healthcare without XELOX in the 1st year and subsequent years	Gamma	70,133	70,133	NCI
Cost of other healthcare without capecitabine in the 1st year and subsequent years	Gamma	70,133	70,133	NCI
Cost of other healthcare without FOLFIRI in the 1st year and subsequent years	Gamma	70,133	70,133	NCI
Annual direct non-medical cost				
At without relapse state				
Out-of-pocket medical cost for patients receiving FOLFOX in the 1st year	Gamma	68,006	33,973	Survey
Out-of-pocket medical cost for patients receiving XELOX in the 1st year	Gamma	188,000	188,000	Survey
Out-of-pocket medical cost for patients receiving capecitabine in the 1st year	Gamma	53,991	22,466	Survey
Out-of-pocket medical cost for patients receiving 5-FU/LV in the 1st year	Gamma	5220	4187	Survey
Out-of-pocket medical cost for patients in the following years	Gamma	15,418	9954	Survey

DMISC: Drugs and medical supplies information center; FOLFOX: Oxaliplatin/5-fluorouracil/leucovorin; 5-FU/LV: 5-Fluorouracil/leucovorin; NCI: National Cancer Institute; SE: Standard error; XELOX: Capecitabine/oxaliplatin.

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Table 2. Input parameters used in economic model (cont.).

Parameter	Distribution	Mean	SE	Ref.
Annual direct non-medical cost				
At without relapse state (cont.)				
Other non-medical costs for patients receiving FOLFOX in the 1st year	Gamma	17,264	4566	Survey
Other non-medical costs for patients receiving XELOX in the 1st year	Gamma	8736	1494	Survey
Other non-medical costs for patients receiving capecitabine in the 1st year	Gamma	8736	1494	Survey
Other non-medical costs for patients receiving 5-FU/LV in the 1st year	Gamma	27,956	4779	Survey
Other non-medical costs for patients in the following years	Gamma	3495	597	Survey
At relapse state				
Out-of-pocket medical cost for patients receiving FOLFOX	Gamma	98,246	58,337	Survey
Out-of-pocket medical cost for patients receiving XELOX	Gamma	364,000	364,000	Survey
Out-of-pocket medical cost for patients receiving capecitabine	Gamma	68,181	27,340	Survey
Out-of-pocket medical cost for patients receiving FOLFIRI	Gamma	70,362	69,639	Survey
Other non-medical costs for patients receiving FOLFOX	Gamma	29,596	7828	Survey
Other non-medical costs for patients receiving XELOX	Gamma	13,978	2390	Survey
Other non-medical costs for patients receiving capecitabine	Gamma	13,978	2390	Survey
Other non-medical costs for patients receiving FOLFIRI	Gamma	29,596	7828	Survey
Annual indirect cost				
At without relapse state				
Indirect cost of patients receiving FOLFOX in the 1st year	Gamma	18,215	3582	Survey
Indirect cost of patients receiving XELOX in the 1st year	Gamma	4625	4625	Survey
Indirect cost of patients receiving capecitabine in the 1st year	Gamma	13,840	8096	Survey
Indirect cost of patients receiving 5-FU/LV in the 1st year	Gamma	10,255	1776	Survey
Indirect cost of patients in the following years	Gamma	1755	80	Survey
At relapse state				
Indirect cost of patients receiving FOLFOX in the 1st year	Gamma	62,550	13,113	Survey
Indirect cost of patients receiving XELOX in the 1st year	Gamma	6845	6845	Survey
Indirect cost of patients receiving capecitabine in the 1st year	Gamma	16,092	8091	Survey
Indirect cost of patients receiving FOLFIRI in the 1st year	Gamma	70,613	8852	Survey
Utility parameters				
Utility of stage III colon patients without chemotherapy	Beta	0.85	0.1	[7]
At without relapse state				
Utility of patients receiving capecitabine	Beta	0.651	0.0473	Survey
Utility of patients receiving intravenous chemotherapy	Beta	0.60	0.0633	Survey
At relapse state				
Utility of patients receiving capecitabine	Beta	0.624	0.0429	Survey
Utility of patients receiving intravenous chemotherapy	Beta	0.56	0.1010	Survey

DMISC: Drugs and medical supplies information center; FOLFOX: Oxaliplatin/5-fluorouracil/leucovorin; 5-FU/LV: 5-Fluorouracil/leucovorin; NCI: National Cancer Institute; SE: Standard error; XELOX: Capecitabine/oxaliplatin.

private clinics, drug store and traditional medicine suppliers, etc.). Indirect costs (i.e., productivity loss due to receiving the treatment and sick leave as well as informal care) were included, while mortality costs were excluded.

In this study, annual direct non-medical and indirect costs were collected from stage III colon cancer patients without relapse and with relapse or stage IV colon cancer patients receiving a chemotherapy regimen as well as their caregivers at the NCI, Thailand. Ethical approval was granted by the Committee on Human Rights Related to Research Involving Human Subjects, Mahidol University Institutional Review Board (MU-IRB) and NCI, and informed consent was given by the patients before data collection. A total of 48 patients, 24 without relapse and 24 with relapse or stage IV colon cancer, were interviewed using a developed questionnaire.

Clinical variables

Transitional probabilities were inputted into the Markov model to simulate stage III colon patients when starting adjuvant chemotherapy regimens. The transitional probability that patients would move from the 'alive without relapse state' to the 'alive with relapse state' was estimated from disease-free survival data obtained from the mixed treatment or indirect comparison meta-analysis of clinical efficacy studies using a Bayesian fixed effects model in stage III colon cancer patients receiving adjuvant chemotherapy [7–9,20,21]. Furthermore, the transitional probability that patients without relapse would move to the 'death' state was estimated from the overall survival curves of stage III colon cancer patients receiving adjuvant chemotherapy [7–9,20–22]. The transitional probability that patients with relapse would move to the 'death' state was obtained from a systematic review and meta-analysis of clinical trials in patients with metastatic disease [23–40]. In addition, the mortality rates of the Thai general population at each age were also applied in the analysis.

Health outcomes

Health outcomes were LY and QALY gained, defined as the multiplication of utility weight or quality of life and life years. The quality of life scores in terms of utility scores were collected from patients receiving chemotherapy and caregivers using the EQ-5D questionnaire at the NCI [41,42]. The utility scores of patients without relapse were collected from two groups (i.e., 12 patients receiving the adjuvant oral capecitabine monotherapy and 12 patients receiving the adjuvant intravenous chemotherapy such as 5-FU/LV, FOLFOX and XELOX). For relapsed patients, the utility scores were collected from 12 patients receiving the first-line capecitabine for metastatic disease and 12 patients receiving the first-line intravenous chemotherapy such as FOLFOX, XELOX and FOLFIRI for metastatic disease. The mean utility score of patients without relapse was 0.85 (SE = 0.1) (Table 2) [43].

Uncertainty analysis

A one-way sensitivity analysis and a probabilistic sensitivity analysis (PSA) was undertaken to address the uncertainty of parameters in the model. The one-way sensitivity analysis was conducted to individually examine the uncertainty surrounding each parameter and presented the results as a tornado diagram. The threshold sensitivity analysis was also carried out to determine the cost-effective price in the case that the price of intervention exceeded the societal WTP threshold. Moreover, the PSA was carried out in order to simultaneously examine the effect of all parameter uncertainties using a second-order Monte Carlo simulation. Microsoft Excel 2007 (Microsoft Corp., Redmond, WA, USA) with the macro function was used to simulate by sampling from the distribution of each variable with 1000 iterations. The probability distributions were assigned to all parameters, such as beta-distribution for all probabilities and utility parameters and gamma-distribution for all cost parameters [44]. Eventually, these provided the average feasible results, expressed in terms of probabilistic values of total costs, LYs and QALYs as well as ICER in baht per LY and QALY gained. The results of the PSA were presented as cost–effectiveness acceptability curves.

Table 3. Total costs, life year and quality-adjusted life years of all interventions for stage III colon cancer patients aged 50 years based on a societal perspective.

Intervention		Total cost (THB)[†,‡]	Total LYs	Total QALYs
First line	*Second line*			
5-FU/LV	Capecitabine	586,000	4.09	3.11
5-FU/LV	FOLFOX	1,182,000	4.37	3.23
5-FU/LV	XELOX	1,211,000	4.16	3.10
Capecitabine	FOLFOX	1,278,000	5.11	3.92
Capecitabine	XELOX	1,301,000	4.91	3.81
5-FU/LV	FOLFIRI	1,311,000	4.25	3.16
Capecitabine	FOLFIRI	1,377,000	5.01	3.86
FOLFOX	FOLFIRI	1,610,000	6.69	5.27
XELOX	FOLFIRI	1,762,000	6.12	4.78

[†]Total costs are calculated in 2010 THB.
[‡]Costs are rounded up to nearest 1000 THB.
5-FU/LV: 5-Fluorouracil and leucovorin; FOLFIRI: Irinotecan plus 5-FU/LV; FOLFOX: Fluorouracil/leucovorin/oxaliplatin; THB: Thai baht; XELOX: Capecitabine/oxaliplatin.

Results

Cost-utility analysis

Total costs, LYs and QALYs of all treatments compared with the adjuvant 5-FU/LV and the first-line capecitabine for metastatic disease in patients aged 50 years based on a societal perspective are shown in Table 3. Progression-free survival of 5-FU/LV, capecitabine, XEROX or FOLFOX as adjuvant therapy was 3.31, 4.14, 5.30 and 5.30 years, respectively. The total cost of the adjuvant 5-FU/LV and the first-line capecitabine for metastatic disease was the lowest (586,000 THB), while that of the adjuvant XELOX and the first-line FOLFIRI for

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Table 4. Incremental cost–effectiveness ratio of all interventions compared with the first-line 5-fluorouracil and leucovorin and the second-line capecitabine.

Interventions		Incremental cost (THB)	Incremental LYs	Incremental QALYs	ICER per LY gained[†]	ICER per QALY gained[†]
First line	*Second line*					
FOLFOX	FOLFIRI	1,024,000	2.60	2.16	394,000	474,000
XELOX	FOLFIRI	1,176,000	2.03	1.66	580,000	707,000
Capecitabine	FOLFOX	691,000	1.02	0.81	677,000	855,000
Capecitabine	FOLFIRI	791,000	0.92	0.70	862,000	1,025,000
Capecitabine	XELOX	715,000	0.82	0.75	867,000	1,055,000
5-FU/LV	FOLFOX	595,000	0.28	0.11	2,137,000	5,205,000
5-FU/LV	FOLFIRI	725,000	0.16	0.05	4,406,000	14,567,000
5-FU/LV	XELOX	625,000	0.07	-0.01	9,485,000	Dominated[‡]

[†]ICERs are rounded up to nearest 1000 THB.
[‡]Negative ICER due to lower effectiveness and higher costs of the first-line 5-FU/LV and the second-line XELOX compared with the first-line 5-FU/LV and the second-line capecitabine.
5-FU/LV: 5-Fluorouracil and leucovorin; ICER: Incremental cost–effectiveness ratio; FOLFOX: Fluorouracil/leucovorin/oxaliplatin; THB: Thai baht; XELOX: Capecitabine/oxaliplatin; FOLFIRI; Irinotecan plus 5-FU/LV.

metastatic disease was the highest (1,762,000 THB). In this study, all interventions had higher cost and yielded more LYs compared with the adjuvant 5-FU/LV and the first-line capecitabine for metastatic disease. In addition, patients receiving adjuvant 5-FU/LV and the first-line XELOX for metastatic disease had more LYs (4.16) but less QALYs (3.10) compared with those receiving the adjuvant 5-FU/LV and the first-line capecitabine for metastatic disease (LYs = 4.09 and QALYs = 3.11). Moreover, patients receiving the adjuvant FOLFOX and then the first-line FOLFIRI for metastatic disease had the highest LYs (6.69) and QALYs (5.27).

The results obtained from the cost-utility analysis were presented as the ICER in THB per LY gained and QALY gained (Table 4) when compared with the adjuvant 5-FU/LV and the first-line capecitabine for metastatic disease. Of all the interventions, patients with stage III colon cancer receiving the adjuvant FOLFOX and the first-line FOLFIRI for metastatic disease had the lowest ICER value (394,000 THB per LY gained), whereas those receiving the adjuvant 5-FU/LV and the first-line XELOX for metastatic disease had the highest (9,485,000 THB per LY gained).

The ICER values in THB per QALY gained of all interventions exceeded the societal WTP threshold for a QALY in the Thai context. It was shown that all of the interventions might not be cost-effective compared with the adjuvant 5-FU/LV and the first-line capecitabine for metastatic disease based on a societal perspective. However, out of all the interventions, the adjuvant FOLFOX and the first-line FOLFIRI for metastatic disease had the lowest positive ICER value (474,000 THB per QALY gained), while the adjuvant 5-FU/LV and the first-line FOLFIRI for metastatic disease had the highest (14,567,000 and THB per QALY gained). Moreover, the adjuvant 5-FU/LV and the first-line XELOX for metastatic disease had a negative ICER value due to higher cost but less QALY gained, indicating that it was inferior to the adjuvant 5-FU/LV and the first-line capecitabine regimen for metastatic disease.

Uncertainty analysis

One-way sensitivity analysis

Figure 2 shows a tornado diagram presenting the results of the one-way sensitivity analysis in patients receiving the adjuvant FOLFOX and the first-line FOLFIRI for metastatic disease (i.e., the intervention with the lowest ICER value in this study). Discount rates of 0 and 6%, the 95% CI of transitional probabilities, utility scores and the minimum and maximum cost of FOLFOX (i.e., 197,000 and 507,000 THB) were used. It was found that when altering the value of each parameter, the ICER per QALY gained was the most sensitive to changes in the price of the FOLFIRI regimen, the discount rate of the outcome, the probability of relapse when treated with FOLFOX, the probability of death when treated with FOLFOX in the fourth year or longer in the 'without relapse' state and the utility score of stage III colon cancer patients.

Threshold sensitivity analysis

For stage III colon cancer patients, since the adjuvant FOLFOX and the first-line FOLFIRI for metastatic disease seemed to be the preferred choice of treatment, a threshold sensitivity analysis was also conducted to calculate the optimal price of FOLFOX and FOLFIRI based on a governmental perspective. If both the prices of FOLFOX and FOLFIRI were decreased by 25% (i.e., 224,000 THB for FOLFOX and 659,000 THB for FOLFIRI), the adjuvant FOLFOX and the first-line FOLFIRI for metastatic disease would be cost-effective with an ICER of 288,000 THB per QALYs gained. Moreover, if both prices of capecitabine and FOLFOX were reduced by 60% (i.e., 49,658 THB for capecitabine and 239,000 THB for FOLFOX), the adjuvant capecitabine and

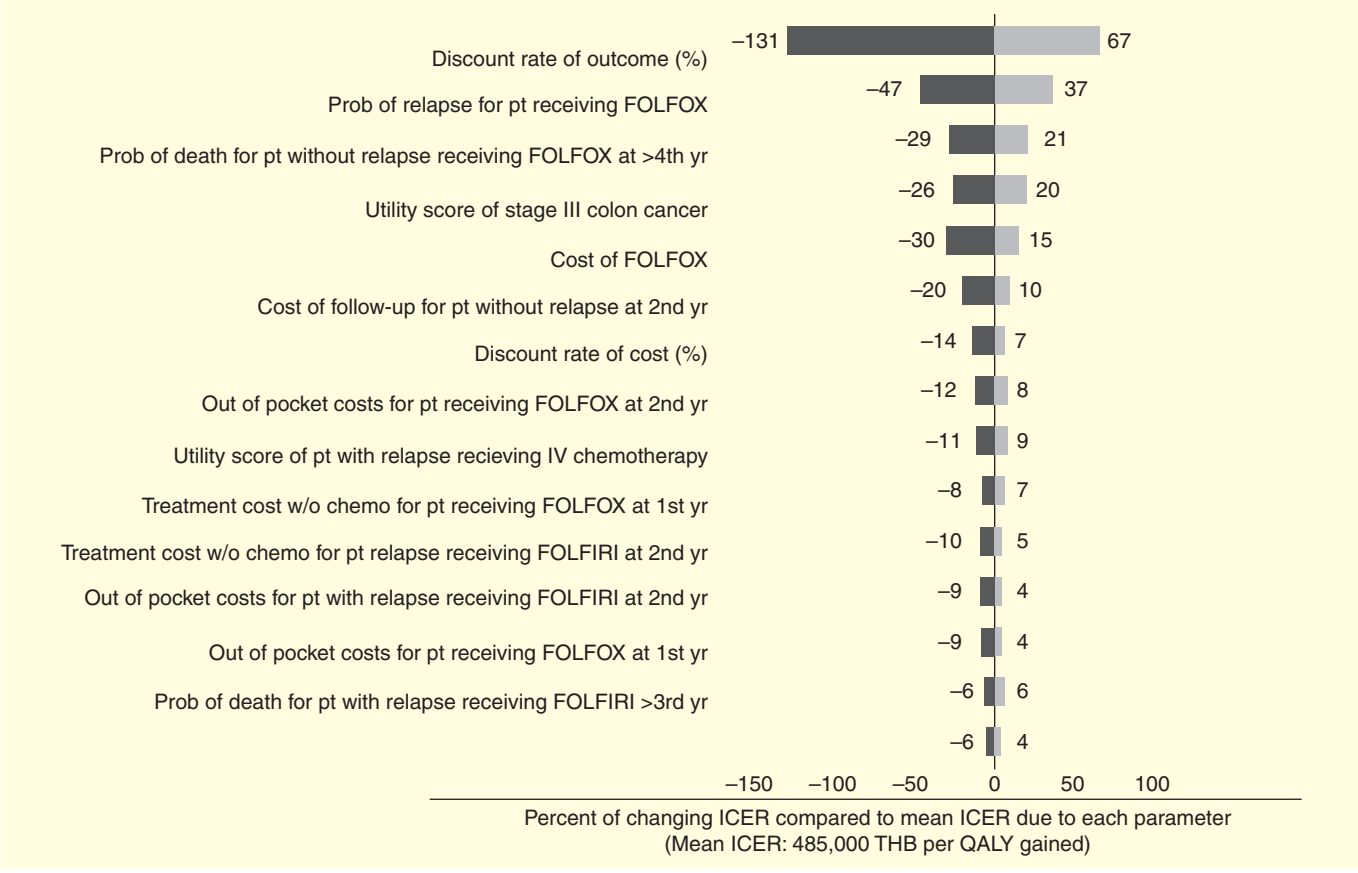

Figure 2. Tornado diagram of patients receiving the first-line FOLFOX and the second-line FOLFIRI.
Tornado diagram illustrates the percentage change in the ICER owing to the change of each individual parameter. The numbers at each end of the bars indicate the most extreme values used in the one-way sensitivity analysis.
FOLFIRI: Irinotecan plus 5-FU/LV; FOLFOX: Fluorouracil/leucovorin/oxaliplatin;
5-FU/LV: 5-Fluorouracil and leucovorin; QALY: Quality-adjusted life year; THB: Thai baht; XELOX: Capecitabine/oxaliplatin.

the first-line FOLFOX for metastatic disease would be cost-effective with an ICER of 282,000 THB per QALYs gained. Furthermore, for those with relapse, the price of FOLFOX in the regimen (i.e., the adjuvant 5-FU/LV and the first-line FOLFOX for metastatic disease) would have to be decreased to 194,000 THB per year in order to make FOLFOX cost-effective, indicating that the mean price of oxaliplatin should be reduced to 24 THB per mg.

Probabilistic sensitivity analysis

Figure 3 demonstrates the cost–effectiveness acceptability curves based on the PSA results among stage III colon cancer patients receiving each chemotherapy regimen. The probabilities of the adjuvant 5-FU/LV and the first-line capecitabine for metastatic disease being cost-effective were 68 and 40%, respectively, at the WTP threshold of 100,000 and 300,000 THB per QALY gained. Moreover, the probabilities of the adjuvant FOLFOX and the first-line FOLFIRI for metastatic disease being cost-effective were 3 and 28% at the WTP threshold of 100,000 and 300,000 THB per QALY gained, respectively. When the WTP threshold was increased, the probabilities of the adjuvant 5-FU/LV and the first-line capecitabine for metastatic disease being cost-effective decreased, while all other interventions increased. For example, as the WTP based on a societal perspective increased to 1,350,000 THB per QALY gained, the probability that the adjuvant 5-FU/LV and the first-line capecitabine for metastatic disease is cost-effective would be decreased to 1%, while the probability that the adjuvant FOLFOX and the first-line FOLFIRI for metastatic disease or other interventions are cost-effective would be increased to 79%.

Discussion

Given that the Thai Subcommittee for Development of the NLEM requested economic evaluation information of an adjuvant chemotherapy regimen, particularly an oxaliplatin-added regimen in stage III colon cancer patients after resection, the results from this study would be applied to determine whether oxaliplatin should be included into the NLEM. The use of oxaliplatin as the adjuvant therapy in stage III colon cancer patients is well established and widely accepted around the world including Thailand, especially in the patients with good performance status [8–10]. Nevertheless, the 5-FU-based chemotherapy including capecitabine has also been accepted as a

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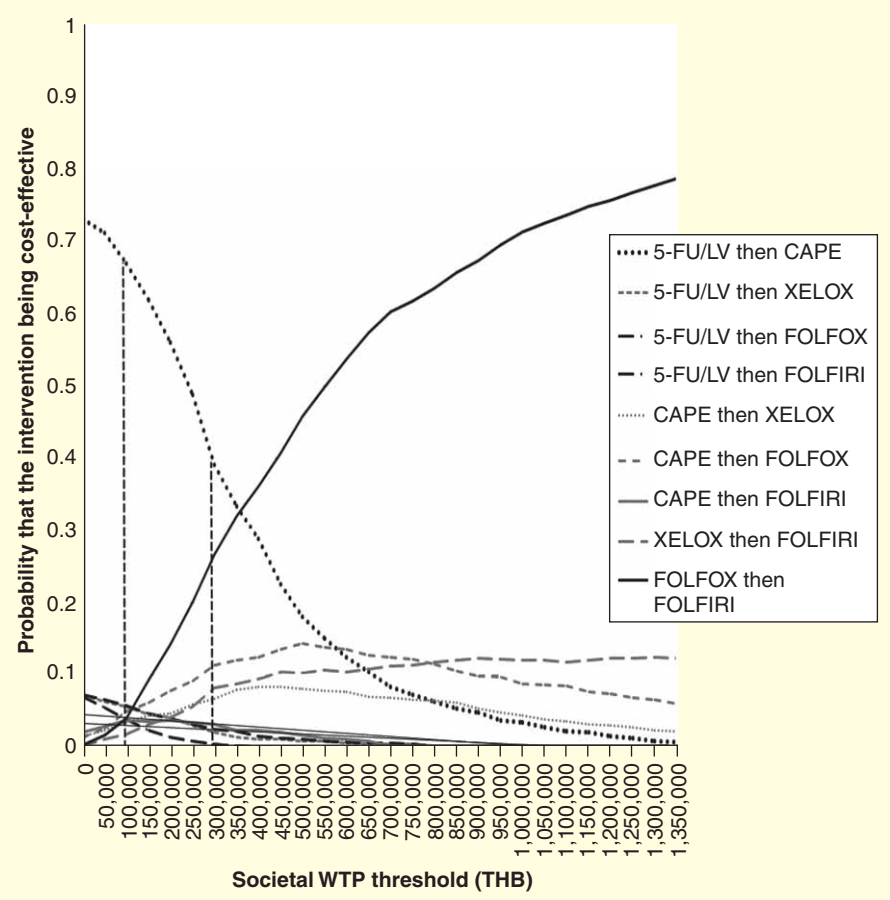

Figure 3. Cost–effectiveness acceptability curves of all interventions for stage III colon cancer patients.
These graphs illustrate the relationship between the probabilities of each intervention being cost-effective and different societal WTP thresholds. Dashed lines represent the thresholds for the adoption of health interventions in Thailand.
FOLFIRI: Irinotecan plus 5-FU/LV; FOLFOX: Fluorouracil/leucovorin/oxaliplatin; 5-FU/LV: 5-Fluorouracil and leucovorin; QALY: Quality-adjusted life year; THB: Thai baht; XELOX: Capecitabine/oxaliplatin.

choice of treatment in the patients with poor performance status, even though it yields an inferior survival when compared with oxaliplatin-based chemotherapy in Thailand. Therefore, this study was the first to compare the cost-utility of all available chemotherapy regimens with the adjuvant 5-FU/LV and the first-line capecitabine for metastatic disease in patients with stage III colon cancer based on a societal perspective in the Thai context.

Based on the results, all of the interventions were not cost-effective compared with the adjuvant 5-FU/LV and the first-line capecitabine for metastatic disease in Thai context since their ICER values were greater than the societal WTP threshold of one-to three-times the GDP per capita (i.e., 100,000–300,000 THB per QALY gained) recommended by the Thai Subcommittee for Development of the NLEM and the Subcommittee of the Development of Benefit Package and Service System, NHSO. The adjuvant 5-FU/LV and the first-line capecitabine for metastatic disease would be the most cost-effective chemotherapy regimen and has already been included in the NLEM. Thus, 5-FU/LV should be considered as the first drug for the treatment of stage III colon patients, and capecitabine should be given for all patients who relapsed and required treatment.

When considering the next best intervention based on a societal perspective, the adjuvant FOLFOX and the first-line FOLFIRI for metastatic disease seemed to be the choice of treatment for stage III colon cancer patients since its ICER value yielded the lowest value compared with other interventions. The threshold sensitivity analysis results suggested that if both prices of FOLFOX and FOLFIRI were decreased by 25%, the adjuvant FOLFOX and the first-line FOLFIRI for metastatic disease would be cost-effective in Thai context. In addition, if both the prices of capecitabine and FOLFOX were reduced by 60%, the adjuvant capecitabine and the first-line FOLFOX for metastatic disease would also be cost-effective in the Thai context.

Moreover, for colon cancer patients with relapse, our results suggested that if the adjuvant 5-FU/LV was given, the first-line FOLFOX for metastatic disease would be the next best intervention. The first-line FOLFOX for metastatic disease yielded higher cost (595,000 THB) and QALYs (0.11) gained compared with the first-line capecitabine for metastatic disease. The price of FOLFOX (i.e., 5-FU/LV plus oxaliplatin) in relapse state would need to be decreased to 75,943 THB per year in order to make FOLFOX cost-effective at the WTP threshold of 300,000 THB per QALY gained. However, this price did not seem possible because the price of only 5-FU/LV without oxaliplatin was already 117,000 THB per year, significantly higher than the price at the cost–effectiveness threshold. The results from this study showed that oxaliplatin with a mean price of 147 THB per mg would not be cost-effective in the Thai context [16]. Since the adjuvant 5-FU/LV and the first-line capecitabine for metastatic disease is the most cost-effective option compared with all other interventions and is already included in the NLEM, a budget impact analysis is not required in this study.

Nevertheless, our study results were not in accordance with other previously published studies. All studies indicated that oxaliplatin was more cost-effective compared with 5-FU/LV [45–47]. This can be explained by the fact that our study considered the set of eight interventions which imitate the

actual current clinical practice in Thailand (including both adjuvant and the first-line chemotherapy for metastatic disease compared with the adjuvant 5 FU/LV and the first-line capecitabine for metastatic disease), while previous studies [45,46] compared only the adjuvant 5-FU/LV with the adjuvant FOLFOX in patients with stage III colon cancer. For example, the expected survival of relapsed patients after receiving FOLFOX in the study by Eggington *et al.* [47] was assumed to be the same as that of relapsed patients after receiving 5-FU/LV, while expected survival data in this study were instead obtained from the meta-analysis of the randomized controlled trails related to the clinical efficacy of each chemotherapy regimen among patients after relapse. However, the health outcomes (i.e., LYs and QALYs) in this study were quite similar to those obtained from previous studies [45–47].

Results and policy recommendations from this study were presented twice to the Subcommittee for Development of the NLEM. Even though the results suggested that FOLFOX, which contains oxaliplatin, was not presently cost-effective at a societal WTP threshold in the Thai context, the committees agreed that it is a very effective adjuvant chemotherapy as clearly demonstrated in the increase in patients' survival (i.e., 6.69 LYs and 5.27 QALYs) [48]. Therefore, the committees reached the consensus that oxaliplatin should be included into the NLEM since this would be greatly beneficial to the patients with stage III colon cancer. Due to the current high price of oxaliplatin, the committees agreed to adopt the estimated cost-effective price from this study and proposed to the Subcommittees for Price Negotiation of the NLEM to negotiate for a price reduction with pharmaceutical companies.

In addition to cost considerations, it is noteworthy to highlight that the use of capecitabine as the first-line chemotherapy for a metastatic disease would be difficult to determine whether stage III colon cancer patients rapidly progressed after 5-FU/LV therapy, since it is inferior to combination therapy. Currently, it is known that capecitabine can be combined with other active drugs such as oxaliplatin and its combination has demonstrated as a new standard of care for metastatic colorectal cancer [49]. Moreover, a reviewed study in Chinese indicated that capecitabine and its combination yielded high clinical response and tolerability in Chinese patients with a metastatic colorectal cancer [50]. Its toxicity is also usually manageable and elderly patients can tolerate well [50]. Similar to Thailand, it is noted that capecitabine is well tolerated and more feasible for state III colon cancer patients when compared with 5-FU/LV. However, compared with 5-FU/LV, capecitabine is not inevitably better tolerated in patients with impaired renal function. The study by Iwai *et al.* suggested that drug dosage of capecitabine should be managed while monitoring the renal function for Japanese patients [51].

Furthermore, when considering the use of adjuvant oxaliplatin therapy, its benefits depending on patient's age should be discussed. The study by Goldberg *et al.* revealed that safety and efficacy of FOLFOX (i.e., oxaliplatin added regimen) was not different between patients aged <70 years and those with age >70 years [52]. In contrast, the analysis results obtained from Adjuvant Colon Cancer Endpoints (ACCENT) database suggested that the benefit of newer chemotherapy regimens might be limited to patients aged <70 years [53]. However, most published studies on safety and efficacy of adjuvant oxaliplatin therapy have been performed in Western countries, while there is very limited information on the benefits of adjuvant oxaliplatin therapy in Asia. Interestingly, the study in Korea found that adjuvant oxaliplatin chemotherapy yielded similar efficacy without significant increase in toxicity in older patients aged ≥65 when compared with younger stage III colon cancer patients after resection. This study recommended the use of oxaliplatin as the safe and effective adjuvant chemotherapy for stage III colon cancer patients after resection in Asia [54].

It is very important to address the limitations in this study. First, due to an incomplete computer-based information system before 2005, direct medical costs used in this study were obtained from the data available during 2005–2010 at the NCI. In addition, direct non-medical and indirect costs as well as utility data were collected from an interview with a relatively small cohort of stage III colon cancer patients with and without relapse, stage IV patients receiving either oral or intravenous chemotherapy regimens and their caregivers in the same hospital. Using the data obtained from a single tertiary hospital in Bangkok could nevertheless overestimate the true costs of direct medical, direct non-medical and indirect costs, as patients might have more complicated conditions which lead to higher healthcare costs compared with those receiving care from other hospitals in rural areas. Second, the utility score of follow-up patients were obtained from published articles in foreign countries, and thus may be different from the utility scores of Thai people due to differences in culture and healthcare infrastructure. This indicates that there is an area where further studies using local data are needed. Third, we assumed that expected survival of patients after relapse was independent from the efficacy of adjuvant treatment initially given due to the lack of survival data. Fourth, even though there are significant differences in benefits dependent on subsets of stage III colon cancer patients (i.e., stage IIIA, IIIB and IIIC) as well as human genetics (e.g., high microsatellite instability [MSI-H] and BRAF tumors), we considered stage III colon cancer patients after resection without the classification of stage III subsets due to a very limited data. Last, our study focused on the cost–effectiveness of adjuvant therapy options, especially oxaliplatin added regimens in stage III colon cancer patients after resection, therefore we did not consider targeted therapy in metastatic disease as an alternative treatment, since it is too expensive for most patients in the country to get an access to the treatment. Future research should be further investigated in these areas.

In conclusion, the adjuvant 5-FU/LV and the first-line capecitabine for metastatic disease is the most cost-effective chemotherapy regimen. The adjuvant FOLFOX and the

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first-line FOLFIRI for metastatic disease, the next best intervention, would be cost-effective based on a societal perspective if both the prices of FOLFOX and FOLFIRI were decreased by 40%. Although 5-FU/LV and capecitabine are already listed in the NLEM, these chemotherapy regimens are still very costly. It is suggested that the price of these regimens should be decreased via negotiation with pharmaceutical companies so that more patients will have access to these treatments.

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Key issues

- Adjuvant chemotherapy regimens can significantly prolong patients' survival; however, oxaliplatin added regimens are very costly. In Thailand, there has been no economic evaluation study of adjuvant chemotherapy for stage III colon cancer patients after resection.
- The total cost of the adjuvant 5-FU/LV and the first-line capecitabine for metastatic disease was the lowest at 586,000 THB, while that of the adjuvant XELOX and the first-line FOLFIRI for metastatic disease was the highest at 1,762,000 THB. All interventions had higher cost and yielded more LYs than the adjuvant 5-FU/LV plus the first-line capecitabine for metastatic disease.
- The adjuvant 5-FU/LV plus the first-line capecitabine for metastatic disease would be the most cost-effective chemotherapy.
- The adjuvant FOLFOX and the first-line FOLFIRI for metastatic disease, the next best intervention, would be cost-effective with an ICER of 299,365 THB per QALY gained based on a societal perspective if both prices of FOLFOX and FOLFIRI were decreased by 40%.

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PLOS ONE

Assessing the Accuracy and Feasibility of a Refractive Error Screening Program Conducted by School Teachers in Pre-Primary and Primary Schools in Thailand

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Abstract

Introduction: As part of the development of a system for the screening of refractive error in Thai children, this study describes the accuracy and feasibility of establishing a program conducted by teachers.

Objective: To assess the accuracy and feasibility of screening by teachers.

Methods: A cross-sectional descriptive and analytical study was conducted in 17 schools in four provinces representing four geographic regions in Thailand. A two-staged cluster sampling was employed to compare the detection rate of refractive error among eligible students between trained teachers and health professionals. Serial focus group discussions were held for teachers and parents in order to understand their attitude towards refractive error screening at schools and the potential success factors and barriers.

Results: The detection rate of refractive error screening by teachers among pre-primary school children is relatively low (21%) for mild visual impairment but higher for moderate visual impairment (44%). The detection rate for primary school children is high for both levels of visual impairment (52% for mild and 74% for moderate). The focus group discussions reveal that both teachers and parents would benefit from further education regarding refractive errors and that the vast majority of teachers are willing to conduct a school-based screening program.

Conclusion: Refractive error screening by health professionals in pre-primary and primary school children is not currently implemented in Thailand due to resource limitations. However, evidence suggests that a refractive error screening program conducted in schools by teachers in the country is reasonable and feasible because the detection and treatment of refractive error in very young generations is important and the screening program can be implemented and conducted with relatively low costs.

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Introduction

Refractive error is a major cause of visual impairment and the second-most common cause of blindness in the world [1]. On World Sight Day in 2006, the World Health Organization (WHO) revealed that 153 million people aged older than five years were visually impaired due to uncorrected distance refractive error [2]. It was also estimated that the productivity lost from refractive error worldwide is over USD 269 billion [3]. In children, the prevalence of refractive errors varies widely across countries. For example, the prevalence of refractive errors was reported in primary school children in rural Tanzania at less than 1% [4], 8% in Kathmandu (Nepal) [5], 15% in Malaysia [6], 37% in Hong Kong [7], and more than 50% in Singapore [8]. In Thailand, the 4th National Survey of Blindness in 2006–07 estimated that 15 million people were living with visual impairment due to uncorrected refractive

error [9]. The prevalence of refractive error in primary school children (6–12 years old) in Bangkok was recently reported at approximately 13% [10].

A refractive error is correctable with spectacles, contact lenses or laser surgery; spectacles are the most available and least expensive method. However, the Refractive Error Survey in Children (RESC) – a cross-country survey about refractive error in children - indicated that the coverage of refractive corrections is no more than 50% in most regions of the world [11]. Severe visual impairment from uncorrected refractive error not only reduces the quality of life for an individual but may also impede education, delay personality development, and obstruct career opportunities [12]. These outcomes can also cause economic burden on the family and society as a whole. A study in India showed that one-fifth of refractive error-related blindness resulted from uncorrected high refractive error during childhood which is preventable if proper screening and provision of spectacles are available [13]. Although the diagnosis and treatment of refractive errors is simple, access to these procedures is still problematic due to many factors such as the lack of conclusive evidence regarding the effectiveness of the screening method, limited resources, and inadequate eye-care services in many countries.

A WHO study titled "Global Magnitude of visual impairment caused by uncorrected refractive errors" suggested that the screening of children for refractive errors should be conducted at the community level and integrated into school health programs where training and information programs should also be designed for teachers and school health-care workers [11]. However, there is no common agreement on what the best screening strategy is because different countries have different levels of health infrastructure development and methods to engage young children and their parents. Another previous study examined different strategies for school children that were conducted by teachers in Africa, Asia, America, and Europe and found that all of the screening strategies combined with the provision of spectacles were very cost-effective [14]. Thus, this study focuses on the development of a system for the screening of refractive error by teachers to formulate a national policy on screening and correcting refractive errors in Thai children.

Methods

i. Ethics Statement

Researchers sent a letter to all parents regarding the details of the study before any type of screening was performed. The written consents from parents were obtained only for children with positive screening results so they could undergo further eye examinations at hospitals. Written consents were not necessary for the screening performed by teachers and health professionals as visual acuity (VA) screening is a standard practice recommended by the WHO and many governments around the world, and is therefore not a harmful procedure. All signed consents from parents were reviewed by teachers and researchers and the consents will be kept for 5 years from the date of October 2011. The researchers received ethical clearance from the ethical committee of Medical Science in July 2011 before the study was conducted.

ii. Study Design and Procedure

A cross-sectional descriptive and analytical study was conducted from October 2011 to January 2012. A two-staged cluster sampling was employed to select four representative provinces from four regions, resulting in the eventual selection of 17 schools. The schools were selected based on two main factors: i) school size (the number of students per school is similar to the third column in Tables S1.2 and S1.3 in File S1), and ii) the willingness of teachers to participate in the study. This was to ensure that the size of participants (screened students) was in proportion to the total population of eligible children in each province. It is important to note that the teachers' willingness to participate in the study was not a main factor because we did not find any school that refused to participate in this study. For the selection of participants, we included all of the students from the selected schools. A total of 5,885 students from pre-primary (4–6 years) and primary school grades (7–12 years) and 223 homeroom teachers participated in the study. A detailed breakdown of the sample size calculation is given in Section S1 in File S1.

In October and November of 2011, a number of ophthalmologists and ophthalmic nurses conducted a one-day training session for pre-primary school teachers in each of the provinces which focused on how to perform VA tests. During the training, the tools that were needed to conduct the VA tests (i.e. the VA screening manual, testing charts, eye occluders, and pinhole occluders) were provided. All teaching-conducted VA testing took place within a month of the teachers having received the training. A research team comprising ophthalmologists and ophthalmic nurses then tested the same pre-primary and primary school students in all of the selected schools between December 2011 and January 2012 using the same tools. The research team subsequently referred all children who had PVA worse than 20/40 in either eye and other eye disorders such as strabismus, latent strabismus, and congenital ptosis, to undergo further examination at the local provincial hospital. The research protocol is provided in Section S2 in File S1.

iii. Ophthalmic Examination

a) Visual Acuity Testing. Participants were tested for 'presenting visual acuity' (PVA) - where participants who own spectacles were tested while wearing them. Testing was conducted on both eyes using the relevant eye chart - the 'Lea symbols distance visual acuity chart' for pre-primary school children (4–6 years old), the 'E chart' for the first years of primary school (7 years old), and the 'Snellen chart' for the remaining primary school children (8–12 years old). For each eye, the PVA was calculated according to the number of symbols or letters read correctly from 20/200 to 20/20. The PVA level was determined at the threshold where the child was able to read more than half of the given line. Children with a PVA level of less than 20/40 in either eye were referred to the local hospital. The guidelines that were used to measure the PVA for each group of children are given in Table S3.1 in File S1.

The PVA was classified according to the WHO ICD 10 classifications as follows: mild or no visual impairment: equal to or better than 20/70; moderate visual impairment: worse than 20/70 - equal to or better than 20/200; severe visual impairment to blindness: worse than 20/200.

b) Eye Examination. All of the children who had taken the tests were then examined at schools by the trained ophthalmologists using the same screening protocol. Any children who had normal VA but displayed symptoms of an eye disorder that required further diagnosis and treatment such as strabismus, latent strabismus, and congenital ptosis were subsequently referred to the local provincial hospital.

c) Diagnostic Procedure. All participants that were referred to the local provincial hospital underwent a thorough ophthalmic examination by both a general and pediatric ophthalmologist (with written informed consent from the parents). Auto refraction was performed and the ocular alignment, external eye, and anterior

segments were examined in all of the referred children. Cycloplegia and dilatation were induced three times at intervals of 5 minutes by instillation of cyclopentolate 1% eye drops in children who had PVA worse than 20/40 in either eye. Auto refraction and manual refraction were then performed 30 minutes after the instillation of the last drop, and the posterior segment was examined after dilatation. A pediatric ophthalmologist made the final diagnosis and prescribed proper spectacle power for individuals who required it free of charge. Section S4 in File S1 contains the definitions that were used to diagnose eye disorders. Section S5 in File S1 describes the criteria used for spectacle prescription.

iv. Statistical Analysis

Statistical analyses were carried out using PVA data from the participants' worst eye because empirical evidence has revealed that treating the worse eye in children has substantial benefits, especially in amblyopia. Thus, this screening program aims to detect all of the eyes with abnormal visual acuity. In the analysis of screening accuracy (i.e. sensitivity, specificity, and detection rate), only children who failed the VA test and were referred to hospitals were included in the analysis.

v. Data Management

A sensitivity analysis was carried out on 5,303 students - 1,132 in pre-primary and 4,171 in primary - all of whom underwent a PVA test conducted by both teachers and professionals. We excluded data from students who were only tested by one group.

vi. Focus Group Discussion

A set of 16 focus groups were convened among parents and teachers between September and October 2012 to understand more about the feasibility and limitations of establishing a school-based refractive error screening program. For teachers, we asked for their opinion regarding the feasibility and willingness to participate in the screening program as well as related factors if implemented. For parents, we focused on their general awareness of refractive error in children, particularly their own, and their attitude towards school-based screening and further treatment. In every province, the focus group discussions were carried out according to the geographic location of the schools (whether they were located in an urban or rural area). Within each area, separate focus groups were held for parents and teachers. In every section, the teachers involved had varying rates of sensitivity value (low, medium, and high) and came from both pre-primary and primary sectors. For the parent groups, we invited the parents of children both with and without refractive errors. All interviews were recorded on audiotape and transcribed verbatim. The first and the fourth authors read all the Thai transcripts to explore the respondents' experience with children with refractive error as well as attitudes and acceptance of the school-based screening.

Results

Overview of the research findings

Out of the 5,885 participating students, 5,703 children were screened by teachers, 5,461 by professionals, and 5,303 by both groups. The average age of pre-primary school students was 5 years (SD $\pm$0.9) while that of primary school students was 9 years (SD $\pm$1.8), with the male and female ratio being nearly equal. The average number of students screened by each pre-primary school teacher was 22 (SD $\pm$10) while that of each primary school teacher was 26 (SD $\pm$13). These general characteristic can be seen in Table 1. Of all the students screened by professionals (n = 5,461), 624 (11.4%) were referred to ophthalmologists at provincial hospitals as a result of exhibiting PVA levels less than 20/40 in either eye and/or abnormal results following an eye examination. However, only 470 (8.6%) children went for further examination at the provincial hospital because some of the children did not obtain consent from their parents or some did not show up at the hospital on the appointed day. Among the children who completed the examination (n = 470), 425 children were diagnosed with at least one eye disorder and 363 students were diagnosed with refractive error. Of the students with refractive error, 226 students received spectacles and 138 students were trained for near point convergence exercise. Ten students who were deemed likely to require surgical interventions were referred to specialist centers. Finally, refractive amblyopia was seen in 36 students, representing a delay diagnosis and correction of refractive error.

Sensitivity and specificity of teachers' screening

Sensitivity values relating to the accuracy of pre-primary and primary school teachers' screening ability were assessed by comparing the accuracy of their diagnosis against three gold standards - Gold Standard 1, which refers to the accuracy rate of VA testing conducted by health professionals in a school setting; Gold Standard 2, which refers to the accuracy rate of VA testing conducted by a pediatric ophthalmologist at a local hospital following referrals resulting from testing in school; and Gold Standard 3, which refers to the accuracy rate of testing for significant refractive error (error requiring corrective eyeglasses) at a local hospital in addition to the Gold Standard 2 requirements. Figure 1 shows the selection process for the sensitivity analysis and outcomes of the screening process by both health professionals and teachers in relation to these three gold standards. Among the students who have low VA, 60 students out of 80 in pre-primary and 74 students out of 207 children in primary school students were misdiagnosed by the teachers as normal. They also incorrectly diagnosed 60 students out of 1,094 in pre-primary and 93 out of 3,964 in primary school students as low VA even though their VA was normal.

Sensitivity values among pre-primary school teachers (when measured against the three gold standards defined) were 25% (95% confidence interval of 23% to 27%), 28% (95% confidence interval of 26% to 30%), and 35% (95% confidence interval of 33% to 37%), while those of primary school teachers were 59% (95% confidence interval of 57% to 61%), 60% (95% confidence interval of 58% to 62%), and 65% (95% confidence interval of 63% to 67%). Specificity values were found to be high at around 97 to 98% in both groups. Table 2 describes the sensitivity and specificity values when compared with the three gold standards for both groups. In addition, results from a subgroup analysis found no significant difference across the categories of the examinee's age.

Detection rate for teachers according to the severity of the visual impairment

Among children with mild visual impairment, pre-primary school teachers were able to detect 8 cases out of 38 while primary school teachers detected 63 out of 122. Detection rates increased for children with moderate visual impairment - pre-primary school teachers were able to detect 8 cases out of 18 while primary school teachers could detect 40 out of 54. Although a number of children were diagnosed with severe visual impairment by the teachers, none of these children were found to have severe visual impairment upon professional examination. Figure 2 shows the

Table 1. Age, gender, and number of students screened by each teacher.

	Age
Pre-primary school students	5 (SD ±0.9)
Primary school students	9 (SD ±1.8)
	Gender (Male: Female)
Pre-primary school students	694 (52%): 641(48%)
Primary school students	2,308 (51%): 2,242 (49%)
	Number of students screened by each teacher
Pre-primary school level	22 (SD ±10)
Primary school level	26 (SD ±13)

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detection rate by teachers for the different levels of impairment severity.

The best cut-off point for defining visual impairment and referral for further investigation

The sensitivity of pre-primary school teachers abruptly rose to 74% when the cut-off point changed from 20/40 to 20/32. The estimated number of students receiving spectacles increased more than twofold with this cut-off point. Although the sensitivity of primary school teachers rose to 70% at the cut-off point of 20/30, the estimated number of students who were prescribed spectacles did not increase significantly. Tables 3 and 4 reveal the estimated number of pre-primary and primary students receiving spectacles at different cut-off points.

Focus group discussion among the teachers

The data collected as part of the focus groups indicated that teachers who screened their homeroom students did not feel that conducting the examinations yearly was a burden; instead, many felt proud to be able to help their students. However, some teachers lacked confidence in their ability to screen because of their perceived lack of experience. They requested that a significant period of time be given to the VA measurement training workshop - which was found to be the most important part of screening program - so that they had sufficient time to

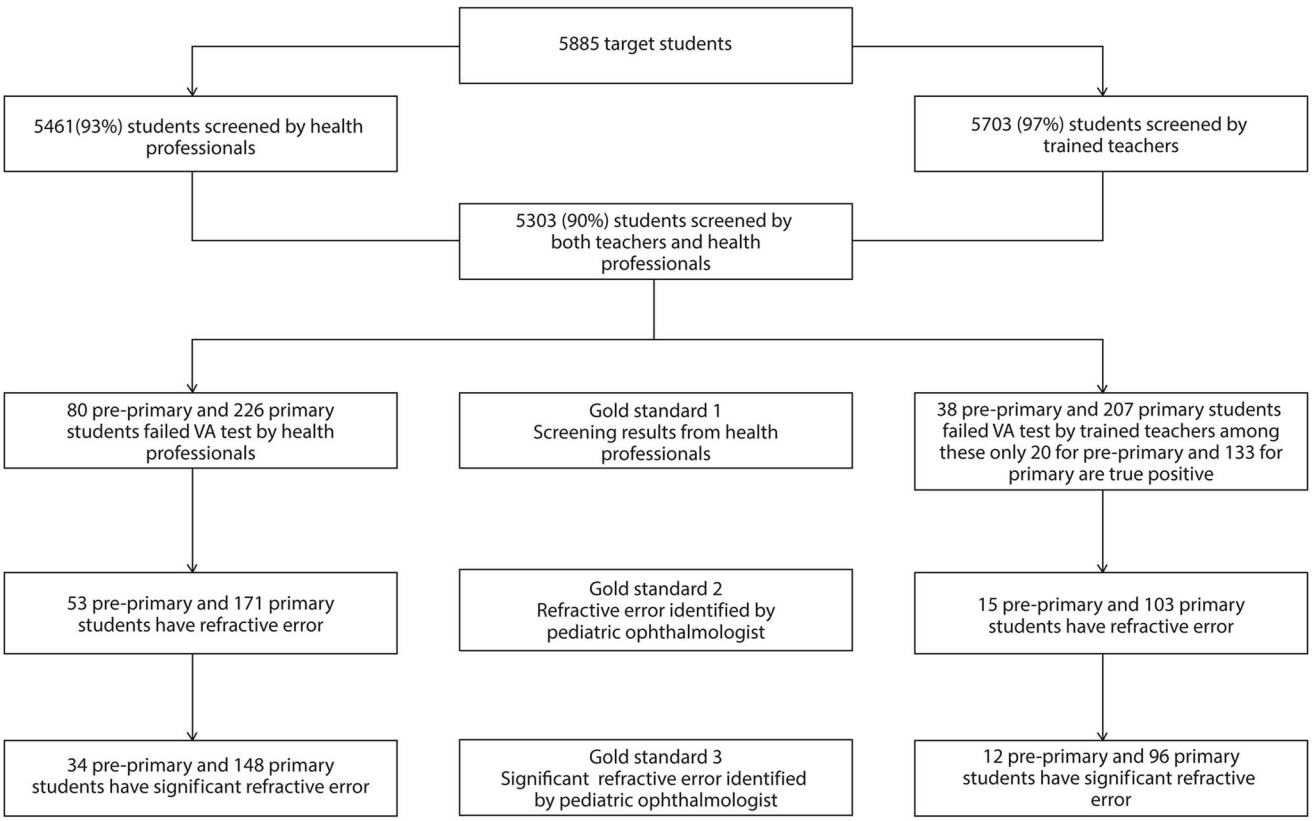

Figure 1. Selection of sample for sensitivity analysis.
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Table 2. Sensitivity and specificity value of the teachers with various levels of gold standards.

Gold standards	Sensitivity	Specificity
Participants	**(95% confidence interval)**	**(95% confidence interval)**
Gold Standard 1: Screening results from the professionals		
Pre-primary school teachers	25% (23% to 27%)	98% (97% to 99%)
Primary school teachers	59% (57% to 61%)	98%
Gold Standard 2: Refractive error identified by pediatric ophthalmologist after screening by professionals		
Pre-primary school teachers	28% (26% to 30%)	98% (97% to 99%)
Primary school teachers	60% (58% to 62%)	97%
Gold Standard 3: Clinically significant refractive error identified by pediatric ophthalmologist after screening by professionals		
Pre-primary school teachers	35% (33% to 37%)	98% (97% to 99%)
Primary school teachers	65% (63% to 67%)	97%

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practice the screening techniques. As such, it is recommended that the training workshop should be provided at least once a year. Although the VA screening manual is very useful, it cannot be used alone without training. Pre-primary school teachers found that screening in very young children was very complicated, took a longer time, and required more patience. As such, it is recommended that at least two people (one teacher and one assistant) conduct the screening among children in this age group. Teachers often repeated measurements when students indicated a visual impairment to be sure that they were assessing the students appropriately. When teachers encountered problems with examining the children, they tended to ask another teacher to help them. Payment was not found to be an important incentive but teachers did indicate that the provision of an extra payment might encourage rapid and willing screening, although it was not a prerequisite for their willingness to conduct the screening.

Teachers found that children who had refractive error and always wore spectacles had better behavior when studying or playing at school than those who needed to wear spectacles but did not. Reasons given for not wearing spectacles included the risk of being teased by friends, the practical annoyance of wearing spectacles, unawareness among parents of the child's need or an unwillingness on the part of parents for their child to wear spectacles, the feeling that spectacles did not fit onto the child's face, or the fact that the spectacles had been lost. Most teachers

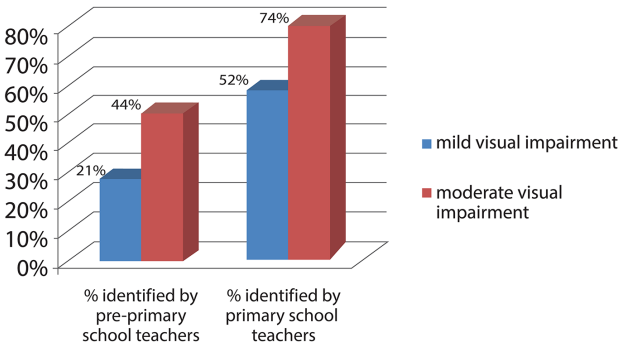

Figure 2. Detection rate of the teachers according to the severity of visual acuity level. Mild or no visual impairment: PVA equal to or better than 20/70; moderate visual impairment: PVA worse than 20/70 - equal to or better than 20/200; severe visual impairment to blindness: PVA worse than 20/200.
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believed that parents were an important part of the screening program. As such, it is vital that parents should be made aware of the risks and symptoms of refractive error in their children. This evidence suggests that an in-school teacher-led screening program will be successful and useful if it is built on a foundation of multidisciplinary cooperation between all stakeholders including policy-makers, local authorities, local hospitals, ophthalmologists, nurses, teachers, and parents.

Focus group discussion among the parents

Most parents whose children were found to have a visual impairment had never suspected that their child might be experiencing difficulties with their sight, even when they observed certain behaviors such as watching TV or reading books very close up or when their child's writing was well outside the lines. Most parents never considered that these behaviors might be related to refractive error; instead, most saw them as quirks of childhood that would disappear as their child grew up. In addition, the majority of parents were under the impression that refractive errors were health problems that only happened to adults and the elderly; indeed, a few thought that spectacle-wearing made the child's visual problem worse and made the child look unintelligent.

Only very few parents had previously brought their children to a local optician or ophthalmology clinics/hospitals upon recognizing that their children might have visual problems. Despite the fact that spectacle costs are lower at ophthalmology clinics or hospitals than at local opticians, many parents preferred to bring children to a local optician rather than an ophthalmology clinic or a hospital because local opticians are regarded as more convenient, e.g. they are usually located nearer to their home, there is relatively little waiting time required, and - as a result of significant TV advertising by many optician companies - the service is regarded as better by many parents.

Having been informed about this study, almost all parents expressed willingness to have their children participate in a school-based screening program. Furthermore, they also asked that teachers provide more information to them about the screening program so that they could cooperate further. Lastly, all parents were willing to pay for spectacles if it was found that their children needed them to correct refractive error, although the amount they were willing to pay per year varied from 500 to 3,500 Baht with an average of 1,000 Baht.

Table 3. Defining the best cut-off point for pre-primary school teachers' screening and estimated cases for a nationwide program.

Possible cut-off points	Sensitivity	Specificity	Estimated number of children referred for diagnosis*	Estimated number of children receiving spectacles*
20/20	93%	22%	1,264,085	46,401
20/25	76%	36%	1,026,454	42,183
20/32	74%	46%	887,250	42,183
20/40	25%	98%	53,432	16,873
20/50	16%	99%	30,934	12,655
20/64	6%	100%	11,249	7,031
20/80	1%	100%	5,624	1,406
20/100	1%	100%	1,406	1,406
20/126	0%	100%	0	0
20/160	0%	100%	0	0
20/200	0%	100%	0	0

** Hypothetical situation for 1,591,704 pre-primary school students [28]; children receiving spectacles are the children who have significant refractive error.*
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Discussion

This study found that the prevalence of refractive error among Thai school children is 6.6%, similar to some Asian countries but lower than in Singapore and China [15–19]. While other countries are struggling in establishing a population-based refractive error screening for children [20–22], this study demonstrates that refractive error screening by teachers is accurate and feasible in Thailand. However, we suggest that the cut-off points used for teacher-conducted screening should be different from those used by health professionals - especially among pre-primary school teachers - to maximize effective diagnosis. In our study, although 58 students already used spectacles (equivalent to 26% of those who needed spectacles), only 14 of them (equivalent to 6% of the children who needed spectacles) had accurate spectacles. Without our school-based screening, 168 students with refractive error (including 36 students with refractive amblyopia) would have never been diagnosed. Given the fact that these 168 students were found to have clinically significant refractive error, it is almost certain that this would have adversely affected their ability to access opportunities for childhood development.

Our study reveals a significant willingness on the part of the teachers to perform the screening. In addition, parents expressed interest in having their children screened by teachers because they trust them and also understand that it is not possible for health professionals to screen every child given their limited numbers. As a result, we strongly believe that with proper training, teachers will be able to conduct an effective school-based refractive error screening program for pre-primary and primary school students, thereby offering significant potential benefits for childhood development. Thus, we believe that a program of this type should be promoted in many resource-limited settings.

Data from this study should also be examined in light of similar studies conducted in other countries on primary school screening. In Iran, for instance, the sensitivity and specificity of teachers' screenings are 37.5% and 92% (at the 20/25 cut-off); in China, the rates are 93.5% and 91.2% (at the 6/12 or 20/40 cut-offs); and in Tanzania, the rates are 80% and 91% (at the 6/12 or 20/40 cut-offs) [4,23,24]. No other study, however, has examined teacher-conducted screening in pre-primary school children; this is the first study evaluating the feasibility and accuracy of non-health professionals screening for refractive errors in this population group. Although the number of children with refractive errors screened by teachers was lower than that of health professionals screened, most of these missed cases were children with mild visual impairment, and therefore does not constitute a serious public health concern. Furthermore, the screening program should be performed annually in order to reduce the undetected cases from previous screenings as well as to find new cases.

Table 4. Defining the best cut-off point for primary school teachers' screening and estimated cases for a nationwide program.

Possible cut-off points	Sensitivity	Specificity	Estimated number of students referred for diagnosis*	Estimated number of students receiving spectacles*
20/20	81%	79%	1,168,923	147,848
20/30	70%	92%	549,810	133,987
20/40	59%	98%	239,098	110,886
20/50	37%	99%	145,538	77,389
20/70	13%	99%	61,218	27,721
20/100	3%	99%	32,342	8,085
20/200	0%	100%	3,465	0

**Hypothetical situation for 4,817,764 students [28]; children receiving spectacles are the children who have significant refractive error.*
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In fact, due to inadequate resources, refractive error screening by health professionals in pre-primary and primary school aged children is not currently implemented in Thailand. Although this study shows that the detection rate of screening by pre-primary school teachers is relatively low compared to that of primary school teachers, the recommendation for refractive error screening for both pre-primary and primary school aged children is warranted given the importance of detection and treatment of refractive error in very young generations and the relatively low cost of the screening program. Moreover, Figure 2 indicates that the detection rate for moderate visual impairment among pre-primary school children is as high as 44%, though the detection rate for mild visual impairment is quite low at 21%. In addition, Tables 3 and 4 reveal that using a higher cut-off point (e.g. 20/30 instead of 20/40) can increase sensitivity and thereby reduce the number of missed children with refractive error at the expense of a considerable increase in the number of students referred, whereas the number of students receiving spectacles will not significantly rise particularly in primary school. As a result, readers who wish to apply this protocol for screening refractive error among children need to carefully consider a cut-off point appropriate to their situation.

Since Thailand has a very high school enrollment rate of 95% for pre-primary [25] and close to universal for primary school [26], the implementation of this school-based screening program is likely to be effective. It is estimated that 260,000 children who require spectacles would have access to them and a number of children with refractive amblyopia would be avoided if this program is implemented nationwide. The results of this study was presented to high ranking decision-makers at the Ministry of Public Health and National Health Security Office (NHSO) in early 2013 and it was agreed that the program would be scaled up into a nationwide program within the next five years [27]. The teachers' screening is currently taking place at pre-primary and primary schools in ten provinces.

Furthermore, based on our experience, it is possible to improve the accuracy of teachers' screening by providing longer training sessions, especially hands-on practice (our training offered only 10 minutes per teacher). Moreover, it is necessary to have at least one assistant to a pre-primary teacher who performs refractive error screening using the Lea chart. The reason for this is that the Lea chart is a picture chart where the children are required to select similar model objects (to what they saw in the Lea chart) and show to the teacher at the same time the teacher needs to point out the Lea chart that is 3 meters far away from the children. We also suggest that further research should be performed in order to improve the techniques and accuracy of measuring VA among very young children.

However, this study does have some limitations. First, the provinces were selected to represent four regions in Thailand, although the selection of the 17 schools was randomly assigned among schools that matched our inclusion criteria, i.e. the number of students and the willingness to participate in the study. Second, because the screening conducted by teachers and health professionals were performed a month apart, 582 (10%) of the students missed a screening session by one of the groups. Third, although professionals recommended that 624 of the students who screened positive should go to the provincial hospital, only 470 (75%) students actually underwent further examination. Fourth, concerning the possible missed cases with hyperopia or astigmatism, we recommended teachers to observe students' reading behavior as indicated in the screening manual. If abnormal behavior such as reading at a very close distance, squinting, or head-tilting is found, the teachers can then refer those students to hospitals for a comprehensive eye examination including cycloplegic refraction. Lastly, this study focuses only on the accuracy and feasibility of refractive error screening by teachers. It does not evaluate the impact of correcting refractive error in children - which will require a longer timeline - nor does it evaluate the validity of recommending annual evaluations of refractive error in children.

Supporting Information

File S1 Section S1: Sample Size Calculation. Section S2: Research Protocol. Section S3: Guidelines for measuring VA and the tools used. Section S4: Definitions used for diagnosis of eye disorders. Section S5: The criteria for prescribing spectacles.
(DOCX)

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Author Contributions

Conceived and designed the experiments: KT KW YT BC SO SK ST WJ. Performed the experiments: KT C-YM KW BC SO SK ST. Analyzed the data: KT C-YM YT. Contributed reagents/materials/analysis tools: KT KW WJ. Wrote the paper: KT C-YM KW YT. Reviewed, commented, and approved the manuscript: BC SO SK ST KJ.

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RESEARCH ARTICLE Open Access

A cost-utility analysis of drug treatments in patients with HBeAg-positive chronic hepatitis B in Thailand

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Abstract

Background: Only lamivudine has been included for patients with chronic hepatitis B (CHB) in the National List of Essential Drugs (NLED), a pharmaceutical reimbursement list in Thailand. There have also been no economic evaluation studies of CHB drug treatments conducted in Thailand yet. In order to fill this gap in policy research, the objective of this study was to compare the cost-utility of each drug therapy (Figure 1) with palliative care in patients with HBeAg-positive CHB.

Methods: A cost-utility analysis using an economic evaluation model was performed to compare each drug treatment for HBeAg-positive CHB patients. A Markov model was used to estimate the relevant costs and health outcomes during a lifetime horizon based on a societal perspective. Direct medical costs, direct non-medical costs, and indirect costs were included, and health outcomes were denoted in life years (LYs) and quality-adjusted life years (QALYs). The results were presented as an incremental cost effectiveness ratio (ICER) in Thai baht (THB) per LY or QALY gained. One-way sensitivity and probabilistic sensitivity analyses were applied to investigate the effects of model parameter uncertainties.

Results: The ICER values of providing generic lamivudine with the addition of tenofovir when drug resistance occurred, generic lamivudine with the addition of tenofovir based on the road map guideline, and tenofovir monotherapy were -14,000 (USD -467), -8,000 (USD -267) , and -5,000 (USD -167) THB per QALY gained, respectively. However, when taking into account all parameter uncertainties in the model, providing generic lamivudine with the addition of tenofovir when drug resistance occurred (78% and 75%) and tenofovir monotherapy (18% and 24%) would yield higher probabilities of being cost-effective at the societal willingness to pay thresholds of 100,000 (USD 3,333) and 300,000 (USD 10,000) THB per QALY gained in Thailand, respectively.

Conclusions: Based on the policy recommendations from this study, the Thai government decided to include tenofovir into the NLED in addition to generic lamivudine which is already on the list. Moreover, the results have shown that the preferred treatment regimen involves using generic lamivudine as the first-line drug with tenofovir added if drug resistance occurs in HBeAg-positive CHB patients.

Keywords: Chronic disease, Hepatitis B, Cost-utility analysis, Treatment

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Background

Approximately 350 million people are chronically infected with the hepatitis B virus (HBV) [1] and nearly 25% of these carriers develop serious liver diseases such as chronic hepatitis, cirrhosis, and hepatocellular carcinoma (HCC), resulting in more than one million deaths every year [1]. Chronic liver diseases and HCC associated with HBV infections are two of the most important public health problems in high-prevalence regions [2]. In particular, most Southeast Asian countries including Thailand have been classified as high prevalence areas of HBV [1].

The goal of drug treatments for chronic hepatitis B (CHB) is to improve quality of life and survival by preventing the disease from developing into cirrhosis, decompensated cirrhosis, end-stage liver disease, HCC, and death by reducing viral replication to the lowest possible level and maintaining it over the long-term. Currently, six CHB medications including both oral (i.e., lamivudine, adefovir, entecavir and telbivudine) and subcutaneous (i.e., conventional interferon and pegylated interferon) dosage forms have been licensed by the Thai Food and Drug Administration (FDA). Additionally, tenofovir – an approved drug for the treatment of HIV but not CHB – is currently being prescribed to CHB patients in 300 mg daily doses due to its high viral efficacy and low resistance rates [3,4].

Previous cost-utility analysis studies of oral CHB medications revealed that telbivudine [5] or adefovir [6,7] was more cost-effective when compared with lamivudine. In addition, most studies performed in the US [8-14], Australia [15], and Asia [16,17] demonstrated that entecavir was superior when compared with lamivudine. Another study by Buti et al. showed that tenofovir was the better cost-effective treatment when compared with entecavir, telvibudine, and adefovir [13]. Moreover, previous economic evaluation studies of subcutaneous CHB treatments indicated that interferon was not cost-effective when compared with lamivudine [18,19] but was more cost-effective when compared to lamivudine with the addition of adefovir when drug resistance occurred [20]. The combination of lamivudine and interferon would increase life expectancy and reduce the lifetime risk of cirrhosis and carcinoma [21,22]. Furthermore, pegylated interferon was more cost-effective when compared with lamivudine [21,23,24] or interferon [7]. Most economic evaluation studies of CHB treatment were carried out in the US and Europe. However, no study has ever been performed in Southeast Asian countries, including Thailand - a high prevalence area of CHB. In addition, there has also been no economic evaluation study of the combination of CHB treatments according to the current clinical practice guidelines on the management of CHB drug resistance until now.

When this study was conducted, only lamivudine - but not other CHB treatments with low rates of drug resistance - had been included for patients with CHB in the National List of Essential Drugs (NLED), the pharmaceutical reimbursement list referred to by three health insurance schemes which are Social Security Scheme (9% of the Thai population), Civil Servant Medical Benefit Scheme (11% of the Thai population) and Universal Coverage Scheme (80% of the Thai population), as a pharmaceutical benefit scheme in Thailand. The selection criteria for the inclusion of the NLED are safety, efficacy as well as cost-effectiveness information of drugs. The Subcommittees for Development of NLED had requested the cost-effectiveness information on CHB treatments from Health Intervention and Technology Assessment Program (HITAP), the institution responsible for appraising a wide range of health technologies including pharmaceuticals, medical devices, interventions, individual and community health promotion and prevention interventions. Therefore, the objective of this study was to compare the cost-utility of each drug therapy (Figure 1) with consideration for the management of CHB drug resistance with palliative care in patients with HBeAg-positive CHB based on a societal perspective. The results from this study would be used as the cost-effectiveness information to assist health policy makers (i.e., the Subcommittees for Development of NLED) to make policy decision whether which CHB drugs should be included in the NLED. The inclusion of CHB drugs to the NLED could have an impact on the reimbursement of CHB drugs for all HBeAg-positive CHB patients under three health insurance schemes (i.e., Social Security Scheme, Civil Servant Medical Benefit Scheme and Universal Coverage Scheme) which accounts for 100% of Thai population.

In Thailand, palliative care has been a usual care for patients with CHB, therefore it was used as a comparator in this study, since CHB-infected individuals usually develop an acute infection which may or may not result in symptoms. Those who do not exhibit symptoms and have never received hepatitis B screening test may not be aware that they have CHB until they finally develop serious liver diseases (e.g., chronic hepatitis, cirrhosis, and HCC) which consequently require palliative care. In addition, the clinical practice guidelines for the diagnosis and management of HBeAg-positive CHB - detailed in the Thailand Consensus Recommendations for Management of CHB 2009 by the former Liver Society Thailand, now known as the Thai Association for the Study of the Liver (THASL) - did not have a recommendation for the most appropriate drug to use as the standard treatment for CHB patients [25,26].

Methods

A cost-utility analysis using a Markov model was conducted to compare the costs and health outcomes of all available drug treatments in HBeAg-positive CHB patients with palliative care; the analysis was performed using a lifetime horizon with a one-year cycle length based on a societal perspective. The study population

Intervention	Scenario	1st Drug	2nd Drug						3rd Drug			
			Original LMV	Generic LMV	ADV	TNV	ETV	TVD	Original LMV	Generic LMV	ADV	TNV
1	-	TNV	-	-	-	-	-	-	-	-	-	-
2-3	1	Original LMV	-	-	✓ or	✓	-	-	-	-	-	-
4-5	1	Generic LMV	-	-	✓ or	✓	-	-	-	-	-	-
6-7	1	ADV	✓ or	✓	-	-	-	-	-	-	-	-
8-9	1	TVD	-	-	✓ or	✓	-	-	-	-	-	-
10-11	1	ETV	-	-	✓ or	✓	-	-	-	-	-	-
12-13	1	PEG	✓	-	-	-	-	-	-	-	✓ or	✓
14-15	1	PEG		✓	-	-	-	-	-	-	✓ or	✓
16-17	1	PEG	-	-	✓	-	-	-	✓ or	✓	-	-
18-19	1	PEG	-				-	✓	-	-	✓ or	✓
20-21	1	PEG	-	-	-	-	✓	-	-	-	✓ or	✓
22	1	PEG	-	-	-	✓	-	-	-	-	-	-
23-24	2	Original LMV	-	-	✓	-	-	-	-	-	✓ or	✓
25-26	2	Generic LMV	-	-	-	-	-	✓	-	-	✓ or	✓
27-28	2	TVD	-	-	✓ or	✓		-	-	-	-	-

Figure 1 All available interventions compared with palliative care. Scenario 1=Adding the second drug when drug resistance occurred; Scenario 2= Adding a more potent drug without cross-resistance when the HBV DNA level more than 60 IU/ml at week 24 based on the road map guideline; LMV=Lamivudine; ADV=Adefovir; ETV=Entecavir; TVD=Telbivudine; PEG=Pegylated interferon.

was a hypothetical cohort of one thousand HBeAg-positive CHB patients aged at least 30 years old who required the treatment based on the following criteria: 1) patients who had detectable serum HBsAg for at least 6 months; 2) patients who had serum ALT levels 1.5 -10 times the upper limit of the normal range for at least 3 months; 3) patients who had a detectable level of serum hepatitis B viral DNA more than or equal to 20,000 IU/ml; and/or 4) patients who had evidence of CHB based on liver biopsy results. Ethical approval for this study was granted by the Institutional Review Board Committees from Mahidol University.

Since this analysis set out to compare all available CHB medications for the treatment of HBeAg-positive CHB with palliative care as a usual care and comparator in Thailand, both oral (i.e., original lamivudine, generic lamivudine, adefovir, entecavir, telbivudine and tenofovir) and subcutaneous dosage forms (i.e., pegylated interferon) were included. Among all the drugs, only tenofovir showed low drug resistance rates in the treatment of CHB [3,4] while others demonstrated high drug resistance rates. Therefore, two scenarios based on the current clinical practice guidelines on the management of CHB drug resistance were created for the study. Figure 1 presents all interventions compared with palliative care.

In the first scenario, if patients taking the original lamivudine, generic lamivudine, adefovir, entecaviror, or telbivudine encountered drug resistance, a second medication would be added to the treatment regimen based on the guidelines (10 interventions). Moreover, for CHB patients receiving pegylated interferon who failed the treatment, the second drug would be added in the third year. Then, a third drug would be added if the patient encountered drug resistance again (11 interventions).

The second scenario involved adding a more potent drug without cross-resistance when the HBV DNA level was more than 60 IU/ml at week 24 based on the road-map guideline, which applies to only low genetic barrier drugs (i.e., lamivudine and telbivudine) (6 interventions). Thus, a total of 28 interventions (i.e., tenofovir monotherapy, 21 interventions of the first scenario and 6 interventions of the second scenario) were compared with palliative care (Figure 1).

Model structure

Figure 2 shows the schematic diagram of the Markov model showing that all hypothetical patients aged at least 30 years old who required the treatment would start at the CHB with HBeAg-positive state. For patients receiving antiviral drugs, they would proceed to the drug

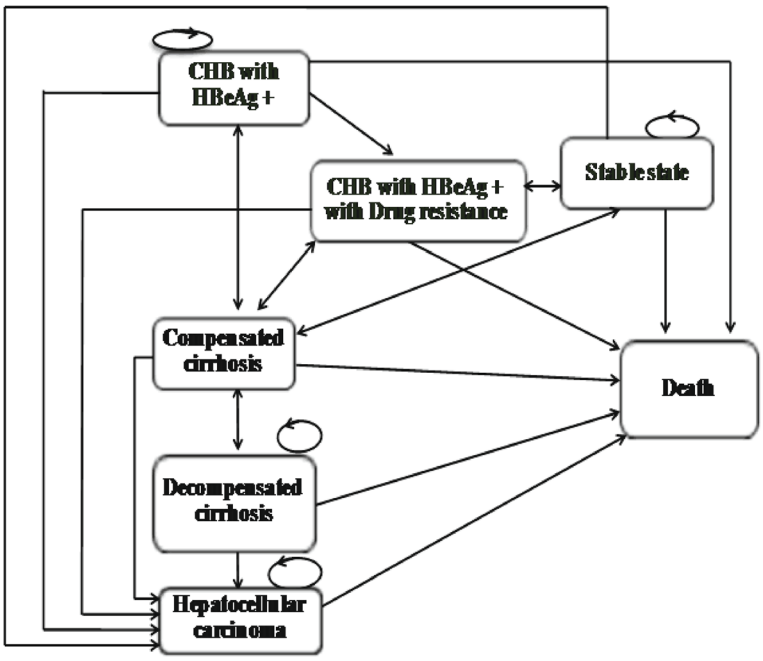

Figure 2 Schematic diagram of the Markov model.

resistance state if drug resistance was detected or the level of serum HBV DNA reached levels higher than 60 IU/ml. Patients receiving palliative care or those successfully treated with pegylated interferon in the first year would move to the stable state, while HBeAG-positive CHB patients – either with or without drug resistance – would also be able to transition to this state if they developed HBeAg seroconversion. In addition, patients in the stable state could also reverse to the CHB with HBeAg-positive state. HBeAg-positive CHB patients - either with or without drug resistance - and those in the stable state could progress to the compensated cirrhosis, decompensated cirrhosis, and HCC states. Patients in either the compensated or decompensated cirrhosis state could reverse to a primary state except for those with HCC, who could move to a death state only. Patients in all states could stay at the same state and could move to a death state. Both scenarios had the same model assumptions, which were: 1) the efficacy of generic lamivudine was the same as that of the original lamivudine, and 2) each treatment had differences in the seroconversion and resistance rates.

Transitional probabilities

Table 1 demonstrates all the parameters used in the model. Due to the limitation of data, especially the clinical efficacy of CHB drugs in Thailand, these parameter values were obtained from internationally published literature [27,28]. However, we performed an indirect comparison meta-analysis of these parameters which represents the highest reliable evidence [29]. The transitional probabilities of clinical efficacy in terms of HBeAg seroconversion of HBeAg-positive CHB treatment options were estimated from a systematic review and meta-analysis using a Bayesian random effects model analyzed by WinBUGS1.4 (Medical Research Council and Imperial College of Science, Technology and Medicine, United Kingdom) [30]. All other transitional probabilities were obtained from published articles in Thailand and other countries [31-44]. In addition, the mortality rates of Thailand's general population at each age were used in the analysis [45]. Time-invariant survival rates for each drug therapy were applied.

Cost

Costs and health outcomes were estimated over a 70-year period in order to cover the expected lifetime horizon. The costs of the CHB state included the costs of antiviral drugs and laboratory and diagnostic tests, which were projected over a 70-year time horizon using the Markov model. For the number of antiviral drug utilization and laboratory and diagnostic tests used, these values were estimated based on the suggested recommendations of the THASL clinical practice guidelines [25,26]. The prices of antiviral drugs were obtained from the reference prices published by the Thai Ministry of Public Health's Drug and Medical Supply Information Center (DMSIC) [46]. The unit costs of the laboratory and diagnostic tests were retrieved using the reference prices published by the Comptroller General's Department of the Thai Ministry of

Table 1 Input parameters used in economic model

Parameter	Distribution	Mean	SE	Reference
Yearly discount rate (%)				
Costs and outcomes (range)		3 (0-6)		[51]
Transitional probability baseline parameters				
Probability of stable to CHB state	Beta	0.143	0.0650	[31]
Probability of CHB to stable state	Beta	0.056	0.0180	[32]
Probability of CHB to compensated in 1^{st}-10^{th} year	Beta	0.054	0.0543	[33]
Probability of CHB to compensated in 11^{th}-20^{th} year	Beta	0.134	0.1338	[33]
Probability of CHB to compensated in $>20^{th}$ year	Beta	0.329	0.3292	[33]
Probability of CHB to HCC in 1^{st}-5^{th} year	Beta	0.000	0.0000	[34]
Probability of CHB to HCC in $6t^{h}$-10^{th} year	Beta	0.006	0.0061	[34]
Probability of CHB to HCC in $>10^{th}$ year	Beta	0.008	0.0081	[34]
Probability of CHB to death in 1^{st}-5^{th} year	Beta	0.010	0.0102	[34]
Probability of CHB to death in 6^{th}-10^{th} year	Beta	0.014	0.0144	[34]
Probability of CHB to death in $>10^{th}$ year	Beta	0.025	0.0252	[34]
Probability of compensated to decompensated in 1^{st}-3^{rd} year	Normal	0.042	0.0003	[35]
Probability of compensated to decompensated in 4^{th}-5^{th} year	Normal	0.094	0.0005	[35]
Probability of compensated to decompensated in $>5^{th}$ year	Normal	0.066	0.0003	[35]
Probability of compensated to HCC in 1^{st}-3^{rd} year	Normal	0.014	0.0002	[35]
Probability of compensated to in HCC 4^{th}-5^{th} year	Normal	0.036	0.0003	[35]
Probability of compensated to HCC in $>5^{th}$ year	Normal	0.030	0.0002	[35]
Probability of compensated to death in 1^{st}-3^{rd} year	Beta	0.014	0.0135	[35]
Probability of compensated to death in $>3^{rd}$ year	Beta	0.046	0.0461	[35]
Probability of decompensated to HCC	Beta	0.035	0.0354	[36]
Probability of decompensated to death in 1^{st} year	Normal	0.260	0.0004	[37]
Probability of decompensated to death in 2^{nd} year	Normal	0.390	0.0005	[37]
Probability of decompensated to death in $>2^{nd}$ year	Normal	0.240	0.0003	[37]
Probability of HCC to death in 1^{st} year	Beta	0.848	0.0011	[37]
Probability of HCC to death in $>1^{st}$ year	Beta	0.920	0.0009	[37]
Transitional probability of treatment parameters				
Probability of CHB to compensated	Beta	0.006	0.0023	[38]
Probability of CHB to HCC	Beta	0.009	0.0045	[39]
Probability of CHB to death	Beta	0.002	0.0023	[39]
Probability of compensated to HCC	Beta	0.015	0.0034	[40]
Probability of compensated to death	Beta	0.007	0.0070	[39]
Probability of decompensated to HCC	Beta	0.035	0.0127	[41]
Probability of decompensated to death	Beta	0.126	0.0291	[42]
Probability of compensated to CHB	Beta	0.478	0.0665	[43]
Probability of HCC to death	Beta	0.034	0.0227	[44]
Relative risk of seroconversion of lamivudine	Normal	3.519	1.3707	[30]
Relative risk of seroconversion of adefovir	Normal	3.028	1.3833	[30]
Relative risk of seroconversion of telbivudine	Normal	4.286	1.4054	[30]
Relative risk of seroconversion of entecavir	Normal	3.846	1.3833	[30]
Relative risk of seroconversion of pegylated interferon	Normal	5.356	1.4987	[30]
Relative risk of seroconversion of tenofovir	Normal	4.167	1.6403	[30]

Table 1 Input parameters used in economic model *(Continued)*

Probability of delay seroconversion of pegylated interferon	Normal	0.410	0.0489	[27]
Probability of lamivudine resistance	Beta	0.214	0.0214	[28]
Probability of adefovir resistance	Beta	0.066	0.0066	[28]
Probability of telbivudine resistance	Beta	0.089	0.0089	[28]
Probability of entecavir resistance	Beta	0.002	0.0002	[28]
Probability of tenofovir resistance	Beta	0.000	0.0000	[28]
Annual direct medical cost				
Cost of generic lamivudine	Gamma	1,797	180	[46]
Cost of original lamivudine	Gamma	34,871	3,487	[46]
Cost of adefovir	Gamma	70,298	7,030	[46]
Cost of telbivudine	Gamma	51,504	5,150	[46]
Cost of entecavir	Gamma	85,745	8,575	[46]
Cost of tenofovir	Gamma	15,559	1,556	[46]
Cost of pegylated interferon	Gamma	527,379	52,738	[46]
Cost of treatment of compensated cirrhosis	Gamma	81,264	81,264	[48]
Cost of treatment of decompensated cirrhosis	Gamma	125,127	125,127	[48]
Cost of treatment of HCC	Gamma	153,021	153,021	[48]
Cost of laboratory for screening (i.e., HBeAg, HBeAb)	Gamma	650	650	[47]
Cost of laboratory for pre-treatment	Gamma	3,350	3,350	[47]
Cost of laboratory for monitoring	Gamma	4,200	4,200	[47]
Cost of laboratory monitoring for pegylated interferon	Gamma	10,620	10,620	[47]
Cost of laboratory monitor for adefovir	Gamma	4,560	4,560	[47]
Cost of laboratory for post-treatment	Gamma	4,900	4,900	[47]
Annual direct non-medical cost				
Cost of transportation	Gamma	571	571	[54]
Cost of food	Gamma	210	210	[54]
Annual indirect cost				
Cost of time loss due to receiving treatment	Gamma	824	824	[49]
Cost of productivity loss of compensated cirrhosis	Gamma	48	48	[48,49]
Cost of productivity loss of decompensated cirrhosis	Gamma	627	627	[48,49]
Cost of productivity loss of HCC	Gamma	1,701	1,701	[48,49]
Utility				
Utility weight for CHB	Normal	0.68	0.00005	[53]
Utility weight for compensated cirrhosis	Normal	0.69	0.00016	[53]
Utility weight for decompensated cirrhosis	Normal	0.35	0.00031	[53]
Utility weight for HCC	Normal	0.38	0.00026	[53]

Finance [47]. Furthermore, the costs of complication states such as compensated cirrhosis, decompensated cirrhosis, and HCC were obtained from a published study based in Thailand [48]. However, the costs of treatment for adverse drug events were not included in this study.

Direct non-medical costs (i.e., the costs of transportation, food, and time loss due to receiving treatment) but not direct medical costs incurred outside the hospital were included. All direct non-medical and the number of days due to sick leave were obtained from a published study [48]. As for indirect costs, these also included morbidity costs and were calculated from the productivity loss due to sick leave. It should be noted that mortality costs were excluded. Indirect costs were calculated from the number of days due to sick leave multiplied by the minimum wage rate of the Thai population obtained from the Thai Ministry of Labor's Department of Labor Protection and Welfare [49]. All costs were converted and reported in year 2010 values using the consumer price index (CPI) [50]

and all future costs were discounted at a rate of 3% [51] due to the time horizon being longer than one year. The average annual exchange rate of Thai baht (THB) to one US dollar was 30 THB in 2010 [52]. For international comparison, costs were converted to international dollars using the purchasing power parity (PPP) $ exchange rate of 1 PPP$ (2010) per 17.8 THB [53].

Health outcomes

Health outcomes were denoted in life years (LYs) gained and quality-adjusted life years (QALYs) gained (i.e., the multiplication of LYs gained and the utility score) and the utility or quality of life scores of patients were obtained from a published study after we performed a systematic review on electronic databases (i.e., Pubmed and Cochrane databases) [54]. The health outcomes of each intervention were compared with palliative care. Future outcomes were also discounted at a rate of 3% [51]. The results were presented as an incremental cost effectiveness ratio (ICER) in Thai baht (THB) per a LY or QALY gained.

Uncertainty analysis

A one-way sensitivity analysis and probabilistic sensitivity analysis (PSA) were conducted to examine the effect of parameter uncertainty in the model. All parameters in the one-way sensitivity analysis were varied across the range of confidence intervals. In addition, net monetary benefit (NMB) was calculated to determine the intervention which gave the maximum expected NMB for each value of the ceiling ratio (i.e., the value of society's willingness to pay (WTP) for an intervention giving one QALY gained). In Thailand, the WTP per one QALY thresholds for the implementation of health technology and intervention based on two subcommittees - the Subcommittee for the Development of the National List of Essential Drugs and the Subcommittee for the Development of the Benefit Packages, National Health Security Office (NHSO) - are 100,000 (USD 3,333) and 300,000 (USD 10,000) THB per QALY gained (i.e., about one and three times the gross domestic product (GDP) per capita) [55]. Once the analysis was completed, the results of the PSA were presented using cost-effectiveness acceptability curves.

Results

The total costs, LYs, QALYs, and ICER values of all treatments compared with palliative care in patients with HBeAg-positive CHB aged 30 years old and above are shown in Table 2. Interventions with negative ICER values indicate that they were more effective and had lower costs compared with palliative care. Thus, it can be seen that providing generic lamivudine and adding tenofovir when drug resistance occurred (ICER = -9,000 THB or USD -300 per LY gained or -14,000 THB or USD -467 per QALY gained) proved to be the most cost-effective option. The next best treatment regimens were generic lamivudine plus tenofovir based on the roadmap guideline (ICER = -5,000 THB or USD -167 per LY gained or -8,000 THB or USD -267 per QALY gained) and tenofovir monotherapy (ICER = -3,000 THB or USD -100 per LY gained or -5,000 THB or USD -167 per QALY gained).

Uncertainty analysis

Figure 3 presents a tornado diagram illustrating the one-way sensitivity analysis results. Only the important parameters of the most cost-saving intervention were selected (i.e., generic lamivudine with the addition of tenofovir when drug resistance occurred). The outcome of this analysis showed which parameters the ICER per QALY gained were most sensitive to when altering the values, and they are listed as follows from most to least sensitive: the cost of treatment of compensated cirrhosis; the price of tenofovir; the price of lamivudine; the cost of treatment of decompensated cirrhosis; the cost of treatment of HCC; the discount rates of 0% and 6% per annum for cost and outcome; the relative risk of seroconversion of lamivudine; and the probability of transitioning from a CHB state to the death state.

The PSA results are presented in Figure 4 using cost-effectiveness acceptability curves. To clearly present the results, other treatment alternatives were omitted except for tenofovir monotherapy, generic lamivudine with the addition of tenofovir when drug resistance occurred, and generic lamivudine with the addition of tenofovir based on the roadmap guideline compared with palliative care. The willingness to pay (WTP) threshold for one QALY for the adoption of health technologies and interventions is designated by the dashed vertical lines. At WTP thresholds of 100,000 (USD 3,333) and 300,000 THB (USD 10,000) per one QALY gained in Thailand, the probabilities for cost-effective treatment via the provision of generic lamivudine with the addition of tenofovir when drug resistance occurred were 78% and 75%, respectively. Moreover, the probabilities of tenofovir monotherapy being cost-effective were 18% and 24%, respectively. However, the probability of providing generic lamivudine with the addition of tenofovir based on the roadmap guideline being cost-effective was 0%, regardless of how much society was willing to pay for one QALY gained.

Discussion

With the intent of aiding policy decision makers on which CHB drugs should be included in the NLED, our study was the first to compare the cost-utility of each drug therapy according to the THASL clinical practice guidelines with palliative care in patients with HBeAg-positive CHB based on a societal perspective. Even

Table 2 Total costs, LYs and QALYs of all interventions for HBeAg positive CHB patients aged 30 years old and above

Interventions First drug (Second drug) Third drug	Total costs (THB)[§]	LYs	QALYs	Incremental cost (THB)	Incremental QALYs	ICER per QALY gained
1. Generic lamivudine (tenofovir)[†]	456,000	20.87	13.66	-72,000	5.03	Dominant*
2. Generic lamivudine (tenofovir)[‡]	490,000	20.87	13.66	-38,000	5.03	Dominant*
3. Tenofovir monotherapy[†]	501,000	20.89	13.67	-26,000	5.04	Dominant*
4. Palliative care	527,000	13.13	8.63	-	-	-
5. Original lamivudine (tenofovir)[†]	937,000	20.87	13.66	409,000	5.03	81,000
6. Pegylated interferon (original lamivudine) tenofovir[†]	953,000	20.89	13.67	426,000	5.05	84,000
7. Original lamivudine (tenofovir)[‡]	971,000	20.87	13.66	444,000	5.03	88,000
8. Generic lamivudine (adefovir)[†]	982,000	20.87	13.66	454,000	5.03	90,000
9. Pegylated interferon (tenofovir)[†]	1,057,000	20.91	13.69	530,000	5.06	105,000
10. Telbivudine (tenofovir)[†]	1,091,000	20.90	13.68	564,000	5.05	112,000
11. Generic lamivudine (adefovir)[‡]	1,134,000	20.87	13.66	606,000	5.03	121,000
12. Telbivudine (tenofovir)[‡]	1,134,000	20.87	13.66	606,000	5.03	121,000
13. Pegylated interferon (original lamivudine) tenofovir[†]	1,325,000	20.89	13.67	798,000	5.05	158,000
14. Adefovir (generic lamivudine)[†]	1,364,000	20.85	13.64	837,000	5.01	167,000
15. Pegylated interferon (lamivudine) adefovir[†]	1,371,000	20.89	13.67	844,000	5.05	167,000
16. Telbivudine (adefovir)[†]	1,429,000	20.90	13.68	902,000	5.05	178,000
17. Pegylated interferon (telbivudine) tenofovir[†]	1,442,000	20.92	13.69	915,000	5.06	181,000
18. Original lamivudine (adefovir)[†]	1,463,000	20.87	13.66	936,000	5.03	186,000
19. Entecavir (tenofovir)[†]	1,519,000	20.88	13.67	991,000	5.04	197,000
20. Entecavir (adefovir)[†]	1,536,000	20.88	13.67	1,009,000	5.04	200,000
21. Adefovir (original lamivudine)[†]	1,564,000	20.85	13.64	1,037,000	5.01	207,000
22. Original lamivudine (adefovir)[‡]	1,616,000	20.87	13.66	1,088,000	5.03	216,000
23. Pegylated interferon (adefovir) generic lamivudine[†]	1,648,000	20.88	13.66	1,120,000	5.04	222,000
24. Telbivudine (adefovir)[‡]	1,657,000	20.90	13.68	1,130,000	5.05	224,000
25. Pegylated interferon (telbivudine) adefovir[†]	1,710,000	20.92	13.69	1,182,000	5.06	233,000
26. Pegylated interferon (original lamivudine) adefovir[†]	1,744,000	20.89	13.67	1,216,000	5.05	241,000
27. Pegylated interferon (entecavir) tenofovir[†]	1,771,000	20.90	13.68	1,243,000	5.05	246,000
28. Pegylated interferon (entecavir) adefovir[†]	1,785,000	20.90	13.68	1,257,000	5.05	249,000
29. Pegylated interferon (adefovir) original lamivudine[†]	1,812,000	20.88	13.66	1,284,000	5.04	255,000

[†]Scenario 1: Adding drug when drug resistance occurred; [‡]Scenario 2: Adding drug based on the road map guideline.
§total costs are calculated in 2010 THB and rounded up to nearest 1,000 THB.
*Negative ICER due to higher effectiveness and lower costs of intervention compared with palliative care.

though the ICER results indicated that these three alternatives were dominant due to higher effectiveness and lower costs when compared with palliative care, it is evidenced that both tenofovir monotherapy and generic lamivudine with the addition of tenofovir when drug resistance occurred were more superior than generic lamivudine with tenofovir added based on the roadmap guideline when taking the uncertainty of all parameters in the model into account. The results have shown that the total cost of generic lamivudine with tenofovir added based on the roadmap guideline was higher compared with generic lamivudine plus tenofovir when drug resistance, whereas total LYs and QALYs obtained from both interventions were not different. As a result, when compared with providing generic lamivudine plus tenofovir added based on the road map guideline providing generic lamivudine plus tenofovir when drug resistance could save healthcare costs of approximately 70,000 THB (USD 2,333) per patient due to the cost avoidance of serious complications in the future. Thus, when considering the provision of CHB treatment to HBeAg-positive CHB patients above 30 years of age (i.e., 40-70 years), providing generic lamivudine plus tenofovir when drug resistance occurred and tenofovir monotherapy were dominant and cost-saving interventions compared with palliative care.

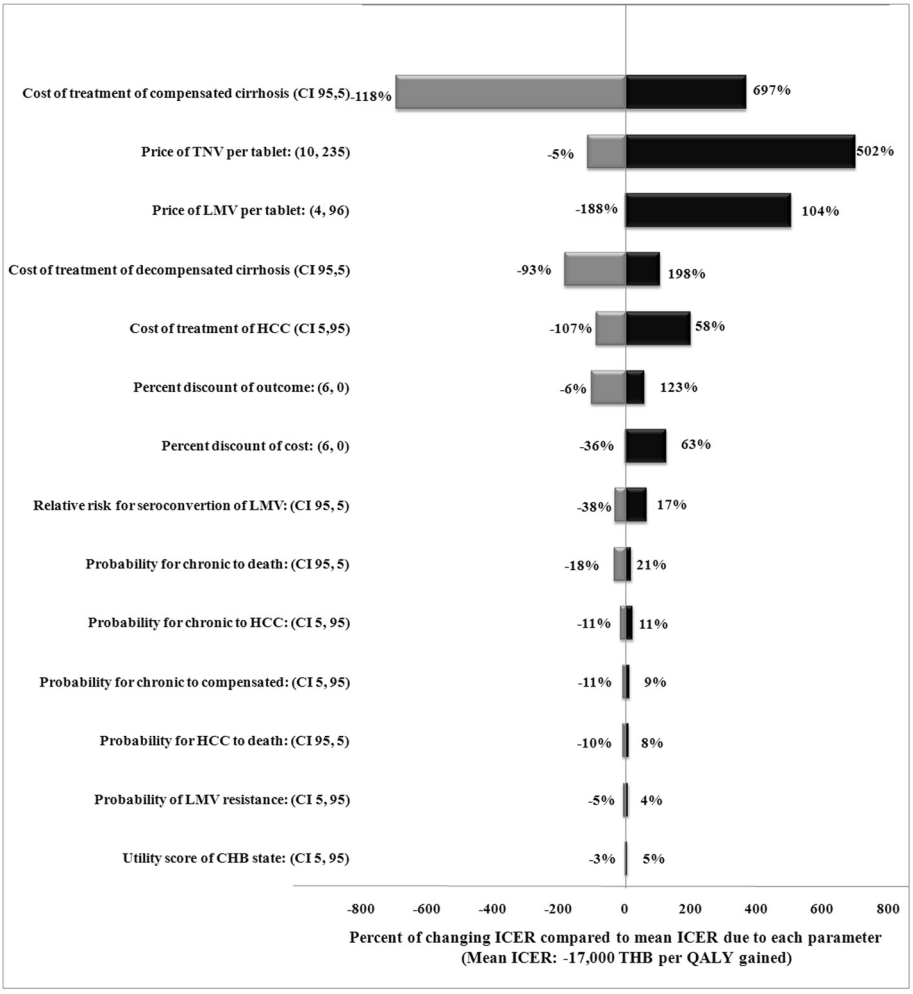

Figure 3 Tornado diagram illustrating the one-way sensitivity analysis results.

Furthermore, generic lamivudine, which has already been included in the NLED, should be considered as the first-line drug for the treatment of HBeAg-positive CHB patients above 30 years of age (i.e., 40-70 years) who require the treatment. In contrast to the findings of other previously published studies, entecavir [8-17], adefovir [6,7], telbivudine [5], and pegylated interferon [21,23,24] were more cost-effective compared with lamivudine. This could be explained by the fact that our study considered drug resistance due to lamivudine to imitate the real current clinical practice. Moreover, generic lamivudine, which is very inexpensive in Thailand, was also included as one of the interventions.

Although lamivudine can cause HBV DNA suppression in most HBeAg-positive CHB patients, it is also associated with a high rate of drug resistance [28]. Our study indicated that tenofovir, which was a cost-saving option, should be used as either the first- or second-line drug for the management of drug resistance due to nucleoside analog such as lamivudine. Similarly, the study of Buti et al. revealed that tenofovir was associated with lower costs and higher efficacy than entecavir, telbivudine, and adefovir [13]. At the time of the study, no other CHB treatments with low rates of drug resistance (e.g., tenofovir) had been included in the NLED yet, even though tenofovir demonstrated high antiviral efficacy and low drug resistance for patients with CHB [3,4]. Therefore, we submitted the cost-effectiveness information of CHB treatments along with policy recommendations to the Subcommittees for Development of NLED in May 2012 that tenofovir should be included in the NLED [56]. After the meeting, it was announced that tenofovir would be included in the NLED only for CHB patients with drug resistance due to nucleoside analog such as lamivudine under the condition that tenofovir should be used as an alternative and not as the first-line therapy.

However, based on the expert's opinion, if both lamivudine and tenofovir were included in the NLED, using tenofovir as the first-line drug would be the better

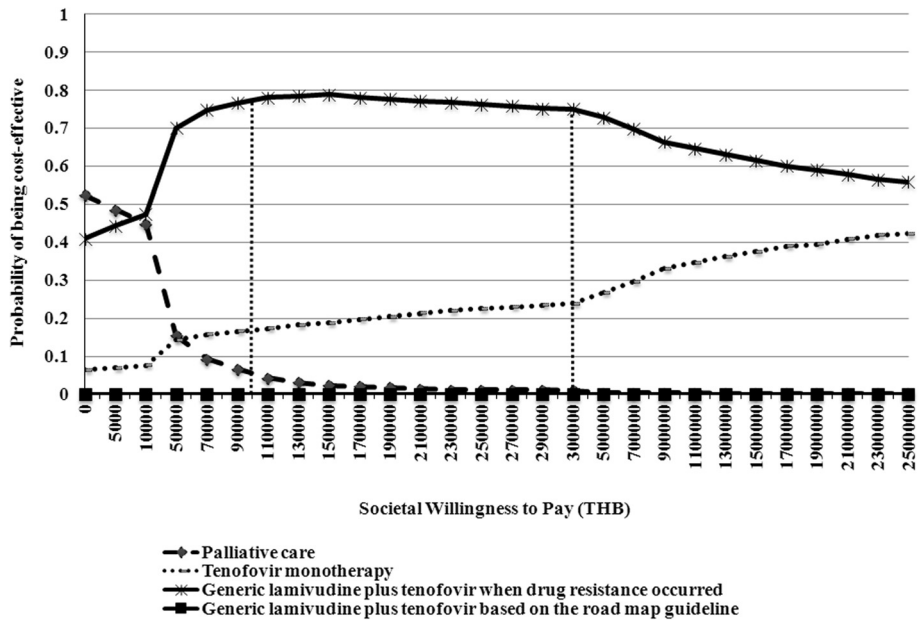

Figure 4 Cost-effectiveness acceptability curves presenting PSA results.

option given that tenofovir has a very low resistance rate. It would be more convenient for clinicians to provide tenofovir as the first-line treatment in order to reduce the time and cost of drug resistance management compared with providing lamivudine as the first-line drug. Even if the patients taking tenofovir developed drug resistance, lamivudine could be added later. It should be noted though that tenofovir has also been implicated in causing renal toxicity. Tenofovir can also cause acute renal failure, Fanconi syndrome, proteinuria or tubular necrosis. These side effects are due to accumulation of the drug in proximal tubules [57].

Moreover, three major issues (i.e., the prices of tenofovir and lamivudine, resistance rate of tenofovir, and costs of all complications and adverse drug events) need to be addressed. First, it was noted that the price of tenofovir in this study was obtained from the current market price of tenofovir in Thailand, which is relatively inexpensive due to the discounted price (43 THB or USD 1.43) proposed by the pharmaceutical company. At present, the price of tenofovir is approximately equal to that of entecavir in many countries. If the maximum expected price of tenofovir was assumed to be equal to the price of entecavir (235 THB or USD 7.83 per tablet), the ICER value would change from a dominant value to 100,000 THB (USD 3,333) per QALY gained when compared with palliative care. Similarly, if the price of lamivudine was adjusted to the price of original lamivudine, the ICER would be adjusted to 81,000 THB (USD 2,700) per QALY gained. Therefore, when changing the prices to current market prices, tenofovir monotherapy or lamivudine would still be cost-effective in the Thai context although they would not be cost-saving interventions [55].

Second, according to the current studies related to drug resistance, the resistance rate of tenofovir used in this study was 0% [28]. If the resistance rate of tenofovir was assumed to be equal to that of entecavir based on expert opinion, it would still be a cost-effective intervention in the Thai context with an ICER of 8,000 THB (USD 267) per a QALY gained compared with palliative care.

Third, the direct medical costs of complication states in this study were obtained from a published multi-center observational study of hepatitis C conducted at five major tertiary care hospitals in Thailand [48]. The costs of all complications (i.e., compensated cirrhosis, decompensated cirrhosis, and HCC) in patients with hepatitis C might be lower than those conducted in CHB patients. Based on the sensitivity analysis results, the costs of all complications had the greatest effect on the changes in ICER values. It is suggested that providing generic lamivudine plus tenofovir when drug resistance occurred and tenofovir monotherapy would be cost-effective options since the ICER values were lower than one times the Thai GDP per capita [55]. In addition, the costs of treatment of the adverse drug events were not considered in the study. In particularly, generic lamivudine may result in more adverse drug events or side-effects. However, it is expected that the adverse drug reactions of generic lamivudine and tenofovir may have little effect on an increase in the ICER values. Lok et al.'s study showed that lamivudine treatment had an excellent safety profile in HBeAg-positive CHB patients [58] and nausea was the only adverse event that occurred more frequently

in CHB patients receiving tenofovir, which may cause little impact on the cost [59].

It is important that the limitations of this study need to be addressed. Due to the lack of transitional probabilities data for CHB patients in Thailand, some transitional probabilities were obtained from published articles in other countries [27,28,31-44]. However, we specifically performed a meta-analysis which could yield the most reliable evidence [30]. Furthermore, the utility data of CHB has been gathered but not for all complication states (i.e., compensated cirrhosis, decompensated cirrhosis, and HCC) in Thai CHB patients; therefore, the utility data of CHB patients with complications were obtained from a multinational study [54].

Conclusions

Our results suggested that providing generic lamivudine with the addition of tenofovir when drug resistance occurred, generic lamivudine with the addition of tenofovir based on the roadmap concept, and tenofovir monotherapy were dominant and cost-saving interventions compared with palliative care. However, when taking into account all parameter uncertainties in the model, providing generic lamivudine with the addition of tenofovir when drug resistance occurred and tenofovir monotherapy would yield higher probabilities of being cost-effective at the societal WTP thresholds in Thailand compared with other alternatives. According to the cost-effectiveness results obtained from this study, the Subcommittees for Development of NLED decided to include tenofovir into the NLED. It is recommended that generic lamivudine should be used as the first-line drug and tenofovir should be considered when drug resistance occurs for HBeAg-positive CHB patients under the condition that tenofovir should be used as an alternative and not as the first-line therapy. Given that tenofovir is included in the NLED, a pharmaceutical reimbursement list of three health insurance schemes (i.e., Social Security Scheme, Civil Servant Medical Benefit Scheme and Universal Coverage Scheme) accounting for approximately 100% of Thai population, the cost of tenofovir incurred by all HBeAg-positive CHB patients under these health insurance schemes could be reimbursed by the Thai government. Consequently, this could definitely help HBeAg-positive CHB patients gain more access to tenofovir when drug resistance occurred and finally could improve patient outcomes and decrease mortality. However, due to a lack of information about drug resistance rate of tenofovir, it is also recommended that intensive monitoring and evaluation of drug resistance should continue to be performed by the Department of Disease Control and the Department of Medical Sciences.

Abbreviations

HBV: Hepatitis B virus; HCC: Hepatocellular carcinoma; HBIG: Hepatitis B Immune Globulin; CHB: Chronic hepatitis B; FDA: Food and Drug Administration; NLED: National List of Essential Drugs; DMSIC: Drug and Medical Supply Information Center; CPI: Consumer price index; PPP: Purchasing power parity; SE: Standard Error; LYs: Life years; QALYs: Quality adjusted life years; THB: Thai baht; ICER: Incremental cost-effectiveness ratio; PSA: Probabilistic sensitivity analysis; NMB: Net monetary benefit; WTP: Willingness to pay; GDP: Gross domestic product; NHSO: National Health Security Office.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

NT and UC performed the research, analyzed data, and drafted the manuscript. TT was involved in clinical research part and drafted the manuscript. PW participated in its design and drafted the manuscript. YT designed the research and drafted the manuscript. All authors read and approved the final manuscript.

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RESEARCH ARTICLE Open Access

Economic costs of obesity in Thailand: a retrospective cost-of-illness study

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Abstract

Background: Over the last decade, the prevalence of obesity (BMI ≥ 25 kg/m^2) in Thailand has been rising rapidly and consistently. Estimating the cost of obesity to society is an essential step in setting priorities for research and resource use and helping improve public awareness of the negative economic impacts of obesity. This prevalence-based, cost-of-illness study aims to estimate the economic costs of obesity in Thailand.

Methods: The estimated costs in this study included health care cost, cost of productivity loss due to premature mortality, and cost of productivity loss due to hospital-related absenteeism. The Obesity-Attributable Fraction (OAF) was used to estimate the extent to which the co-morbidities were attributable to obesity. The health care cost of obesity was further estimated by multiplying the number of patients in each disease category attributable to obesity by the unit cost of treatment. The cost of productivity loss was calculated using the human capital approach.

Results: The health care cost attributable to obesity was estimated at 5,584 million baht or 1.5% of national health expenditure. The cost of productivity loss attributable to obesity was estimated at 6,558 million baht - accounting for 54% of the total cost of obesity. The cost of hospital-related absenteeism was estimated at 694 million baht, while the cost of premature mortality was estimated at 5,864 million baht. The total cost of obesity was then estimated at 12,142 million baht (725.3 million US$PPP, 16.74 baht =1 US$PPP accounting for 0.13% of Thailand's Gross Domestic Product (GDP).

Conclusions: Obesity imposes a substantial economic burden on Thai society especially in term of health care costs. Large-scale comprehensive interventions focused on improving public awareness of the cost of and problems associated with obesity and promoting a healthy lifestyle should be regarded as a public health priority.

Keywords: Cost-of-illness, Obesity, Overweight, Thailand, Economic

Background

Obesity (defined as having a Body Mass Index (BMI) greater than or equal to 30 Kilogram (Kg)/Meter(M)^2) [1], is a growing health concern worldwide. It is a known risk factor for a number of chronic diseases including cardiovascular diseases, diabetes, musculoskeletal disorders, and some cancers [2-5]. Aside from increased morbidity, obesity has also been found to increase premature mortality [6-8], decrease productivity due to absenteeism and presenteeism [9], and decrease quality of life [10-13].

As a result of increasing global urbanisation, changes in dietary habits, and declining levels of physical activity, the obesity epidemic is no longer limited to populations in Europe and North America [14-17]. Today, it affects populations in most countries, including those in Latin America and Asia. According to the World Health Organisation (WHO), the global prevalence of obesity has more than doubled between 1980 and 2008 [18]. In 2008, the WHO estimated that more than 1.4 billion adults aged 20 and over were overweight (a BMI greater than or equal to 25 Kg/M^2) [18]. Of these overweight adults, 500 million were obese [18].

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The economic cost of obesity is substantial. According to one estimate from a recent systematic review, the health costs associated with obesity may account for between 0.7% and 2.8% of a country's total health care expenditure [19]. In another review of data from ten Western European countries, estimated obesity costs were found to be as high as 0.09% to 0.61% of Gross Domestic Product (GDP) [20]. Estimating the cost of obesity to society is critical for policy makers, public health planners, and other health stakeholders. Not only can the cost estimate be used to establish priorities for research and health resource use, but it can also be used to improve public awareness of the negative economic impacts of obesity. In the past, many attempts have been made to estimate the economic cost of obesity in western countries [21-24]; few studies of this kind were conducted in Asia. However, in light of the rapid and continuous increase in obesity prevalence, several countries in Asia including Korea [25], Taiwan [26], China [27], and Hong Kong [28] have begun to assess the economic cost of obesity.

In line with global trends, the prevalence of obesity in Thailand almost doubled between 1991 and 2009. According to the fourth National Health Examination Survey (NHES) 2008-9 [29], 28.4% of adult Thai men and 40.1% of women were classified as obese (BMI ≥ 25 Kg/M^2). More importantly, the NHES also found that obesity levels had risen disproportionately in rural areas [30], indicating that obesity was no longer only found in higher socioeconomic groups. Despite this rapid increase in obesity over the last ten years, no research has yet been conducted into the economic cost of obesity in Thailand. Our study aims to estimate the economic costs of obesity in Thailand, 2009.

Methods

This is a prevalence-based, cost-of-illness study. Costs included in the analyses were health care cost, cost of productivity loss due to premature mortality, and cost of productivity loss due to hospital-related absenteeism.

Obesity and co-morbidities

In this study, obesity is defined as having a BMI of 25 Kg/m^2 or higher. To estimate the cost associated with obesity, a number of co-morbidities were identified and their respective costs calculated. Based on the degree of association with obesity, the availability of existing information and its importance in the Thai context, the following 12 co-morbidities were selected in our study: colon and colorectal cancer, breast cancer, endometrial cancer, hyperlipidemia, diabetes mellitus, depression, hypertension, ischemic heart disease, pulmonary embolism, stroke, gall bladder disease, and osteoarthritis. For each co-morbidity, the Obesity Attributable Fraction (OAF), the proportion of the incidence of a co-morbidity in the population that is due to obesity, was calculated using the following formula [31]:

$$OAF_j = \frac{\sum_{i=1}^{2} P_i\left(RR_{ij}-1\right)}{\sum_{i=0}^{2} P_i\left(RR_{ij}-1\right)+1}$$

Where

i = Body Mass Index (BMI) level (i = 1 means BMI ≥ 25.0-29.9 kg/m^2 and i = 2 means BMI ≥ 30 kg/m^2)

j = Co-morbidity related to obesity (j = 1 -12)

P_i = Prevalence of obesity at BMI level i

RR_{ij} = Relative Risk of co-morbidity j associated with obesity level i compared with the non-obese population

In this study, obesity prevalence (P_i) was obtained from the 4th NHES [17] while the Relative Risks (RR_{ij}) were derived from meta-analyses [32-34] as well as studies conducted in Asia [26,35].

Health care cost

The health care costs of obesity and the 12 co-morbidities were estimated for both inpatient and outpatient services. For each co-morbidity, the inpatient and outpatient healthcare costs attributable to obesity were calculated by multiplying the total number of patients with the given co-morbidity in Thailand by the corresponding OAF, and the average cost of each co-morbidity per person per year. Each co-morbidity total was then added together to give a total healthcare cost for obesity.

The outpatient data on the total number of patients and the data on the cost of outpatient visit(s) for each co-morbidity per person per year in 2009 were obtained from the database of the Center for Health Equity Monitoring (CHEM), Faculty of Medicine, Naresuan University. This database includes outpatient information covered by the two major public health insurance schemes in Thailand—the Universal Coverage Scheme (UCS) and the Civil Medical Service Scheme (CSMBS)—from 675 out of 843 public hospitals (80%) across all 76 provinces throughout the country. These two public health schemes cover approximately 80% of the total Thai population (approximately 67 million); the remaining 20% are covered by the Social Security Scheme (SSS), which is offered to formal private sector employees. To estimate the total number of outpatient visits in Thailand in 2009, it was assumed that 64% of total outpatient visits in Thailand would be those covered by the CHEM database.

The inpatient data on the total number of patients and the data on the cost of inpatient visit(s) for each co-morbidity per person per year were obtained from the Central Office for Health care Information (COHI)

database, 2009, which contains hospital admission data from all public hospitals for patients covered by the UCS and CSMBS (but not the SSS). It was assumed that the COHI data would represent 80% of total inpatients in Thailand.

Cost of productivity loss due to premature mortality

The costs associated with productivity loss due to premature mortality were calculated for each co-morbidity using the human capital approach. The number of deaths that could be attributed to obesity in 2009, disaggregated by age and gender, were multiplied by the average wage each person would receive if he or she lived through his or her lifespan. A discount rate of 3% was employed [29]. The data on the total number of deaths from each co-morbidity were obtained from the 2004 Thai Burden of Disease (BOD) project, and data on average earnings were calculated from the 2009 National Economic and Social Survey.

Cost of productivity loss due to hospital related absenteeism

The cost of hospital-related absenteeism was also calculated using the human capital approach. To estimate the cost of productivity loss due to hospital related absenteeism, the number of days that inpatients and outpatients with obesity-related conditions were absent from work in 2009 as a result of their obesity was multiplied by the average daily wage. Outpatient absentee data was obtained from the CHEM database; inpatient absentee data was obtained from the COHI database. The calculation was based on the assumption that the average outpatient visit took 0.5 days. The average daily wage was calculated by dividing Thailand's 2009 GDP per capita [36] by the number of working days in the same year.

Results

The overall relative risk estimates and OAFs for obesity and the 12 co-morbidities, disaggregated by gender, are presented in Table 1. OAF estimates indicate that about 24% to 52% of all cases of diabetes mellitus, 25% to 33% of all cases of ischemic heart disease, and 15% to 23% of all cases of osteoarthritis in Thailand are attributable to obesity, respectively.

Estimates of the overall economic costs of obesity, disaggregated by types of cost, gender, and co-morbidity are displayed in Table 2. With regard to total cost, the three conditions that are found to incur the highest costs are diabetes mellitus (6,385.7 million baht), ischemic heart disease (2,168.4 million baht), and stroke (2,017.6 million baht).

As shown in Table 2, the estimated health care cost attributable to obesity is 5,584 million baht. Obesity-related health care costs for women are about 2.5 times higher than for men (4,015 million baht VS 1,569 million baht). The three conditions that incur the highest health care costs are diabetes mellitus (3,386.6 million baht), ischemic heart disease (1,070.6 million baht), and colorectal cancer (377.3 million baht).

The estimated cost of premature mortality as a result of obesity-related conditions is 5,864 million baht. The premature mortality costs incurred by men are 1.5 times higher than they are in women (3,531 million baht VS 2,333 million baht). The three conditions that incur the highest premature mortality costs are diabetes mellitus (2,550.2 million baht), stroke (1,800.6 million baht), and ischemic heart disease (1,034.9 million baht).

The estimated cost of productivity loss due to absenteeism as a result of obesity-related conditions is 694 million baht. Of this total, 448.8 million baht results from diabetes mellitus, 102.3 million baht from hypertension, and 62.8 million baht from ischemic heart disease.

A summary of all of the estimated costs attributable to obesity is presented in Table 3. The total estimated economic cost of obesity in Thailand is 12,142.1 million baht (725.3 million US$PPP, 16.74 baht =1 US$PPP [36] or 0.13% of GDP [36]. Health care costs account for 46% of the total cost or about 1.5% of the national health care expenditure [37], while productivity loss costs account for 56% of the total cost.

Discussion

Many studies have shown that obesity exerts a significant cost burden on a country's health system and productivity [19,20]. This was also found in this first analysis of obesity cost in the Thai context, where obesity-attributable costs were found to be substantial, accounting for 0.13% of GDP or 1.5% of the total national health expenditure. In addition, the analysis revealed that costs associated with heath care provision and costs associated with productivity loss were broadly similar, which are in line with the findings of previous studies [22,38,39]. The cost identified in this paper should be regarded as a minimum estimate since other related costs such as the cost of absenteeism not related to hospitalization, cost of presenteeism, and unemployment costs were not included in the analysis. Furthermore, due to the unavailability of data in Thailand, the cost of premature mortality due to obesity and the following five co-morbidities—gall bladder disease, obesity, hyperlipidemia, pulmonary embolism, and depression—were not included in the analysis.

A WHO report [18] found that, globally, obesity and overweight account for 23% of coronary heart disease cases, 7-14% of cancer cases, and 44% of diabetes mellitus cases. These general proportions were also found in our analysis, which suggested that about 25-33% of ischemic heart cases, 2% of breast cancer cases, 17% of endometrial cancer cases, 8-9% of colon cancer cases, and 24-52% of diabetes mellitus cases in Thailand were associated with obesity. Unlike in Western countries [21-23], our study

Table 1 Relative risks for selected co-morbidities in obese subjects and Obesity Attributable Fraction (OAF)

Diseases/conditions	Relative risk of developing diseases				Obesity attributable fraction (OAF) (%)	
	Male		Female		Male	Female
	1*	2**	1*	2**		
Breast cancer [32]	-	-	1.08	1.13	-	2
Colon and colorectal cancer [32]	1.51	1.95	1.45	1.66	8	9
Depression [32]	1.30	1.31	0.98	1.67	4	3
Diabetes mellitus [32]	2.40	6.47	3.92	12.41	24	52
Endometrial cancer [32]	-	-	1.53	3.22	-	17
Gall bladder [32]	1.09	1.43	1.44	2.32	2	12
Hyperlipidemia [26]	1.95	1.76	1.95	1.76	11	15
Hypertension [32]	1.28	1.84	1.65	2.42	5	15
Ischemic heart disease [35]	3.02	4.37	3.02	4.37	25	33
Obesity	1.00	1.00	1.00	1.00	100	100
Osteoarthritis [32]	2.76	4.20	1.80	1.96	23	15
Pulmonary embolism [32]	1.91	3.51	1.91	3.51	15	22
Stroke [32]	1.23	1.51	1.15	1.49	4	5

*1 = BMI25.0-29.9 kg/m^2 **2 = BMI ≥ 30 kg/m^2.

did not find cardiovascular disease related to obesity to be the primary leading cause of economic burden. In line with a previous study in Asia [25], and giving weight to recent concerns that have been voiced regarding the epidemic of obesity and type 2 diabetes in Asia [16], we found diabetes mellitus to be the first leading cause of obesity cost (6,385.7 million baht), followed by ischemic heart disease (2,168.4 million baht), and stroke (2017.6 million baht). Nevertheless, previous studies indicate [40,41] that reducing weight by 5–10% can improve blood sugar control and help reduce the risk of developing cardiovascular disease. Given the rise of obesity in Asia, and the prevalence of related conditions—particularly diabetes mellitus and cardiovascular disease [16]—interventions aimed at obesity control clearly deserve more attention.

In line with findings from previous studies in the US [6,42,43], which found that obesity had a health impact equal or exceeding that of smoking and drinking, our

Table 2 Estimates of the economic costs of obesity in Thailand 2009 by types of costs, gender, and co-morbidity

Disease	Health care cost (Million baht)		Cost of premature mortality (Million baht)		Cost of productivity loss due to hospital-related absenteeism (Million baht)		Total cost (Million baht)		
	Male	Female	Male	Female	Male	Female	Male	Female	All
Diabetes mellitus	663.8	2,722.8	1,302.6	1,247.6	88.1	360.7	2,054.5	4,331.2	6,385.7
Ischemic heart disease	521.5	549.1	761.6	273.3	29.6	33.2	1,312.7	855.7	2,168.4
Stroke	98.9	99.6	1,236.1	564.5	9.2	9.4	1,344.1	673.5	2,017.6
Colon and rectal cancer	188.0	189.3	203.5	119.0	6.0	6.3	397.4	314.7	712.1
Hypertension	31.4	146.4	26.5	26.1	18.6	83.7	76.5	256.2	332.7
Osteoarthritis	46.3	113.6	0.7	0.6	8.2	17.6	55.2	131.8	187
Gall bladder	11.5	101.0	-	-	1.1	8.9	12.6	109.9	122.5
Endometrial cancer	-	42.3	-	2.8	-	2.5	0	47.6	47.6
Breast cancer	-	36.6	-	99.3	-	1.7	0	137.6	137.6
Obesity	3.8	4.6	-	-	1.2	2.5	5.0	7.1	12.1
Hyperlipidemia	0.9	2.1	-	-	1.1	2.5	2.0	4.6	6.6
Pulmonary embolism	1.8	5.9	-	-	0.1	0.5	1.9	6.5	8.4
Depression	0.8	1.8	-	-	0.4	0.7	1.3	2.5	3.8
Total	1,568.7	4,015.1	3,531.0	2,333.2	163.6	530.2	5,263.2	6,878.9	12,142.1

Table 3 Summary of the estimated economic costs of obesity in Thailand 2009

Cost	Million baht	%
Direct cost (health care cost)	5,584	46
OPD	850	
IPD	4,734	
Indirect cost (productivity loss)	6,558	54
Premature mortality	5,864	
Hospital-related absenteeism	694	
Total cost	12,142	100
% of total cost in term of GDP	0.13	
% of Health care cost in term of National health care expenditure [37]	1.5	

results indicate that health care costs attributable to obesity are the same as those attributable to alcohol consumption, which was estimated at 5,491 million baht in 2006 [44]. Despite this, the numbers of public health campaigns targeting obesity are fewer than those related to smoking and drinking. One explanation may be that obesity and the condition of being overweight are perceived as personal issues rather than social problems. However, our findings clearly show that the effect of obesity on the country's economy is significant, especially in terms of health care costs, which are currently shouldered by all tax payers in Thailand. It is clear that, to effectively tackle obesity in Thailand, a public health campaign targeting obesity epidemic should place emphasis on the impact of obesity on society as well as social responsibility without stigmatising those who are obese.

In this study, BMI was used as a measure to determine the prevalence of obesity. According to the WHO [45], a BMI reading of 25-29.9 kg/m^2 is indicative of an overweight condition, while a reading of 30 kg/m^2 or higher indicates obesity. However, in Asia, the risk of type 2 diabetes mellitus and cardiovascular disease is already high in those whose BMI is below 25 kg/m^2. In addition, at the same BMI, Asian populations are found to have higher levels of body fat than Western populations [46,47]. Therefore, it has been proposed that lower BMI readings should be used to identify those who are overweight or obese in the Asian population. A 2004 WHO expert consultation proposed that an appropriate cut off to measure the condition of being overweight and obese in Asian populations would be 23-24.9 kg/m^2 and 25 kg/m^2, respectively [47]. To permit comparison across previous studies in estimating the economic cost of obesity, a BMI reading of at least 25 kg/m^2 was used to define obesity in our study. Nevertheless, it should be noted that the estimate impact of obesity will be lower if a BMI reading of 30 kg/m^2 is used to define obesity.

In this study, the prevalence of obesity in 2009 was used to calculate the OAF. The estimated prevalence constitutes people with a varied time period of obesity. As induction times for chronic diseases may differ across persons and diseases and are not exactly known, we might have overestimated the cost from the impact of obesity as the lapse time need for developing comorbidity as well as duration of obesity were not taken into account. Nevertheless, these figures do inform at what cost the societal inevitably need to shoulder in the future without effective interventions to mitigate the current burden of obesity. In addition, the identification of induction times for chronic diseases is a priority area for future research related to obesity.

Another limitation that warrants further discussion is the reliance on estimated costs. While we acknowledge that the validity of our findings relies on the accuracy of a number of estimated parameters and assumptions, we are confident that the estimates are reasonably accurate. For instance, the CHEM and COHI databases (which were used to estimate health care costs) are the largest hospital databases available in Thailand. Nevertheless, we assumed that the COHI accounted for 80% of all inpatients in the country. However, based on the recent figures [48], patients in COHI database may account for 83% of the total population. Therefore, our results might slightly overestimate the impact of obesity. In addition, while these databases only include data from patients who are covered by the UCS and CSMBS schemes, we assume that obesity prevalence among beneficiaries of these two schemes will be comparable to those of the SSS. We acknowledge, however that this assumption may be somewhat limited as the SSS scheme covers those who are healthy enough to be employed in the private sector; this may mean that they suffer from lower levels of obesity. If this is the case, then the total cost of obesity would be somewhat lower than what we have estimated in this study. Lastly, since there was no Thai-specific relative risk data available, the relative risk data were obtained from meta-analysis review of global literature, including a number of Asian studies [26,32-35]. Future research on relative risk in Thailand, particularly for diabetes and cardiovascular disease, would be beneficial.

Conclusions

This study confirmed that obesity imposes a substantial economic burden on Thai society. In terms of health care cost, it is equivalent to that imposed by alcohol consumption. In light of the rapid and continuous increase in obesity prevalence in Thailand, large-scale comprehensive interventions for the prevention and control of obesity should be regarded as of public health priority in Thailand.

Competing interests
The authors declare that they have no competing interests.

Authors' contributions
PP participated in study design, data collection, data analysis, and drafted the manuscript. NS participated in its design and coordination, data collection, and data analysis. RB participated in its design and data analysis. JY participated in its design and data collection. WA participated in its design, data collection and data analysis. YT conceived of the study, participated in its design and data analysis, MT conceived of the study, participated in its design and coordination, data collection, data analysis, and helped to draft the manuscript. All authors read and approved the final manuscript.

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Cost-Utility Analysis of Dasatinib and Nilotinib in Patients With Chronic Myeloid Leukemia Refractory to First-Line Treatment With Imatinib in Thailand

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ABSTRACT

Background: Recently, the second-generation tyrosine kinase inhibitors dasatinib and nilotinib have emerged as alternative treatments in patients with chronic myeloid leukemia (CML) who are resistant to or intolerant of imatinib.

Objective: This article aimed to assess the cost utility and budget impact of using dasatinib or nilotinib, rather than high-dose (800-mg/d) imatinib, in patients with chronic phase (CP) CML who are resistant to standard-dose (400-mg/d) imatinib in Thailand.

Methods: A Markov simulation model was developed and used to estimate the lifetime costs and outcomes of treating patients aged ≥38 years with CP-CML. The efficacy parameters were synthesized from a systematic review. Utilities using the European Quality of Life–5 Dimensions tool and costs were obtained from the Thai CML population. Costs and outcomes were compared and presented as the incremental cost-effectiveness ratio in 2011 Thai baht (THB) per quality-adjusted life year (QALY) gained. One-way and probabilistic sensitivity analyses were performed to estimate parameter uncertainty.

Results: From a societal perspective, treatment with dasatinib was found to yield more QALYs (2.13) at a lower cost (THB 1,631,331) per person than high-dose imatinib. Nilotinib treatment was also found to be more cost-effective than high-dose imatinib, producing an incremental cost-effectiveness ratio of THB 83,328 per QALY gained. This treatment option also resulted in the highest number of QALYs gained of all of the treatment options. The costs of providing dasatinib, nilotinib, and high-dose imatinib were estimated at THB 5 billion, THB 6 billion, and THB 7 billion, respectively.

Conclusions: Treatment with dasatinib or nilotinib is likely to be more cost-effective than treatment with high-dose imatinib in CP-CML patients who do not respond positively to standard-dose imatinib in the Thai context. Dasatinib was found to be more cost-effective than nilotinib. (*Clin Ther*. 2014;36:534–543) © 2014 Elsevier HS Journals, Inc. All rights reserved.

Key words: chronic myeloid leukemia, cost-utility analysis, dasatinib, imatinib, leukemia, nilotinib, Thailand.

INTRODUCTION

Chronic myeloid leukemia (CML) is a malignant disorder characterized by abnormal proliferation of white blood cells. CML can be diagnosed by the presence of the Philadelphia chromosome, which results from a reciprocal translocation between chromosomes 9 and 22.[1] The new fusion gene, *BCR-ABL*, has been identified as the key factor in the development of CML. The disease is classified into 3 phases: (1) the chronic phase (CP); (2) the accelerated phase (AP); and (3) the blast phase (BP). Most patients are diagnosed with CML when the disease is in CP, which is generally asymptomatic. However, patients may show some symptoms, such as malaise, weight loss, and an enlarged spleen, during this phase, in

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which they may remain for 3 to 5 years.[2,3] Without treatment, the disease will progress from CP to AP, a more aggressive phase characterized by high proportions of blast cells (20%–30%), promyelocytes (>20%), and basophils (>20%). AP lasts ~4 to 6 months, after which most patients move into BP. During BP, CML takes on its most aggressive form, characterized by a high proportion of blast cells (>30%) in the peripheral blood or bone marrow. Patients may experience fever, fatigue, bone pain, and infections. Median survival in patients with BP-CML ranges from 3 to 6 months.[3] The incidence of CML in Thailand is ~0.5 case per 100,000 population per year.[4] Most new diagnoses of CML in Thailand are made in patients aged between 38 and 42 years.[5]

In the past decade, imatinib, the first available tyrosine kinase inhibitor (TKI), has been used widely as a first-line treatment of newly diagnosed CML.[6] Despite the high efficacy of imatinib, ~20% to 30% of patients with CML are resistant to or intolerant of the drug, and half of cases are due to a genetic mutation in the ABL domain.[7–9] Recently, the second-generation TKIs dasatinib and nilotinib have emerged and have been used as alternative treatments in patients with CML who are resistant to or intolerant of imatinib. Several experimental clinical studies have revealed that dasatinib or nilotinib use has a higher success rate than does the use of high-dose imatinib,[7,10,11] and the US Food and Drug Administration has recently approved the use of dasatinib and nilotinib as first-line treatments of newly diagnosed CML.[12] Economic evaluation studies have found that dasatinib offers good value-for-money in patients with CML who are imatinib resistant or intolerant in Sweden,[8] as well as nilotinib does in the United Kingdom. As a result, there are growing calls from Thai clinicians to include dasatinib and nilotinib in the National List of Essential Medicines (NLEM). Given the differences in health care infrastructure and economic parameters between Thailand and Sweden/United Kingdom, the data available from those economic evaluations might not be applicable for decision making in Thailand. This study aims to assess whether these 2 treatments are cost-effective in the Thai context, and the results will be used to inform decisions regarding the coverage of these drugs in the NLEM.

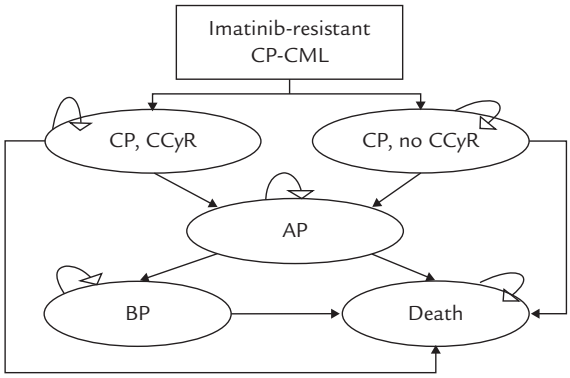

Figure 1. Structure of the Markov model. AP = accelerated phase; BP = blast phase; CCyR = complete cytogenetic response; CML = chronic myeloid leukemia; CP = chronic phase.

MATERIALS AND METHODS

Markov Model

A Markov model with a 2-month cycle length was developed based on typical treatment of patients with CP-CML, consisting of 5 initial health states: (1) CP with a *complete cytogenetic response* (CCyR), defined as no Ph-positive metaphases found in the bone marrow[13]; (2) CP without CCyR; (3) AP; (4) BP; and (5) death (Figure 1). In this Markov model, a cohort of patients with CP-CML aged ≥38 years (the median age of patients with CML in Thailand[5]) who failed to respond to first-line imatinib 400 mg/d were followed until death. Because this study focused on the costs and outcomes of CML treatment in patients in CP, it was assumed that patients who progressed to other phases would receive similar treatment. Because dasatinib 100 mg/d, nilotinib 800 mg/d, and high-dose imatinib (800 mg/d) are each used to treat patients in AP, the model assumed that the 3 treatments would be equally likely choices in patients who progressed to AP. In patients in BP, however, there is only 1 routine treatment—hydroxyurea 2000–3000 mg/d. The model took a societal perspective, meaning that the costs shouldered by both provider and household were taken into account. Future costs and outcomes were discounted at a rate of 3% per annum.

Model Input Parameters

Efficacy Data

The treatments were deemed *effective* if a patient experienced CCyR. The efficacy of each treatment was

assessed based on a systematic review. We conducted a literature search using the electronic databases PubMed and Cochrane Central Register of Controlled Trials (CENTRAL). Searching was performed separately for articles on dasatinib, nilotinib, and high-dose imatinib on February 21, 2012; March 9, 2012; and June 6, 2012, respectively. The following search terms were used: *leukemia, myelogenous, chronic, BCR-ABL, positive MeSH, CML, chronic myelogenous leukemia, chronic phase, nilotinib, dasatinib,* and *imatinib*. A total of 255 abstracts (114 pertaining to dasatinib, 45 pertaining to high-dose imatinib, and 96 pertaining to nilotinib) were identified. Studies were included if they met the following criteria: the population was composed of patients with CP-CML who were resistant to standard-dose (400-mg/d) imatinib; intervention was with imatinib 800 mg/d, dasatinib 100 mg/d, or nilotinib 800 mg/d; outcomes included the percentage of patients who achieved CCyR within 24 months; and the dose used was similar to that used in clinical practice in Thailand. Only 1 study eligible based on our selection criteria was identified for each treatment option.[7,10,14] The results of the systematic review indicated that the efficacy values (CCyR rates) of high-dose imatinib, nilotinib, and dasatinib were 18% (5.48%), 41% (3.83%) and 44% (2.74%), respectively (**Table I**).

Adverse Events

Data related to adverse events (AEs) were obtained from our systematic review (**Table I**). Serious AEs occurring in ≥10% of the treatment population were selected; we identified the following: grade 3/4 neutropenia, grade 3/4 thrombocytopenia, grade 3/4 anemia, grade 3/4 leukopenia, and all-grade pleural effusion.[7,10,14] Data regarding the costs of treating each AE were garnered based on a hematologist's opinion; in addition, the unit costs of the resources associated with AE management were taken from the Comptroller General's Department, Thailand.[19] The Comptroller General's Department maintains a database of standard costs of health care services for all hospitals and health care centers under the Ministry of Public Health. In this study, AEs were included only in the first cycle of the model due to a lack of long-term data.

Transitional Probabilities

The risk for transitioning from CP to AP was calculated from progression-free survival (PFS). CCyR was associated with PFS,[20,21] which means that patients achieving CCyR had a lower risk for transitioning from CP to AP. In this study, therefore, patients were classified into 2 groups: (1) those who achieved CCyR and (2) those who did not. At 24 months, the PFS in the first group was 95% and in the second group was 74%.[15,16] A transitional probability from AP to BP was also calculated from PFS (median PFS, 49 months).[17] A transitional probability from BP to death was calculated from overall survival (median survival, 7 months).[17] The risks for death in CP and in AP were extrapolated from the average Thai life expectancy of patients whose cause of death was unspecified.[22] The 2-month transitional probabilities were calculated according to the following formula:

$$\text{Transitional probability per cycle} = 1 - \exp\left[\ln(P)/t\right],$$

where P is the PFS or overall survival at time T (in months), and t is T/2.

Costs and Utility Estimates

The study protocol was approved by the ethics clearance committees of the Faculty of Medicine, Ramathibodi Hospital, Mahidol University, and of the Faculty of Medicine, Khonkaen University. Direct medical costs, such as polymerase chain reaction testing, complete blood count, cytogenetic analysis, bone marrow aspiration, other laboratory tests, as well as inpatient costs, were obtained through medical chart reviews from Ramathibodi Hospital. The costs of dasatinib, nilotinib, imatinib, and hydroxyurea were derived from the Thai FDA (personal communication, [2011]). Direct nonmedical costs (ie, costs for transportation, meals, accommodation, facilities, and costs pertaining to productivity loss) were collected during face-to-face interviews with patients with CML or with caregivers at Ramathibodi or Srinakarin Hospital, and from the domestic literature if interviews did not provide the necessary data.[18] All cost parameters are presented in 2011 Thai Baht (THB) (THB 31 = US $1).

Utility scores were elicited by applying the European Quality of Life–5 Dimensions (EuroQol Group, Rotterdam, the Netherlands) (EQ-5D) instrument to data garnered during interviews that took place in May 2012 and June 2012 with Thai patients with CML aged between 15 and 60 years who were receiving treatment at Ramathibodi or Srinakarin

Table I. Parameters used in the model.

Parameter	Distribution	Mean (SE)	
CCyR, % (24-mo follow-up)	β		
High-dose imatinib 800 mg/d		18 (5)	Ref 7
Dasatinib 100 mg/d		44 (4)	Ref 10
Nilotinib 800 mg/d		41 (3)	Ref 14
Adverse events, %	β		
High-dose imatinib			Ref 7
Thrombocytopenia grade 3/4		14 (5)	
Neutropenia grade 3/4		39 (7)	
Anemia grade 3/4		8 (4)	
Leukopenia grade 3/4		16 (5)	
Dasatinib			Ref 10
Thrombocytopenia grade 3/4		23 (3)	
Neutropenia grade 3/4		35 (4)	
Anemia grade 3/4		13 (3)	
Leukopenia grade 3/4		18 (3)	
Pleural effusion all grades		14 (3)	
Nilotinib			Ref 14
Thrombocytopenia grade 3/4		30 (3)	
Neutropenia grade 3/4		31 (3)	
Anemia grade 3/4		11 (2)	
Pleural effusion all grades		1 (1)	
Transitional probabilities per cycle	β		
CP to AP for responder*		0.005 (0.000)	Refs 15,16
CP to AP for nonresponder†		0.025 (0.004)	Refs 15,16
AP to BP‡		0.028 (0.002)	Ref 17
BP to death§		0.180 (0.020)	Ref 17
Drug costs per day, THB	Fixed		Thailand FDA
High-dose imatinib (800 mg/d)		7,333	
Dasatinib 100 mg/d		5,136	
Nilotinib 800 mg/d		5,961	
Hydroxyurea 2000–3000 mg/d		130	
Direct medical costs, THB	γ		
CP (per y)			Chart review
High-dose imatinib		26,105 (28,006)	
Dasatinib		40,399 (40,570)	
Nilotinib		54,782 (47,638)	
AP (per y)		37,992 (42,454)	
BP			
Outpatient (per y)		26,933 (23,558)	Chart review
Hospitalization (per mo)		15,522 (19,818)	Thailand CHI
Direct non-medical costs, THB			
CP (per 6 mo)			Interview

(continued)

Table I. (continued).

Parameter	Distribution	Mean (SE)	
High-dose imatinib		4,282 (4,282)	
Dasatinib		47,578 (40,615)	
Nilotinib		14,331 (3,942)	
AP (per 6 mo)		3,429 (1,715)‖	Interview
BP—palliative care at home (per 6 wk)		45,010 (22,505)‖	Ref 18
Treatment cost related to adverse events (per episode), THB	γ		Ref 19
Thrombocytopenia grade 3/4		2,315 (1,157)	
Neutropenia grade 3/4		7,661 (3,830)	
Anemia grade 3/4		1,989 (994)	
Leukopenia grade 3/4		7,661 (3,831)	
Pleural effusion all grades		7,889 (3,945)	
Utility (EQ-5D)	β		
CP			Interview
High-dose imatinib		0.648 (0.064)	
Dasatinib		0.749 (0.042)	
Nilotinib		0.810 (0.041)	
AP		0.514 (0.257)‖	Interview
BP		0.314 (0.157)‖	Assumed

AP = accelerated phase; BP = blast phase; CCyR = complete cytogenetic response; CHI = Central Office for Healthcare Information; CP = chronic phase; EQ-5D = European Quality of Life–5 Dimensions (EuroQol Group, Rotterdam, the Netherlands); FDA = Food and Drugs Administration; PFS = progression-free survival; THB = 2011 Thai Baht (THB 31 = US $1).
*Achieving CCyR; PFS at 24 months was 95%.
†Not achieving CCyR; PFS at 24 months was 74%.
‡Median PFS in AP was 49 months.
§Median overall survival in BP was 7 months.
‖Set to 50% of mean.

Hospital. The Thai scoring function was used to transform multi-attribute health status to utility scores.[23] Unfortunately, no patients with BP-CML were identified during the data-collection period. Prior studies in other settings have reported that utilities in patients with BP-CML were lower than those in patients with AP-CML by ~0.2.[4,8] On the basis of this, we assumed that the utility score of patients with BP-CML would be 0.31 (Table I).

Data Analysis

The results of the analysis are presented as incremental cost-effectiveness ratios (ICER), in THB per quality-adjusted life year (QALY) gained. The Subcommittee for Development of the National List of Essential Medicines sets the cost-effectiveness ceiling threshold as equal to 1 gross domestic product per capita.[24] As a result, we used the ceiling threshold of THB 120,000 (US $3870) per QALY gained in our analysis.

A one-way sensitivity analysis was undertaken to explore the uncertainty in each input parameter individually (taking into account a discounted rate of 0% and 6% per annum, the CCyR rate, the probability of transitioning from CP to AP, the utility, and the cost); the findings are presented in a tornado diagram. A probabilistic sensitivity analysis was carried out to assess the effect of all parameter uncertainties together, using a Monte Carlo simulation approach in Excel 2007 (Microsoft Corporation, Redmond, Washington). A thousand simulations were

run to yield a range of possible values for ICERs in THB per QALY gained. Average ICERs are presented on a cost-effectiveness plane.

Lastly, a budget impact analysis was performed to forecast the budget necessary for the next 5 years if dasatinib and/or nilotinib were to be included in the NLEM in Thailand. Data on the current number of patients with CML in Thailand were not available, but expert opinion was canvassed, and 1400 was given as an estimate, of whom 32.5% were estimated as failing to respond to standard-dose imatinib.[25–27] Thus, in the cumulative case, 445 cases (1400 × 32.5%) were estimated as needing second-line treatment, with ~60 new cases of patients with CML who are resistant to first-line treatment emerging each year (incidence rate, 0.5 per 100,000 population × 32.5%).[4] Currently, there is an access program for nilotinib, in which the cost of the treatment is shared between the Thai government and the private sector; in this program, the treatment is offered at a price 83% lower than the current market price. We therefore performed a budget impact analysis using this additional scenario.

RESULTS

Dasatinib and nilotinib were found to be more effective treatment options than high-dose imatinib in patients with CML who were resistant to first-line treatment. Once second-line treatment was commenced, median predicted survival in patients treated with dasatinib or nilotinib was 14 years. Of these, the patients treated with dasatinib lived slightly longer, on average, than did those treated with nilotinib (Figure 2).

Derived from the probabilistic model, the data from Table II illustrate estimated lifetime costs and outcomes with the different treatment options, ranging from THB 24 to 28 million in costs and 6.59 to 9.16 QALYs gained. Treatment with dasatinib exhibited the lowest cost and greatest life expectancy among the treatment options. Conversely, nilotinib revealed the highest cost and outcome (in terms of QALY) as well. It also yielded a life expectancy similar to that with dasatinib. High-dose imatinib proved less effective than other treatments.

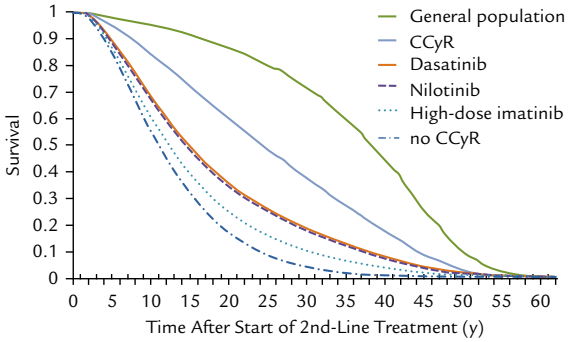

Figure 2. Estimated survivals of hypothetical patients aged 38 years. CCyR = complete cytogenetic response.

Both dasatinib and nilotinib were found to be more cost-effective compared with high-dose imatinib (Figure 3). Dasatinib was less costly (THB 1,631,331) than was high-dose imatinib and resulted in more QALYs (2.13). Nilotinib was found to be more costly than high-dose imatinib and generated more QALYs for patients compared with high-dose imatinib, yielding an ICER of THB 83,328 per QALY gained. A 1-way sensitivity analysis indicated that the variation in CCyR rate and discounting rate had a significant effect on the model (Figure 4).

Table II. Lifetime costs and outcomes of different treatment regimens.

Treatment Options	Cost, THB		LYs	QALYs
	Societal Perspective	Government Perspective		
High-dose imatinib	27,438,778	27,184,602	11.17	6.59
Dasatinib	25,807,447	24,732,470	12.87	8.72
Nilotinib	27,653,184	27,213,170	12.71	9.16

LYs = life-years; QALY = quality-adjusted life-years; THB = 2011 Thai Baht (THB 31 = US $1).

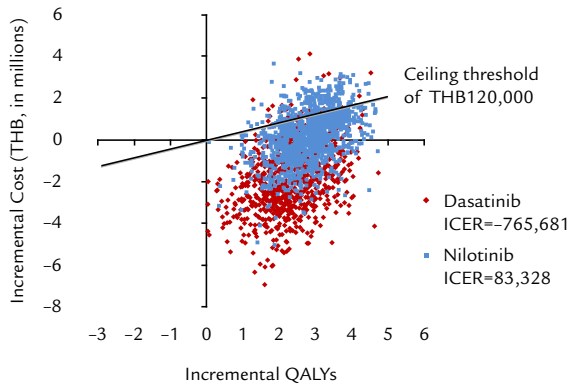

Figure 3. Incremental cost-effectiveness plane illustrating ICER of nilotinib and dasatinib. ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-years; THB = 2011 Thai Baht (THB 31 = US $1).

Five-year budgets for providing dasatinib, nilotinib, and high-dose imatinib were estimated at THB 5 billion, THB 6 billion, and THB 7 billion, respectively (Table III). If the current nilotinib treatment program, which is supported by the private sector and offers treatment at a price 83% lower than that of the market, was to be extended for an additional 5 years, the cost of including nilotinib on the NELM would be THB 1.5 billion.

DISCUSSION

Compared with high-dose imatinib, both dasatinib and nilotinib are considered to be more cost-effective options for treating patients with CP-CML who are resistant to or intolerant of imatinib 400 mg/d in the Thai context. The budget impact analysis revealed that offering dasatinib or nilotinib was less expensive than offering high-dose imatinib.

The results of this study contrast with those obtained from a recent UK study, which indicated that only nilotinib treatment represented good value-for-money in the UK context.[28] This can be explained by the fact that the UK study used major cytogenetic response (MCyR) as its indicator of success, which represents a less-effective response in terms of blast cell reduction than does CCyR (1%–35% compared with 0%). Using MCyR as an efficacy indicator, dasatinib, nilotinib, and high-dose imatinib yielded efficacy rates of 58.1%, 52.4%, and 44%, respectively.[28] Meanwhile, our study, which used CCyR as an efficacy indicator, found that dasatinib, nilotinib, and high-dose imatinib yielded efficacy rates of 43.7%, 41.1%, and 18.37%.[7,10,14] Efficacy was associated with PFS, which is typically used to predict time spent on treatments in economic models. An *effective* treatment has increased both the patient's life-expectancy and costs due to the long-term nature of the treatment, especially in patients with chronic

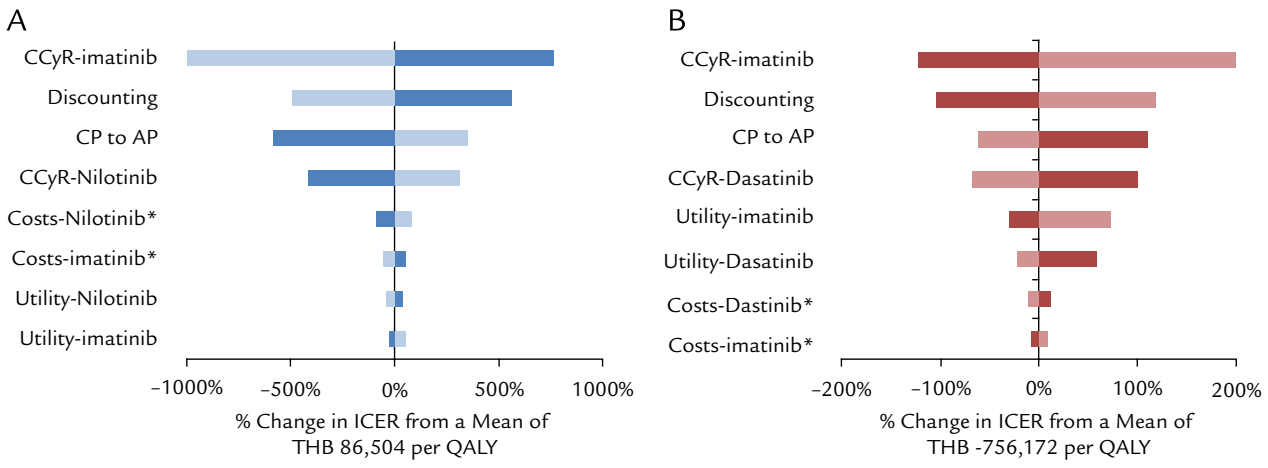

Figure 4. Tornado diagram. A, nilotinib versus high-dose imatinib; B, dasatinib versus high-dose imatinib. *Direct medical costs excluding drug price. AP = accelerated phase; CCyR = complete cytogenetic response; CP = chronic phase; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-years; THB = 2011 Thai Baht (THB 31 = US $1).

Table III. Estimated budgets of implementing dasatinib and nilotinib. Data are THB, in billions.

Year	High-Dose Imatinib	Dasatinib	Nilotinib	Nilotinib (Access Program)
1	1.16	0.83	0.96	0.19
2	1.27	0.94	1.08	0.26
3	1.38	1.04	1.18	0.32
4	1.46	1.13	1.28	0.37
5	1.54	1.21	1.36	0.41
Total	6.81	5.16	5.85	1.54
Difference vs high-dose imatinib	—	−1.65	−0.95	−5.27

THB = 2011 Thai Baht (THB 31 = US $1).

diseases such as CML. The UK study supports that dasatinib would become a cost-effective treatment if the PFS (time spent on treatment) for dasatinib were lowered to the same level as nilotinib.[28] The difference in the efficacy indicators used in both studies would result in different study conclusions. This is also proved by our results from the 1-way sensitivity analysis, which demonstrates that a variation in CCyR rates (particularly for high-dose imatinib) strongly influences the ICER. The use of CCyR as an efficacy indicator has become the current clinical practice both in Thailand and around the world.[13,29] Our study corroborates findings from a study in Sweden, which also found dasatinib to be a more cost-effective alternative than high-dose imatinib.[8]

In our study, the lifetime treatment cost per patient was estimated to be THB 27 million with dasatinib and THB 29 million with nilotinib. These figures are high compared with those from other studies.[8,28] The difference in the age at which patients typical begin second-line treatment in the Thai and European contexts may account for some of this difference. The median age of the onset of CML in Asian populations (45 years) is less than that in Western populations (~69 years).[4] Most of the lifetime treatment costs in patients arise from drug expenditure. With this in mind, it is notable that drug costs per day of dasatinib and of nilotinib are higher in Thailand than in the United Kingdom (dasatinib costs THB 5136 in Thailand compared with THB 4096 in the United Kingdom, and nilotinib costs THB 5961 in Thailand compared with THB 4262 in the United Kingdom).[28] This is likely to be a significant cause of the high total cost in our study. Importantly, the 83% reduction in the cost of nilotinib offered by the access program would reduce the lifetime cost per patient in our model by 70%.

One of the strengths of this study was the use of CCyR as an indicator of patient survival, in contrast to previous studies, which employed MCyR. In addition, treatment duration is a major factor determining CCyR/MCyR; this study therefore identified the efficacies of the treatments by assessing studies with the same follow-up period (24 months). Nonetheless, this study contains some limitations. First, the efficacy data used in this study were obtained from 3 different clinical trials because we could not identify a study that compared all 3 medicines. Second, this analysis did not consider allogeneic stem cell transplantation because very few patients (<20 patients per annum) have access to that treatment[30] due to the limited number of matched donors and to a shortage of health care professionals who are able to perform it.

Dasatinib and nilotinib should be included in the NLEM. Nilotinib was found to be an option superior to dasatinib from the governmental perspective due to the greater number of QALYs gained and the lower procurement costs (due to the subsidy program). This recommendation also aligns with that of the National Institute for Health and Care Excellence.[31] However, dasatinib and nilotinib have distinctive response patterns according to their mutation status[15,32] and cannot be used as substitutes for each other. Therefore, both should be included in the NELM. Nilotinib should be considered as the first option for the

treatment of patients with CML who are resistant to or intolerant of standard-dose imatinib and who are eligible for the subsidy program.

CONCLUSIONS

Treatment with dasatinib or nilotinib is likely to be more cost-effective than treatment with high-dose imatinib in patients with CP-CML who do not respond positively to standard-dose imatinib in the Thai context. Dasatinib was found to be more cost-effective than nilotinib.

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CONFLICTS OF INTEREST

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Original article

A cost–utility analysis of alternative drug regimens for newly diagnosed severe lupus nephritis patients in Thailand

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Abstract

Objective. The aim of this study was to assess the value of four drug regimens for newly diagnosed severe LN from a societal perspective.

Methods. A model-based cost–utility analysis was devised to measure lifetime costs and health outcomes. Current treatment options consisting of different combinations of i.v. CYC, AZA and MMF were compared with a baseline regimen of i.v. CYC in both the induction and maintenance phases. Resource use and costs were derived from medical records reviews and databases. Event rates were elicited from randomized controlled trials. Relative treatment effects were obtained from meta-analyses. Health utilities were obtained from a real cohort of patients to estimate the outcome of quality-adjusted life years.

Results. It was found that a treatment regimen that combined i.v. CYC in the induction phase with AZA in the maintenance phase was cost saving compared with the baseline regimen. Treatment with i.v. CYC in the induction phase and MMF in the maintenance phase and treatment with MMF in the induction phase and a reduced dose of the same in the maintenance phase turned out to be a negatively dominated regimen.

Conclusion. In the Thai context, the combination of i.v. CYC for the induction phase followed by AZA for the maintenance phase should be considered as the first-line therapy for newly diagnosed severe LN, as it seems to be the most cost-saving regimen.

Key words: lupus nephritis, mycophenolic acid, cyclophosphamide, azathioprine, immunosuppressive agents, health care rationing, decision support techniques, costs and cost analysis, economic models, Thailand.

CLINICAL SCIENCE

Introduction

SLE is an autoimmune disease with symptoms ranging from minor skin and joint complaints to serious organ issues, such as nephritis and neuropsychiatric problems. Although the disease is found in populations all over the world, its prevalence, clinical spectrum, seriousness and burden differ depending on the location [1]. In developing countries, patients with SLE are far more likely to exhibit LN than patients in more developed countries and this impacts directly on their morbidity and mortality. The existing evidence has shown that 64–69% of SLE patients in South East Asia have LN compared with 28% in Europe [2]. LN, in Thailand, presents a 5-year survival rate of 77%, with infection (51%) and renal failure (29%) as the main causes of death [3].

LN treatment is usually administered in two phases—the first phase aims to halt progression (known as the induction phase) and the second phase aims to avoid recurrence and prevent end-stage renal disease (ESRD), renal and extra-renal lupus activity and death (known as the maintenance phase). Current Thai clinical practice guidelines recommend oral prednisolone (60 mg/day) plus i.v. CYC (0.5–1 g/m^2) as appropriate treatment

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during both the induction phase (monthly for 6 months) and the maintenance phase (every 3 months for 2 years) [4]. However, this approach can cause adverse effects in patients, including major and minor infections, amenorrhoea and haematological and gastrointestinal events [5, 6].

Evidence from a number of randomized control trials (RCTs) has suggested that there are other drugs that may be more appropriate for treating LN. Oral AZA, for instance, which has limited use in induction therapy due to its relatively high relapse rate, has shown efficacy in treating LN in the maintenance phase and has a better safety profile than i.v. CYC [7]. In addition, there is evidence that MMF, which is increasingly being used as an immunosuppressive agent in autoimmune disease, can be used in both the induction and maintenance phases for LN with equal efficacy and fewer side effects than the standard therapy of i.v. CYC [8].

Effective treatment of LN at an early stage reduces the number of patients who go on to suffer irreversible ESRD and thus reduces the cost of treatment [9]. Given the high cost of renal dialysis (which has a lifetime cost at an onset age of 30 years of ~8 000 000 baht) [10], the prevention of ESRD in severe LN patients is likely to be a cost-saving intervention. Policymakers must decide how best to distribute health resources in a way that guarantees the best outcomes for patients while maintaining financial efficiency. Economic evaluations are an essential tool in the decision-making process of any healthcare system.

To date, no economic evaluation studies have been conducted that examine this issue in the context of developing countries. This study was conducted in response to a request from the Subcommittee for Development of the Health Benefit Package and Service Delivery of the National Health Security Office in the hope that the data will inform recommendations on the best treatment option for patients with LN within the Universal Coverage scheme in Thailand [11]. This study aims to compare, from a societal perspective, the cost and utility of different drug regimens for both the induction and maintenance phases of newly severe LN treatment in patients.

Methods

Lifetime costs and outcomes were simulated for a hypothetical cohort of newly diagnosed active severe LN patients at an average age of 40 years receiving different immunosuppressive therapy drug regimens. All future costs and outcomes were discounted at a rate of 3% per annum, as recommended by Thailand's health technology assessment guidelines [12]. Primary outcomes of interest were lifetime costs, quality-adjusted life-years (QALYs) and the incremental cost-effectiveness ratio (ICER) in Thai baht per QALY gained.

Intervention and comparators

The current Thai guidelines for the management of severe LN recommend a treatment of oral prednisolone plus i.v. CYC monthly (in the induction phase), followed by i.v. CYC treatment administered every 3 months (in the maintenance phase); this treatment was thus set as the baseline comparator. A number of immunosuppressive agents, such as AZA and MMF, which have been widely available and commonly used in the treatment of autoimmune diseases, were assessed to see whether they can be used as effective alternative interventions for LN patients.

Although treatment dosage can vary from patient to patient, for our analysis we examined RCTs that included the most common dosages. The dosages of the drug regimens included in this economic evaluation were as follows:

Regimen 1: i.v. CYC at an average dose of 1000 mg/m^2 monthly for 6 months during the induction phase followed by i.v. CYC every 3 months to complete 3 years during the maintenance phase (i.v. CYC → i.v. CYC as the baseline comparator).

Regimen 2: i.v. CYC at an average dose of 1000 mg/m^2 monthly for 6 months during the induction phase followed by AZA at an average dose of 50 mg/day to complete 3 years during the maintenance phase (i.v. CYC → AZA).

Regimen 3: i.v. CYC at an average dose of 1000 mg/m^2 monthly for 6 months in the induction phase followed by MMF at an average dose of 1000 mg/day to complete 3 years in the maintenance phase (i.v. CYC → MMF).

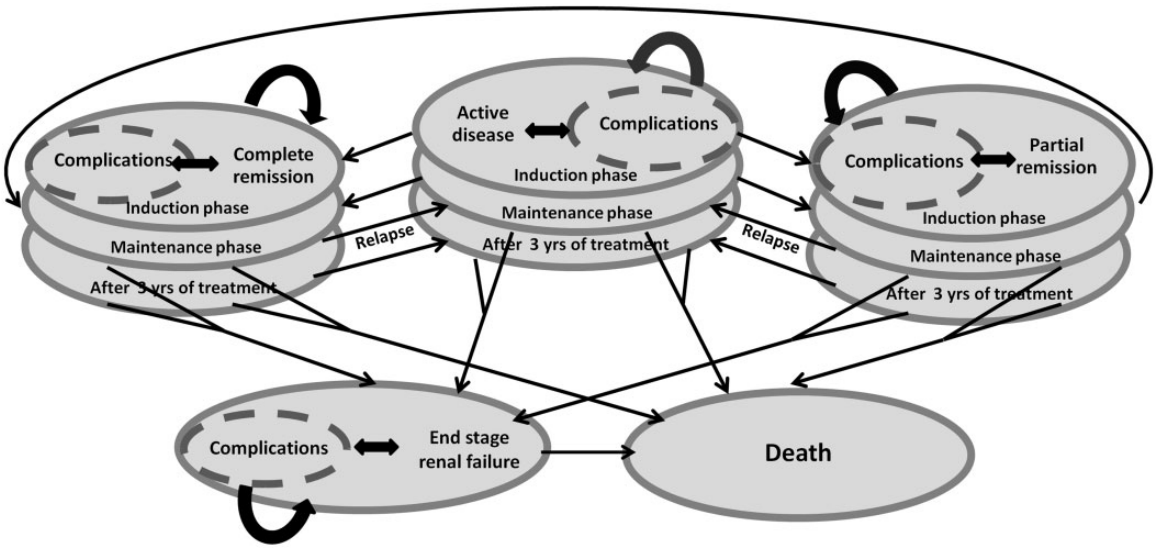
Regimen 4: MMF at an average dose of 2000 mg/day for 6 months in the induction phase followed by a reduced dose of MMF of 1000 mg/day for 6 months and then AZA at an average dose of 50 mg/day to complete 3 years in the maintenance phase (MMF → low-dose MMF).

Model structure

A Markov simulation model was constructed with Microsoft Excel 2007 (Microsoft Corp., Redmond, WA, USA) to calculate the lifetime costs and health outcomes of the patient sample. The time horizon used in this study was the patient's lifetime. The cycle lengths were set at 6 months in the first year and 12 months in the following year—reflecting the induction and maintenance phases. Three mutually exclusive alternative regimen treatment options (i.v. CYC → AZA, i.v. CYC → MMF and MMF → low-dose MMF) were compared with the baseline comparator (i.v. CYC → i.v. CYC).

Five represented health states (active disease, complete and partial remission, ESRD and death) were defined to reflect the main outcome measurement typically reported by RCTs in the area of LN treatment (Fig. 1). For the active disease, complete and partial remission were divided into three substates (induction phase of treatment, maintenance phase of treatment and after 3 years of treatment) to reflect the fact that cost components and transition probabilities among various health states vary depending on treatment time. Treatment complications were included within health states as, typically, they

Fig. 1 Markov model of treatment for newly diagnosed severe LN patients.



were resolved in <1 year. The arrows in the figure represent the possible transitions from one state to another at the end of each cycle length. Parameters that were employed in the model include transitional probability, relative treatment effect, resources use and cost and utility.

Transitional probabilities and relative treatment effects

An extensive literature review was conducted and several relevant studies were identified that compared alternative treatment strategies for LN. The PubMed database was searched using the following keywords: (lupus nephritis [MeSH]) AND (cyclophosphamide [MeSH] OR azathioprine [MeSH] OR mycophenolic acid [MeSH]). Only articles published between January 2000 and July 2012 that were written in English, Spanish or Thai were considered, and only studies pertaining to humans were included in the sample. Study types that were considered included controlled clinical trials, RCTs, clinical trials and comparative studies. We identified 10 studies that met the inclusion criteria; that is, they gave details of the dosage of the drugs under consideration and examined the treatment outcomes for any of our five defined health states.

The baseline transitional probabilities of patients who received the treatment regimen of i.v. CYC → i.v. CYC (baseline comparator) were retrieved from three eligible studies. The probability of transitioning from partial to complete remission was obtained from Melo *et al.* [13]. The rest of the transitional probabilities were obtained from Ong *et al.* [14] and Illei *et al.* [15], for induction and maintenance data, respectively. Age-specific data on the probability of dying for the Thai general population was taken from the Thai Working Group on Burden of Disease and Injuries report [16] to account for deaths that were not caused by LN disease. Lastly, a hazard function from Teerawattananon *et al.* [10] was included to calculate the renal death risk of ESRD in Thai patients. This study assumed that patients in the cohort would not suffer from ESRD during the first 6 months of treatment.

Relative treatment effects of intervention regimens in the induction phase were retrieved using the same approach. The PubMed database was searched using the same keywords mentioned above but examined only systematic reviews and meta-analyses. The study by Lee *et al.* [17] was selected to estimate the relative treatment effect in the induction phase, since this study provided the most comprehensive set of treatment effect parameters, including complete and partial remission, ESRD and death.

Due to the absence of any meta-analyses that compare all maintenance treatment comparators simultaneously in head-to-head RCTs, it was necessary to create an indirect evidence synthesis to establish the efficacy of the treatments. Six RCTs that investigated the therapeutic strategies of interest were identified [18–23]. An observational study by Mok *et al.* [24] was also included to complement the data from the RCT by Yee *et al.* [21]. A fixed effects multitreatment meta-analysis of unobserved heterogeneity among treatment strategies was performed using WinBUGS 1.4.3. (Medical Research Council, Cambridge, UK and Imperial College London, UK). This approach allowed us to combine direct with indirect comparisons; the concurrent analyses of the relative effects of several treatment strategies were performed with 50 000 iterations.

Rates of major infection occurring as a severe complication in patients receiving different regimens were retrieved from five RCTs that explicitly reported patients suffering from major infections [18, 19, 22–24]. To account for heterogeneity in the included studies, a random effects pooled mean meta-analysis was performed using WinBUGS 1.4.3 with 50 000 iterations.

Resource use and costs

Resource use and costs were measured in terms of direct medical and non-medical costs. Direct medical costs

consisted of drug costs and health care services costs for treatment of LN and its complications. Drug costs were calculated on the basis of the median procurement price for the drug from all public hospitals across the country, as collected by the Ministry of Public Health [25]. Health care resource use was estimated using data from a medical records review on LN treatment at four tertiary care hospitals in Thailand (laboratory tests and drug administrative costs). The resources used were multiplied by the unit costs from the standard costing list for health technology assessment to estimate the total direct medical costs of the treatment [26]. The health care cost of treating major infections (the main complications that require hospitalization) was obtained from the Thai hospitals database [27]. The cost of treating Thai patients with ESRD was retrieved from Teerawattananon *et al.* [10].

In addition, direct non-medical costs (costs of transportation, meals, accommodations, facilities and informal care) and the costs of productivity loss due to sick leave were estimated from the standard costing list for health technology assessment [26]. As this study was a comparison of treatment strategies, cost items that were approximately identical in all of the assessed regimens were excluded, such as the cost of prednisolone among treatment options. All costs were adjusted using the consumer price indexes published by the Ministry of Commerce in Thailand for the price year 2012 [28].

Utility weights

Using the EQ5D instrument, utility weights in which values ranged from 0 (death) to 1 (full health) for calculating QALY were obtained from 216 observations of patients (18 patients for 12 visits each, on average) in four tertiary care hospitals in Thailand. The subjects' written consent was obtained according to the Declaration of Helsinki and the study was approved by the Committee on Human Rights related to Research involving Human Subjects from Chulalongkorn Hospital, Nopparat Rajathanee Hospital, Tammasart Hospital and Srinakarin Hospital. The mean age of patients was 40 years. The LN patients' quality of life, classified by the disease health stage of interest—namely complete remission, partial remission, active disease, renal failure and major infection—presented utility weights of 0.94, 0.85, 0.764, 0.689 and 0.223, respectively.

Uncertainty analysis

Two types of uncertainty analysis were conducted to estimate the impacts of parameter uncertainty. A probabilistic sensitivity analysis (PSA) was performed to examine the effect of all parameter uncertainty simultaneously. Using a Monte Carlo simulation, PSA was performed using Microsoft Excel 2003 with 1000 iterations to yield a range of probable values for the ICERs. In addition, one-way sensitivity analyses were performed to examine the uncertainty surrounding each parameter individually in order to define the most influential parameters on the ICER. The input parameters used in the model are shown in supplementary Tables S1 and S2, available at *Rheumatology* Online. Finally, the model was validated by comparing the estimated life-years with those of a study in Thailand [3] and another conducted in multiple countries [29].

Results

The cost-utility of alternative treatment regimens was assessed by calculating the ICERs. Three treatment regimens were compared with the one used as the baseline comparator (i.v. CYC → i.v. CYC). It was found that, for patients at the average age of 40 years, the regimen of i.v. CYC → AZA was a better option, as it both saves cost (13 300 baht) and offers more benefits in terms of QALYs gained (0.27). However, in comparison with the baseline regimen, the regimen of i.v. CYC → MMF and MMF → low-dose MMF were found to provide more benefits, albeit at a higher cost (ICER = 618 000 and 350 000 baht/QALY, respectively). Three regimens (i.v. CYC → i.v. CYC, i.v. CYC → MMF and MMF → low-dose MMF) are dominated by i.v. CYC → AZA (Table 1). These results suggest that the regimen of i.v. CYC → AZA was likely to be the most effective regimen of all the alternatives. The regimen of MMF → low-dose MMF and i.v. CYC → MMF could be considered as inferior alternatives, as they provided similar benefits but at a higher cost. A cost-effectiveness plane was used to illustrate the findings in Fig. 2.

After conducting a PSA with 1000 iterations, the maximum expected net monetary benefit was estimated for each ceiling ratio value in which society would be willing to pay for a QALY gained. It was found that at the current cost-effectiveness ceiling threshold in the Thai context of 120 000 baht/QALY gained [11], the regimen of i.v. CYC → AZA constituted the highest probability of a cost-effective regimen at this threshold and also across a wide range of willingness to pay (WTPs), ranging from 50 000 to 1 000 000 baht/QALY gained (supplementary Figs S1 and S2, available at *Rheumatology* Online). In addition, one-way sensitivity analysis indicated that the parameters of drug efficacy, especially the relative risks of complete remission, partial remission and renal failure, were the most influential parameters on the level of ICER uncertainty (supplementary Figs. S3–S5, available at *Rheumatology* Online).

Discussion

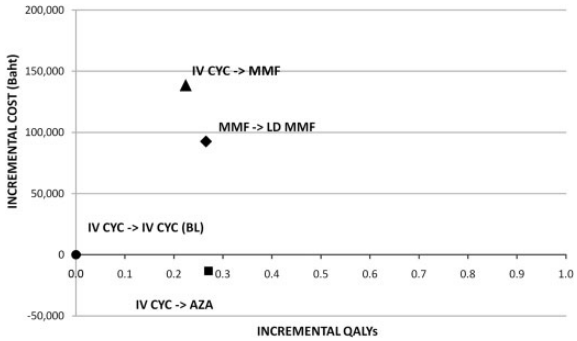
This study compares the cost-utility of alternative treatment regimens for LN. The analysis indicates that, in the context of developing countries, the regimen of i.v. CYC → AZA was likely to be the cost-saving regimen compared with baseline regimen (i.v. CYC → i.v. CYC). To compare this finding with other previous study results, another analysis that evaluated the cost-effectiveness of MMF and i.v. CYC in the context of induction therapy for active LN in developed countries was conducted in 2007 [30]. The results suggested that MMF was the best choice for first-line therapy, since it led to better quality of life and cost less than i.v. CYC. However, it was conducted with a short-term time horizon for the induction phase and did not consider critical outcomes such as renal failure and

Table 1 Results of the ICER among alternatives compared with the baseline regimen

Alternative treatments	Average lifetime cost (baht)	Average QALYs	Incremental cost from BL (baht)	Incremental QALYs from BL (QALY)	ICER compared with BL (baht/QALY)	ICER compared with the alternative having a smaller ICER (baht/QALY)
i.v. CYC → i.v. CYC (BL)	3 979 910	9.439	—	—	—	Dominated
i.v. CYC → AZA	3 966 611	9.710	−13 299	0.2705	−49 167	Dominant
MMF → low-dose MMF	4 072 513	9.705	92 602	0.2653	349 029	Dominated
i.v. CYC → MMF	4 118 461	9.663	138 550	0.2242	618 014	Dominated

BL: baseline regimen.

Fig. 2 Cost-effectiveness plane.



death, which occur later in treatment. To our knowledge, our analysis was the first study that considered all possible regimens for both the induction and maintenance phases of LN treatment in a developing country. Moreover, this study took into account the main critical consequences (ESRD and death) influencing cost and outcome in the long run.

The findings from the 2007 developed country study indicated that MMF induction therapy was likely to give patients with LN a better quality of life at a lower cost than i.v. CYC. This is predominantly due to the fact that MMF requires no day-case procedures to be administered, unlike i.v. CYC. Moreover, MMF treatment also resulted in significantly decreased incidences of adverse events, particularly major infection, compared with i.v. CYC [30]. In contrast, in the context of Thailand, our study found that the costs of i.v. CYC treatment were not particularly high. The hospital costs for administering this regimen in day-case procedures and the patient costs for transportation, informal care and productivity loss due to sick leave accounted for 6000 baht/year. This does not represent a high burden when compared with the cost of MMF as first-line therapy (78 000 baht in the first year of treatment). Moreover, while the rate of major infection for the MMF regimen was considerably lower than for the regimen of i.v. CYC → i.v. CYC, it was not found to be significantly lower than that for the regimen of i.v. CYC → AZA. Therefore our study identified the regimen i.v. CYC → AZA as the best treatment option due to the relatively low drug costs and long-term benefits that were comparable to those of MMF regimens.

The findings in our study should be interpreted with caution, given the following limitations of the study. First, only the most severe adverse effect (major infection) was taken into account, while other adverse effects, such as haematological and gastrointestinal events, alopecia and amenorrhoea, were not considered. Therefore, although the regimen of i.v. CYC → AZA was found to be the most appropriate treatment option, other alternative MMF regimens that offered a better safety profile for gastrointestinal events and amenorrhoea may be considered as appropriate. Second, this model estimate was based on fixed dose regimens regardless of the outcomes of treatment and complications that may lead physicians to reduce the dose of drugs, which would then potentially reduce the treatment benefits accordingly. Third, due to policy-related time constraints and the rarity of the condition, the sample size for estimating some utility parameters was not big enough to obtain high statistical power to represent the Thai patient population. Fourth, the generalizability of results is restricted to similar patient populations from contexts with similar characteristics to Thailand. Issues such as the structure of healthcare delivery and ethnicity may play an important role in limiting the use of these results in other settings and therefore careful judgment should be used for their extrapolation.

A number of parameter limitations were identified and this suggests that our findings require further research. The sensitivity analysis indicated a wide range of parameter uncertainty, especially in the parameter of efficacy leading to complete or partial remission and renal failure in all alternative drug regimens compared with the baseline regimen. An analysis that takes into account a selection of head-to-head RCTs that examine both the induction and maintenance phases and concurrently compares all possible treatment regimens will be required to derive precise efficacy parameters. Moreover, this study did not include treatment data on rituximab and new immunomodulatory agents since their role has yet to be fully explored [31]. Therefore economic evaluation studies should be conducted in this area when data become available.

Finally, due to the scope of the study focusing only on newly diagnostic LN patients, the recommendation on treatment for complicated cases of relapse or resistant

proliferative LN should be the subject of further study. An economic evaluation alongside a clinical trial has been registered since 2009 at ClinicalTrails.gov (NCT01015456) and the results are to be published in 2014.

In conclusion, this study highlighted that, at the current price, the regimen of i.v. CYC for the induction phase followed by AZA for the maintenance phase (i.v. CYC → AZA) should be recommended as the first-line therapy for newly diagnosed severe LN patients, as it seems to be the most cost-saving regimen. These recommendations have been endorsed by the Subcommittee for the Development of the Health Benefit Package and Service Delivery in Thailand.

Rheumatology key messages

- Intravenous CYC followed by AZA appears to be a cost-effective treatment in newly diagnosed LN treatment.
- MMF offers limited value to newly diagnosed severe LN patients in Thailand.

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Supplementary data

Supplementary data are available at *Rheumatology* Online.

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RESEARCH Open Access

Advanced health biotechnologies in Thailand: redefining policy directions

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Abstract

Background: Thailand faces a significant burden in terms of treating and managing degenerative and chronic diseases. Moreover, incidences of rare diseases are rising. Many of these—such as diabetes, cancer, and inherited inborn metabolic diseases—have no definite treatments or cure. Meanwhile, advanced health biotechnology has been found, in principle, to be an effective solution for these health problems.

Methods: Qualitative approaches were employed to analyse the current situation and examine existing public policies related to advanced health biotechnologies in Thailand. The results of this analysis were then used to formulate policy recommendations.

Results: Our research revealed that the system in Thailand in relation to advanced health biotechnologies is fragmented, with multiple unaddressed gaps, underfunding of research and development (R&D), and a lack of incentives for the private sector. In addition, there are no clear definitions of advanced health biotechnologies, and coverage pathways are absent. Meanwhile, false advertising and misinformation are prevalent, with no responsible bodies to actively and effectively provide appropriate information and education (I&E). The establishment of a specialised institution to fill the gaps in this area is warranted.

Conclusion: The development and implementation of a comprehensive national strategic plan related to advanced health biotechnologies, greater investment in R&D and I&E for all stakeholders, collaboration among agencies, harmonisation of reimbursement across public health schemes, and provision of targeted I&E are specifically recommended.

Keywords: Advanced health biotechnologies, Advanced therapies, Pharmacogenomics, Stem cell therapy, Gene therapy, Tissue engineering therapy, Qualitative research, Biomedical research policy, Health policy, Thailand

Background

Although Thailand has been classified as a technology-recipient country [1], significant research and development (R&D) in several areas of biomedicine has been undertaken in recent years [2]. A number of excellence centres for biomedical research have been established in universities and other institutions, some of which work on advanced health biotechnologies. Furthermore, a number of private companies for stem cell research are operating in the country [3-8].

Prior to 2009, stem cell therapy interventions in clinical practice were entirely unregulated in Thailand. This led to many incidents of exaggerated and false claims and a number of cases of misconduct among clinicians offering stem cell therapy, which prompted increased worldwide attention on these issues [9-12]. In Thailand, stem cell therapy was provided by a number of institutions and individuals before sufficient research and development had been undertaken to ensure the safety of the procedure.

Despite the fact that there is significant regulation of stem cell research and unproven treatment is now forbidden, there continue to be breaches in the law. However, many positive advances in the field of pharmacogenomic/pharmacogenetic (PGx) testing have been made in recent years, with some testing already taking place in public hospitals [13]. At the same time, however, little attention

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has been paid to areas such as tissue engineering and gene therapy, which have advanced more slowly as a result.

To plan more effectively for the future, the Thai National Science, Technology and Innovation Policy Office commissioned the Health Intervention and Technology Assessment Program (HITAP), a research arm of the Health Ministry, to conduct research for the development of advanced health biotechnologies in Thailand. This paper provides an assessment of the current situation in Thailand, including a review of relevant public policy. Based on this review and analysis, we make a number of policy recommendations.

Methods

A review of existing literature on advanced health biotechnologies in Thailand was undertaken using relevant bibliographic databases, search engines, and websites. The data was then organised into a conceptual framework. For benchmarking purposes, research was also conducted for regions such as the United States and Europe. This literature review was complemented by information garnered during four focus group discussions involving a number of relevant stakeholders, including Thai researchers, administrators of research institutes, policymakers, regulators, patient representatives, and physicians. These took place between October and December 2011 in the premises of HITAP. Expert opinions and data on the current situation and existing policies were also collected following attendance at an external consultation, convened by the National Science and Technology Development Agency (NSTDA). Two case studies on facilitators and barriers to the adoption and diffusion of advanced health biotechnologies were developed, and the findings from these also informed the study. Finally, two consultative meetings were held in HITAP in June 2011 and March 2012 to gather additional information, verify the initial results, and fine-tune the recommendations. Finally, triangulation was applied to verify the findings and recommendations. More detail on the research methods, including details of the relevant materials and definitions can be found in the full report, which is available upon registration at www.hitap.net/en/research/10664.

Review of the situation and public policies

Research and development

Our research revealed that, while a policy document on advanced health biotechnologies has been developed by the NSTDA, [14] it fails to provide clear policy directions for undertaking research in this area. However, this finding is disputed by the key informant of the medical cluster of the NSTDA, which is responsible for R&D, technology transfer, human resources, and infrastructure development associated with science and technology. Nevertheless, as a result of the complex management structures that are in place at the NSTDA (each cluster has its own director), it is unclear how the policy outlined in the paper is actually implemented. This lack of a clear national policy and recommendations on research in advanced health biotechnologies has meant that many R&D activities are conducted outside of the scope of the National Research Council (NRC) and NSTDA. There is also very little communication between the relevant national bodies on which areas of advanced health biotechnologies in Thailand are supported.

It is recognised that large pharmaceutical firms may be hesitant to conduct R&D on advanced health biotechnologies for a number of reasons, including uncertainty surrounding the potential benefits and risks of these technologies, high production costs, strict regulations, and logistical difficulties [15]. Moreover, to overcome this, it may be necessary to develop innovative financial mechanisms for R&D and public-private partnerships (PPPs) in this field [16-20]. However, with no clear national policy in place, the benefits of such partnerships might not be maximised or might even result in serving mainly the commercial interests of those involved.

Owing to the lack of uniformity on international ethical standards in biomedical R&D, very little attention on this has been paid in Thailand. The system for the ethical approval of medical research has improved very little in four decades. One recent survey found that many of these ethical committees have poor capacity, lacking codes of conduct and proper regulations to avoid conflicts of interest [21]. In the area of advanced health biotechnologies, the situation may be worse even than in conventional biomedical research because of the rapid progress of scientific knowledge, involvement of human donors, and disclosure of close relatives' genetic information, *inter alia* [22,23]. As a result, researchers have tended to conduct R&D without applying for ethical clearance. Moreover, even when ethical clearance is sought, it is frequently given routinely, with little or no analysis of the ethical implications of the research.

There have also been several cases where advanced health biotechnologies were applied in ways that violated public trust [24-26]; as a consequence, the Medical Council (MC), which is the medical professional regulatory body, has drafted stricter regulations that explicitly cover all stem cell research and practice conducted by medical doctors (except for bone marrow transplantation, which is viewed as a conventional procedure). Under these new regulations, all physicians wishing to undertake research on stem cell therapy must obtain both scientific and ethical approval from the MC. However, Thai experts suggest that many scientists regard this regulation as an obstacle to advancement in this field of research. At the same time, it appears that these

regulations are not fully enforced, perhaps because of inadequate regulator capacity and the potential for conflict of interest [27]. This echoes a case in the US, where the California Institute for Regenerative Medicine (CIRM)—the funding agency with the largest amount of public funds in the state—had on its board a number of experts from leading research organisations who were responsible for approving grant applications, including those of their own institutes and their competitors [28].

Despite this, the CIRM funding approach has a number of notable benefits. Significantly, it implements a system where more stable funding of research is guaranteed by the provision of grants over several years, rather than on a year-by-year basis (which had been the case in previous years) [28]. This year-by-year allocation system of the limited government budget is the current practice among almost all Thai research granters, including the NRC and NSTDA. This system hampers the progress of research, as suggested by the Tufts Center for the Study of Drug Development, which estimates that one advanced health biotechnology product requires an average of 8 years at a cost of USD 1.2 billion, compared to the average period of seven years and cost of USD 800 million for one conventional medical product [28].

Authorisation

Many advanced health biotechnologies do not fall clearly into the classic categories used by many regulatory agencies. In Thailand, the Thai Food and Drug Administration (TFDA), Department of Medical Sciences (DMSc), and MC share responsibility for the authorisation of medical products, medical and laboratory practice, and related advertising. These organisations do not have a clear and uniform way of defining and classifying advanced health biotechnologies. In contrast, in Europe a consensus was reached in 2007, in the form of the Advanced Therapies legal and regulatory framework (Regulation (EC) No 1394/2007). In addition, the US Food and Drug Administration (FDA) has also developed definitions for regenerative medicine products (neither framework covers PGx tests, which fall under a different classification). Having clear definitions and classification is very important, as regulators can use them to set standards of information requirements for authorisation, reimbursement, and post-authorisation activities.

Evidence suggests that, in Thailand, there is both insufficient demand for regulation of advanced health biotechnologies and inadequate capacity to implement this regulation should the demand arise. This results from a number of factors. First, there is a lack of clarity regarding which body would be responsible for regulating these kinds of technologies. For instance, the TFDA oversees only pharmaceutical products (including biologics) and medical devices, unlike the European Medicines Agency (EMA) and the FDA, which have specific expertise in these kinds of technologies. Furthermore, private biotechnology companies are not pushing for approval of their products because this may not suit their business needs; for example, many PGx tests are locally produced by healthcare facilities, which renders them outside the remit of the TFDA's regulations. In addition, the Thai market for advanced health biotechnologies is relatively small and, as such, private biotechnology manufacturers do not prioritise marketing in Thailand.

Post-authorisation

We have classified post-authorisation regulatory activities into the following four areas:

Post-marketing surveillance In the US, the FDA plays a major role in post-marketing surveillance of advanced health biotechnologies, including cell therapy, tissue engineering, and other regenerative medicines [29]. In Europe, the EMA is responsible for product surveillance, but it varies in the case of monitoring of services, which is conducted by either national drug regulatory agencies or health care quality inspectorates [30]. Given that there is no clear definition or classification of advanced health biotechnologies in Thailand, we predict that ensuring safety, effectiveness, and quality of these technologies after approval is likely to be a challenge. Recently, the MC prohibited any stem cell therapies except bone marrow transplantation. This should only be regarded as a short-term solution to ensure the safety, effectiveness and quality of stem cell treatment; moreover, this regulation does not extend to surveillance after approval, which means that many therapies continue to be conducted without sufficient regulation or monitoring.

Quality assurance of laboratories in the service sector There is no national authority in place in Thailand to regulate laboratory practice and quality related to advanced health biotechnologies—although the DMSc is responsible for Good Laboratory Practice (GLP) compliance monitoring. The DMSc is also increasing the capacity of its 15 laboratories across the country in order to perform a number of PGx tests, mainly focusing on preventing severe adverse reactions from anti-retroviral therapy and epilepsy treatment. It is unlikely that the DMSc will support the private laboratories in their attempt to build their PGx testing capacity. In addition, the Department has no plan to widen its scope to support lab activities related to regenerative therapies [31].

Quality assurance of medical services The quality assurance system of medical services in Thailand is passive; that is, the MC only comes into play when complaints are

made by patients. The MC investigates and punishes medical practitioners if their practice is substandard or negligent, or if they make exaggerated claims or undertake false advertising, but only after a report or complaint is made. Patients can also file a lawsuit in the civil and criminal courts. In addition, the MC controls the quality of services by defining those who are permitted to provide various services. This means that only those who are licensed as physicians can prescribe and perform medical care. At present, because there is no individual or body specifically tasked with setting standards of care for advanced health biotechnologies, undertaking quality control of medical services in this area is certain to be a challenge.

Promotion/advertisement regulation In Europe, the advertising of regenerative medicine services has been prohibited by the European Commission, while the EMA regulates the advertising of advanced therapy products.

The US allows the advertising of prescription-only drugs, and, in principle, this should extend to approved advanced health biotechnology products. However, despite the FDA's considerable capacity, problems are still encountered in terms of regulating advertisement and sales for approved advanced health biotechnology products. In particular, there are calls to restrict direct-to-consumer (DTC) genetic test advertisements and sales. In Thailand, the DTC sale of prescription-only products is prohibited by law, and the legal regulation of medical service advertising is supervised by the Bureau of Sanatorium and Art of Healing. Despite this, there are still many public advertisements for advanced health biotechnologies, almost all of which make exaggerated claims [25,32,33].

Reimbursement and related service provision models

The reimbursement of products related to advanced health biotechnologies is challenging even in the US and Europe. The assessment of safety, efficacy/effectiveness, acceptability, and other social consequences is difficult and varies depending on context, due to differences in patient and clinician behaviour and delayed health outcomes, among others. Moreover, the information available for reimbursement of advanced health biotechnology products is often inadequate when compared to that available for conventional treatment. The third party payer is often pressured to approve these technologies because of the lack of available alternatives. Thus, a number of scholars have recommended that those payers that are faced with a promising advanced health biotechnology that may improve patient safety and outcomes, but which still has significant uncertainty associated with it, introduce coverage with evidence development (CED) [34,35]. For example, in 2009, the US Center for Medicare and Medicaid Services initiated CED for warfarin PGx testing, given the clinical promise but inconclusiveness or contrary results that had emerged on the back of the few small randomised controlled trials (RCTs) that had been conducted at the time [35].

The service and financing models that are currently available in Thailand were designed for conventional medical technologies. Commonly, public providers buy medicines and medical devices (including medical supplies) from the private sector and manage them themselves, which can be seen as a pure purchaser-supplier relationship. The National Health Security Office (NHSO), which manages the Universal Health Coverage Scheme—the largest of the three public health plans in Thailand, also buys commodities at the central level and allocates them to local public providers. The latter business model is believed to increase system efficiency because the buyer has more price negotiation power, although this may come at the expense of future market competition and the providers' autonomy [36]. In recent years, the NHSO has started to buy services from private companies, for example, cataract surgery, renal dialysis, and heart surgery. In addition, some public hospitals lease public space out to private companies to develop and operate service delivery units (SDUs), such as medical scanning or renal dialysis units; these arrangements operate under informal contracts [37]. This does not comply with government regulations and creates difficulties [38]. For instance, one study has indicated that most public hospitals do not have access to sufficient information and do not exert much power when conducting negotiations with private companies. As a result of this misconduct, these privately-run SDUs are unevenly introduced across regions, sometimes resulting in the overprescribing of services [37].

We believe that, if advanced health biotechnologies—and regenerative medicine in particular— are to be made available under public health plans, their delivery model is likely to take a similar form to that of the privately-run SDUs; this is because, while the technological know-how will belong to private sector entities, these entities will not be able to operate these services completely on their own. As a consequence, new models need to be developed for PPPs in the health sector in Thailand that can be tailored specifically tor advanced health biotechnologies.

Information and education

It is widely recognised that provision of information and education (I&E) for all stakeholders is critical if society is to maximise the benefits from advanced health biotechnologies. For instance, most clinicians in the US and Europe have little knowledge on genomic medicine or the benefits and risks of specific PGx tests. Moreover, many of them are concerned about the consequences of their inadequate knowledge and how this could potentially lead to mistakes and even liability [39]. This appears to

delay the translation of advanced health biotechnologies into clinical practice.

In most countries, including Thailand, related research organisations and networks provide public I&E; however, given the limited capacity and the potential for conflict of interest, society should not rely only on these sources. In the US, the National Human Genomics Research Institute (NHGRI) established the Education and Community Involvement Branch (ECIB), a body specifically responsible for public education on genomics-related issues.

Similarly, many non-governmental organisations (NGOs) and patient advocacy groups have in place key policies to disseminate I&E as part of their strategy to garner public support for advanced health biotechnologies. Evidence from the US and EU suggests that, while NGO provision of I&E can be very effective, it can also create misunderstandings. In Thailand *ad hoc* public I&E sharing was conducted by the TFDA at the time when stem cell banks became a public interest. Currently, no public body actively provides I&E on advanced health biotechnologies to the public.

In Thailand, there are currently no effective programs to help health professionals update their knowledge on advanced health biotechnologies. Moreover, there is no license revalidation policy for health professionals, despite an attempt a few years ago to put one in place. In the US, the NHGRI is planning to recommend to professional associations that they integrate genomic medicine education into curricula and revalidation processes [40]. Approximately 30,000 doctors currently practice medicine in Thailand, and every year 1,000 newly graduated physicians enter the profession [41]. The majority of the workforce graduated before the application of these biotechnologies came into clinical practice. If more advanced health biotechnologies are approved for the market, it may be necessary to better regulate the provision of I&E pertaining advanced health biotechnologies by sales representatives to Thai physicians and other health professionals because of its importance [42,43]. Alternatively, or in addition, it may be useful for private companies who are involved in these technologies to invest in professional I&E rather than public. (Figure 1 provides a timeline of key events in the area in Thailand).

Establishment of a specialised institute for advanced health biotechnologies

Having identified a number of significant gaps in the current system involving advanced health biotechnologies in Thailand, and mindful of the lessons learnt from the EU and US that are outlined above, we identified the need to establish an organisation focusing on advanced health biotechnologies in Thailand (sharing some characteristics with the Andalusian Initiative for Advanced Therapies [18,19] or the CIRM [28]). Such an organisation could be entitled the 'Advanced Health Biotechnologies Institute' ('AHBI') and would be tasked with overseeing the technologies under the scope of our study as well as other advanced health biotechnologies, such as nanomedicines. It should be an autonomous institute established outside the umbrella of the Ministry of Public Health and NSTDA of the Ministry of Science and Technology, because of the complex factors and implications involved with regulating

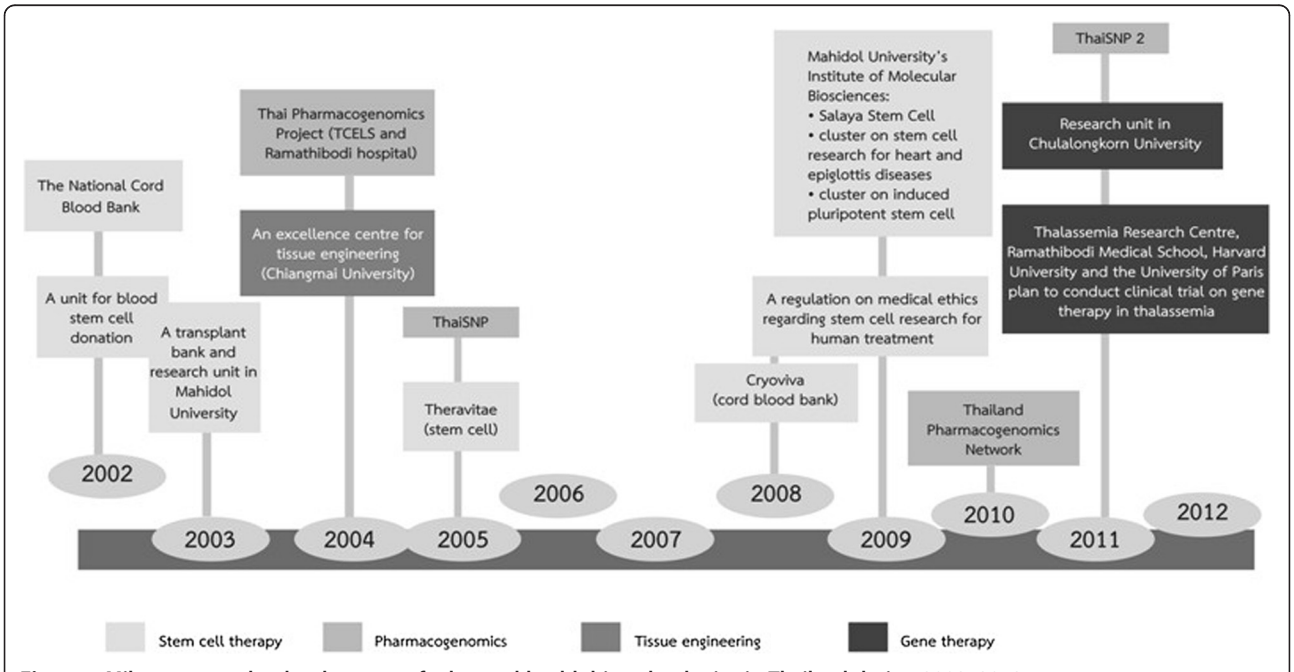

Figure 1 Milestones on the development of advanced health biotechnologies in Thailand during 2002–2012.

advanced health biotechnologies, including environmental health, animal health, human health, and science characteristics. This is to avoid political conflict between the two Ministries, and is also aligned with the establishment of the National Research Council, under the Office of the Prime Minister rather than any particular Ministry.

The proposed responsibilities of this institute are as follows:

- To provide national policy directions regarding R&D and related infrastructure, clinical application, I&E, and capacity strengthening, with reference to all stakeholders.
- To provide research funding (including setting priorities for research and developing human resources).
- To provide ethical/scientific approval for research.
- To issue guidelines on good practice and clinical practice.
- To provide public I&E and ensure that the quality of information offered by other public organisations is of the requisite standard.
- To create a certification system, similar to the HONCode system, to control the quality of information published in websites, leaflets, magazines, and other media. This information should then be collated into a public database, which can serve as a resource for the public (including healthcare professionals) to access validated data on advanced health biotechnologies [44,45].
- To cooperate with the school consortia of health professions for formal education, and the Royal Colleges to plan for and develop strategies relating to continuing education for health professionals after formal education.
- To strengthen existing regulatory bodies (Department of Health Service Support, TFDA, Bureau of Sanatorium and Art of Healing, MC), to provide support for approval and post-approval activities, and cooperate with the Consumers' Protection Office, TFDA and MC, in terms of advertisements and complaints.

Particular recommendations for five key areas in Thailand

Research and development

It is essential that a national policy regarding R&D for advanced health biotechnologies in Thailand be established, including a prioritisation framework and scope. This national policy would be introduced not only by the 'AHBI' but also by other public fund-holders, such as the NRC and the NSTDA. To better respond to the rapid progress of the field, we recommend that the national strategic plans be five-yearly, with an option of rolling revision if needed. The plan should be developed under the 'AHBI' by a multi-sectoral team, including health professionals, scientists, policy researchers, patient groups, and the private sector. The national plan should include clear targets, and evaluation of its impacts in terms of population health, innovation, and national economics and competitiveness is also needed.

It is anticipated that the R&D market for advanced health biotechnologies will gradually develop; it is also likely that this market will be monopolised by one or a few firms. This may differ from the market in advanced economies because Thailand has a relatively small service market and limited human resources for R&D. The government should have strategies in place to avoid monopolies by private manufacturers or providers. Starting from the R&D process, the 'AHBI' should facilitate PPPs in an appropriate manner; particular care should be taken to avoid over-reliance on a single group of scientists or one private firm.

As previously discussed, as there is unlikely to be sufficient incentive for the private sector to invest in the R&D of advanced health biotechnologies as opposed to conventional health technologies, we recommend that the government allocate more resources to this field, to ensure that the public can take advantage of the benefits it offers. In addition, funding should be provided in a long-term, collaborative way, rather than on a year-by-year basis, as evidence suggests that it takes at least eight years to develop a final advanced health biotechnologies product [29]. This justification has informed funding policy in Europe and the US, as is evident from the approach of the CIRM and others. Furthermore, ethical standards for R&D must be clearly set by the 'AHBI' in order to avoid research misconduct. To this end, the 'AHBI' first needs to strengthen the capacity of the medical ethics committees through training. Secondly, for projects that are controversial or pose high risk of harm, the 'AHBI' should be ultimately responsible for appraising them [46]. Lastly, the 'AHBI' should open channels for complaints against suspected violation of research ethical standards.

Authorisation

We anticipate regulatory gaps and stress the need for collaboration among regulatory bodies to address these shortcomings, which include a lack of common definitions/classifications used by all regulators. Therefore, we recommend that the 'AHBI' work in conjunction with all stakeholders to establish agreed definitions/classifications of advanced health biotechnologies in Thailand. This can be done after conducting a review of experiences in the US, EU, and other Asian countries that are active in this field.

Second, regarding the approval of products, we recommend that the TFDA expand its current limited capacity

to ensure the appropriate authorisation of advanced health biotechnologies. Currently, there is a gap in that there is no legal authority to approve individual health services (e.g., stem cell treatment). Although Royal Colleges in Thailand do play a role in setting standard clinical practice, this is informal. We recommend that the Bureau of Sanatorium and Art of Healing, in collaboration with the Royal Colleges, approves the use of individual advanced health biotechnology services, because of the uncertainties of safety and effectiveness, and the social and ethical implications.

In addition, the criteria for the authorisation of products and individual services should be harmonised using a modified framework for priority setting, as described above. Moreover, the developed framework should fully engage all relevant stakeholders (e.g., insurance managers, ethicists, HTA researchers, religious leaders, NGO representatives, etc.). The 'AHBI' should also play a consultation role for all regulatory bodies regarding the authorisation of advanced health biotechnologies. Another shortfall that needs to be addressed is the lack of capacity among regulators. We propose that the 'AHBI' invest in the capacity strengthening of regulators across the system, to ensure that there is uniformity across national policy and that, within networks, all knowledge and skills that are offered are relevant and up to date.

Post-authorisation

We expect that post-authorisation activities will be critical in the field of advanced health biotechnology because, as discussed, there is, as yet, no established requirement on evidence for authorisation; this means that many randomised controlled trials, if available, are likely to be so small that they cannot confirm long-term safety and effectiveness. Therefore, we offer the following recommendations for four elements of post-authorisation:

Post-marketing surveillance/withdrawal The implementation of a stronger surveillance system, one which extends to patient registries, is necessary. So too is a risk management and a long-term monitoring and reporting system, which should be developed and maintained by manufacturers, working closely with health providers. Guidelines provided by the 'AHBI' should be followed by manufacturers (including hospitals), and those who do not comply should be held liable.

Quality assurance of laboratories in the service sector Reinforcement of good practice guidelines should fall under the responsibility of the DMSc, and capacity strengthening should be provided by the 'AHBI'. Quality assurance and the inspection of laboratories in the service sector should be conducted by the DMSc in collaboration with the TFDA.

Quality assurance of medical services The 'AHBI' and the Royal Colleges should set the medical standards for those well-established advanced health biotechnologies that already have proven safe and effective. This will not only ensure quality of practice, but will also promote their use. In light of the fact that national standards related to conventional medical interventions were often established once these interventions had been accepted for reimbursement (because payers want to estimate costs and develop systems for monitoring and evaluation), we recommend that the standards for advanced health biotechnologies be set at the early stage of the introduction of these advanced health biotechnologies.

Promotion/advertising regulation The 'AHBI' should implement a system similar to the HONCode system to certify the quality of information published in websites, leaflets, magazines, and other media. This information should then be collated into a public database, which can serve as a resource for the public (including healthcare professionals) to access validated data on advanced health biotechnologies. This is to complement the TFDA's activities.

Reimbursement

Because many advanced health biotechnologies are likely to be expensive and will need close monitoring and evaluation for cohort patients, we strongly suggest that the reimbursement of these technologies be harmonised across public health plans in Thailand to facilitate the monitoring of safety and effectiveness. CED should be

Table 1 Information and education targets according to level of evidence (partly based on [48])

	Level 1 Well-established safety and effectiveness	Level 2 Established safety and efficacy, promising effectiveness	Level 3 Clear evidence on harm or disutility
Regulators/payers	✓		✓
Health professionals	✓	✓	✓
Research funders/ researchers		✓	
Media			✓
Public	✓		✓

Note: in the case of PGx tests, efficacy and effectiveness should be replaced with validity and utility, respectively.

introduced for selected advanced health biotechnologies whose safety and effectiveness is as yet not fully proven. This also facilitates access to interventions for patients in need (complying with restricted criteria from both the TFDA and insurance managers), while collecting more evidence on effectiveness and safety.

Since Thailand has three major public health schemes managed by different bodies (i.e., NHSO, the Comptroller General's Department, and the Social Security Office), we recommend that the coverage decision-making body be co-chaired by representatives of the three health schemes, with technical support provided by the 'AHBI', relevant professional associations, and HTA agencies. We recommend that some relevant indicators from a European framework be adopted (e.g., safety; knowledge/education; broader health impacts; and social, ethical, legal, and organisational aspects) [47]. In addition, there should be more collaboration between regulators, HTA agencies, and insurance managers in relation to information exchange and post-marketing surveillance, including CED.

For those products that involve a service, such as a medical/surgical procedure or diagnosis offered by the private sector in public hospitals (and we believe that most regenerative medicine technologies will take this form), the development of new purchasing models between public health insurance plans and private companies is needed, to ensure both effective administration and the equitable distribution of advanced health biotechnology services across the country. In addition, revision of the public procurement law is a necessary prerequisite because the current regulation does not allow private companies to provide clinical services within public health facilities.

Information and education

The 'AHBI' should be the organisation responsible for the provision of I&E for all stakeholders. To maximise the benefits that advanced health biotechnologies can offer society, the 'AHBI' should classify I&E activities for advanced health biotechnologies into three levels, and target stakeholders accordingly (Table 1).

Conclusion

In this paper, we outline a set of recommendations that aim to address the multiple gaps and weaknesses concerning advanced health biotechnologies in Thailand, ranging from underfunding of research to regulatory deficits. We conclude that the establishment of a specialised institute to fill the gaps in this area may represent the most practical approach to tackle the existing deficiencies in the Thai setting. Under a uniform national strategic plan, the government should also invest more in R&D and provide targeted I&E for all stakeholders in this area. All regulators would also need to work together with insurance providers and other stakeholders to ensure the safety, effectiveness and quality of advanced health biotechnologies. Moreover, the reimbursement of advanced health biotechnologies should be harmonised across public health plans in the country, and access to new technologies should be provided to restricted patient groups, if any impact on population health is to be realised.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

RPV coordinated the project, reviewed the European situation, participated in the planning and implementation of the overall research, and contributed to the analysis and the writing of the draft. CYM reviewed the US situation, participated in the planning and implementation of the overall research, contributed to the analysis and the writing of the draft. UC, RK, and ST reviewed the Thai situation, analysed the focus group data, participated in the planning and implementation of the overall research, and contributed to the analysis and the writing of the draft; YT supervised the project, moderated the focus groups and consultations, and contributed to the analysis and the writing of the draft. All authors read and approved the final manuscript.

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ANALYSIS

Universal coverage of renal dialysis in Thailand: promise, progress, and prospects

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Abstract

Thailand's experience in introducing renal replacement therapy as part of its universal health coverage scheme shows the importance of evidence and stakeholders' active participation in all phases of policy development, say **Sripen Tantivess and colleagues**

Thailand is one of the few developing countries that ensures access to essential health services for all its citizens. Instigated in the early 2000s, the universal health coverage scheme (UCS), extended basic coverage to everyone not already covered by existing public schemes and has been popular, persisting through political instability over the past decade.[1] The benefits and costs of the UCS have increased since it was introduced. New benefits have included antiretroviral drugs for HIV, in 2004, and renal replacement therapy for end stage renal disease, in 2008.[1]

Renal replacement therapy is expensive and complex, and—unlike HIV/AIDS—kidney diseases afflict a relatively small percentage of the population and have never reached the global or national health agenda. We examine the rationale and factors that influenced the adoption of universal funding of renal replacement therapy, what can be learnt from the decision making process, and the challenges of maintaining funding.

Setting the scene

Health benefit policies in Thailand developed to cover different groups of the population. The civil servant medical benefit scheme for government employees was instigated in 1982 and the social security scheme for formal private employees in 1990. This left a substantial portion of Thai people uninsured. Although healthcare reformers put great efforts into advocating expansion of the health safety net for all, it was not until 2001 that a political party pledged to introduce universal health coverage. The UCS was introduced in 2002, a year after the party's election.

UCS managers adopted almost the same benefit package as offered by the social security scheme because both schemes were funded through capitation. This included chemotherapy and radiation for specific cancers, open heart surgery, prosthetic hip or shoulder replacement, and neurosurgery.[2] However, because of the relatively high prevalence of end stage renal disease and HIV infection among UCS beneficiaries, the scheme initially excluded treatments for these conditions.

Kidney transplantation has been performed in Thailand since 1972 and has been financed within the civil service scheme since 1980. However, the numbers of donated kidneys have never met the demand[3] because many people in Thailand believe that their body should remain intact after death, for the next life.[4] The number of renal transplants in Thai patients has risen from 229 in 2001 to only 308 in 2009, while over 4000 patients wait for a kidney.[5]

Most Thais with end stage renal disease must therefore rely on renal replacement therapy, which is expensive. The two pre-existing public schemes have included peritoneal dialysis and haemodialysis in their benefit packages since 1985 and 1990. However, for those who had to pay for it themselves expenditure on dialysis accounted for 25-70% of household income.[6] People coped by reducing the frequency of seeking dialysis; treating anaemia with blood transfusion rather than erythropoietin; restricting spending on transport, food, and education; and borrowing money at high interest rates, something that was especially common in poor households.

Pressure to introduce universal access

Renal replacement therapy had not originally been covered by the UCS because of its cost.[7] However, nephrologists and kidney patient groups as well as some health officials and researchers who had helped establish the UCS campaigned for it to be introduced on the grounds of equity, emphasising the disparity between the three public schemes, as well as the catastrophic expenditures incurred by patients on low incomes. Although the patient groups were small and not well known in Thai society, they gained considerable support, not only from longstanding networks of HIV and cancer patients but also from the Thai Nephrologists Association. Furthermore, health policy researchers and nephrologists jointly conducted a series of

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studies to support renal replacement therapy, with their focus on determining appropriate policy options.[8]

In 2004 the National Health Security Office (NHSO), which is responsible for the UCS, commissioned research to determine the value for money of dialysis, including the costs of providing renal replacement therapy in the UCS over 15 years.[9] It also carried out a survey of public opinion on different options for renal replacement therapy.[9] Neither peritoneal dialysis nor haemodialysis was shown to be cost effective, but peritoneal dialysis offered better value than haemodialysis. The annual incidence of end stage renal disease was estimated to be 121.9[10] to 158.9[11] per million population (7873 to 10 016 cases) in 2004 and 2007, respectively. If the government decided to provide universal access to renal replacement therapy, assuming an annual incidence similar to that in developed countries at about 300 per million,[12] the number of patients receiving dialysis would increase to more than 100 000 cases in the tenth year. The NHSO would spend a significant proportion of its annual budget on renal replacement therapy, accounting for 3% in the first year and 15% in the fifteenth year.

Although most nephrologists preferred haemodialysis to peritoneal dialysis, all the haemodialysis machines and people with the skills to use them were concentrated in greater Bangkok. This made haemodialysis inaccessible to patients in remote areas. The survey among Thais aged 18-60 years showed that most respondents supported the inclusion of renal replacement therapy in the UCS, and most suggested that if rationing were needed priority should be given to patients with urgent health needs, those who were poor and underprivileged, and bread winners with several child dependants. When asked about a contribution from patients themselves, around 80% of the respondents were willing to pay 100 baht (£2; €2.5; $3) a dialysis session, far below the actual cost.

Despite continuing concerns about the cost, mounting evidence suggested that dialysis could be provided more cheaply than originally estimated and with better outcomes. Advocates increased the pressure to fund renal replacement therapy and the government finally agreed to universal funding in October 2007. The decision was influenced by the health minister,[13] who had long term relationships with health reformists and non-governmental organisations.

Key features of the programme

The inclusion of renal replacement therapy in the UCS was accompanied by a series of measures to ensure the effectiveness of the coverage and efficient use of resources. The first element was to strengthen measures to prevent end stage renal disease by encouraging the early detection and treatment of hypertension and diabetes through community screening, with financial incentives for health workers.

Secondly, a policy of using peritoneal dialysis first was introduced, with haemodialysis as a second line treatment for those not suitable for peritoneal dialysis. Although nephrologists initially opposed this because of their poor experience with peritoneal dialysis, they accepted it because it was the only way that poorer patients would be able to obtain dialysis.[9] In addition, peritoneal dialysis could be administered on a "self care" basis in patients' homes, saving them travel costs for hospital haemodialysis.

The third element involved financing. While most ambulatory services in the UCS are paid for through capitation payments, the peritoneal dialysis first policy was incentivised through a fixed fee for each patient started and maintained on peritoneal dialysis.[14] Patients who seek haemodialysis as first line treatment have to shoulder the costs. Cost containment measures—namely central tendering and bulk purchasing—were also introduced for medicines and supplies.

The NHSO encouraged the establishment of peritoneal dialysis in district hospitals and other public healthcare facilities. An advantage of operating peritoneal dialysis centres in district hospitals is that these hospitals are well connected with comprehensive primary care networks at the subdistrict and community levels. It also created treatment partnerships with private facilities to overcome the limited capacity in the government sector for both haemodialysis and peritoneal dialysis, setting fixed prices for reimbursement.

In response to the prevailing shortages of physicians and nurses, the NHSO and its partners organised training in peritoneal dialysis and related care for these and other health professionals, such as nutritionists.[15] Task shifting was another crucial strategy. As peritoneal dialysis centres reach patients in communities through existing primary care networks, subdistrict health workers and village volunteers, patient groups, and even individual patients and family members were also trained to provide information and education.

Finally, a renal disease registry was set up to provide information on resources and patient profiles for strategic management, planning, quality assurance, and regulation. The NHSO also set up an inventory and procurement system connecting the providers of peritoneal dialysis with suppliers of medicines and materials; this is used for inventory control and to ensure timely delivery of erythropoietin, dialysates for peritoneal dialysis, and catheters.

Effect of the new policy

The universal renal replacement therapy programmes have been continually developed since 2008. Between January 2008 and 2012 the number of peritoneal dialysis units increased from 23 to 160 and the number of peritoneal dialysis nurses from 56 to 423; 345 physicians were trained in inserting Tenckhoff catheters.[15]

UCS patients who had paid for haemodialysis before October 2008 and decided to continue haemodialysis were required to pay 500 baht per session, while the NHSO subsidised the remaining cost (1000-1200 baht). There is no subsidy for patients who start peritoneal dialysis but choose to switch to haemodialysis in the absence of contraindications. The reimbursement of erythropoietin started in 2009. Initially it was funded only for patients complying with the peritoneal dialysis first policy but was provided to all dialysis patients registered in the NHSO database from 2011.[15]

The number of patients having peritoneal dialysis increased steeply after 2008, even though the number of peritoneal dialysis units, which are mostly in public health facilities (90%), reached a plateau, indicating that peritoneal dialysis units were able to increase their capacity (fig 1⇓). Haemodialysis units face more difficulty in meeting larger demands because they rely heavily on trained nurses and machines.

There are no data on the numbers of patients who paid for renal replacement therapy before 2008. The analysis of life expectancy of dialysis patients before 2008 was based on registered patients under the civil service and social security schemes.[9] There are no data to compare life expectancy of those diagnosed with end stage renal dialysis before and after the introduction of the universal dialysis policy, but we can assume that before the programme 90% of patients died within 3-6 months. At present patients may survive for at least 5-10 years.[16]

Analysis of catastrophic spending on health problems—defined as household health expenditures ≥10% of total expenditure—show that the introduction of the UCS in 2001 benefited the poor more than the rich (fig 2⇓).[17] The expansion of universal access to antiretroviral treatment during 2002-07 resulted in another decline in the incidence of catastrophic health expenditure in both rich and poor households.[14] However, there is insufficient evidence that the introduction of universal renal replacement therapy has had a further effect on catastrophic health expenditure, though it may be too early to tell.

Lessons for decision makers

Thailand's success in introducing a universal health coverage that includes high cost interventions such as renal replacement therapy provides valuable lessons for other settings.

Firstly, evidence is necessary for policy development, particularly in decisions about covering high cost interventions in resource limited settings. Local evidence played a crucial role in the adoption and implementation of universal renal replacement therapy in Thailand. This also reflects the need for local capacity in policy and health systems research.

Secondly, the participation of key stakeholders, including politicians, health providers, professional associations, academics, and researchers, is vital. This is not only to increase the sense of ownership of such a policy but also to reduce conflicts between different interests. Information sharing among stakeholders was successful in making health professionals, who had favoured haemodialysis, accept the peritoneal dialysis-first policy.

Since resources are scarce, it is important to emphasise to everyone that rational allocation of health resources is best practice. The philosophy behind universal health coverage means that everybody in society recognises the limitations of what the government can offer and tries to find the best solution to particular problems. Not everybody can get what they think is the best treatment, but everybody can get good treatment.

Finally, although agencies such as the World Health Organization, underline "health financing" as a key element of universal health coverage,[18] Thailand's renal replacement therapy policy shows that health financing is not the sole factor for achieving the policy goal. Strengthening the capacity of the health system, including workforce development, selection of appropriate health technologies, and effective monitoring and evaluation are also important.

Challenges and opportunities

Despite the careful implementation of funding for renal replacement therapy, the sustainability of this ambitious policy is in question, given the rising incidence of end stage renal disease and the proportion of the UCS budget devoted to dialysis (table⇓). This may reflect inadequate control of hypertension, despite the efforts to control it. Though the number of people needing dialysis has escalated, renal transplant services still face a shortage of kidney donors.[19]

Some nephrologists are pressing the NHSO to revoke its peritoneal dialysis first policy because they believe that haemodialysis is better and that the NHSO is offering a second class treatment. This campaign is in line with the pressure being exerted by private providers, who support an extension of haemodialysis. Research has suggested that after all possible confounders were adjusted for, patients who start haemodialysis as first line treatment under the other insurance schemes live longer than those treated under the peritoneal dialysis first policy (odds ratio=3.25).[16] But different mortality rates were observed across regions, with those having dialysis by either means in greater Bangkok having a better chance of survival than those in the north east and south of the country. If UCS patients were offered haemodialysis from the outset the NHSO would need to invest annually in an additional 1000 haemodialysis machines and 500 trained haemodialysis nurses, which are unlikely to be affordable in the long run. Also, evidence from the US and Canada suggests that although the mortality rate of people having peritoneal dialysis was relatively higher than for those being treated with haemodialysis during the first few years after peritoneal dialysis was introduced, the gap was eliminated once nephrologists became more competent in peritoneal dialysis.[20 21] Therefore the NHSO's renal replacement therapy programmes need to put more effort into improving the quality of peritoneal dialysis through professional training.

The Thai policy on renal replacement therapy remains an unfinished agenda and continues to be central to policy debates. In this it reflects debates in many health systems about high cost treatments and how to balance equity, cost effectiveness, and affordability.

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Table

Table 1| Budget allocation to renal replacement therapy compared with total budget (million baht), 2008-12

Fiscal year	Total budget	Renal replacement therapy (%)
2008	76 800	160 (0.2)
2009	80 600	1400 (1.7)
2010	89 400	2700 (3.0)
2011	101 100	3200 (3.2)
2012	114 500	3900 (3.4)

100 baht= £2; €2.5; $3.

Figures

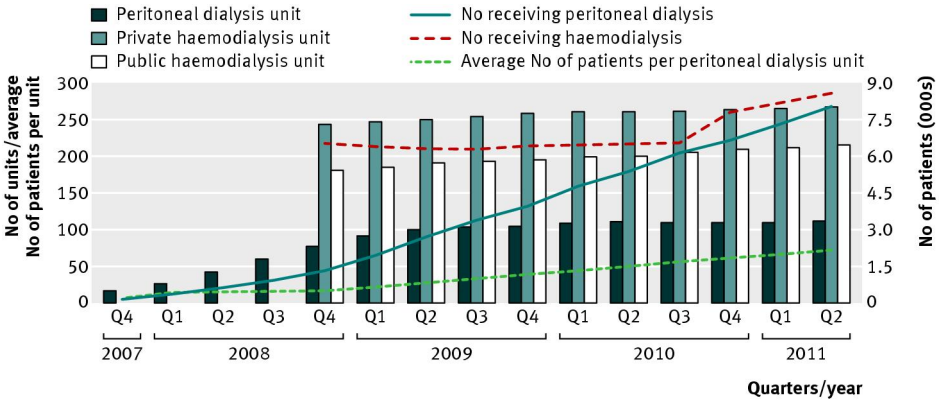

Fig 1 Numbers of peritoneal dialysis and haemodialysis units, patients having each type of dialysis, and the average number of patients per peritoneal dialysis unit

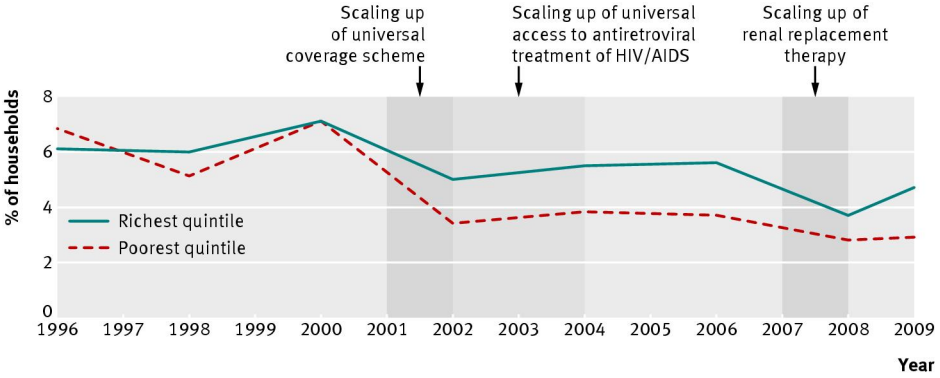

Fig 2 Proportion of households in which health accounts for more than 10% of total expenditure among richest and poorest quintiles

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Cost-utility analysis of 10- and 13-valent pneumococcal conjugate vaccines: Protection at what price in the Thai context?

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ABSTRACT

Objective: This study aims to evaluate the costs and outcomes of offering the 10-valent pneumococcal conjugate vaccine (PCV10) and 13-valent pneumococcal conjugate vaccine (PCV13) in Thailand compared to the current situation of no PCV vaccination.
Methods: Two vaccination schedules were considered: two-dose primary series plus a booster dose (2 + 1) and three-dose primary series plus a booster dose (3 + 1). A cost-utility analysis was conducted using a societal perspective. A Markov simulation model was used to estimate the relevant costs and health outcomes for a lifetime horizon. Costs were collected and values were calculated for the year 2010. The results were reported as incremental cost-effectiveness ratios (ICERs) in Thai Baht (THB) per quality adjusted life year (QALY) gained, with future costs and outcomes being discounted at 3% per annum. One-way sensitivity analysis and probabilistic sensitivity analysis using a Monte Carlo simulation were performed to assess parameter uncertainty.
Results: Under the base case-scenario of 2 + 1 dose schedule and a five-year protection, without indirect vaccine effects, the ICER for PCV10 and PCV13 were THB 1,368,072 and THB 1,490,305 per QALY gained, respectively. With indirect vaccine effects, the ICER of PCV10 was THB 519,399, and for PCV13 was THB 527,378. The model was sensitive to discount rate, the change in duration of vaccine protection and the incidence of pneumonia for all age groups.
Conclusions: At current prices, PCV10 and PCV13 are not cost-effective in Thailand. Inclusion of indirect vaccine effects substantially reduced the ICERs for both vaccines, but did not result in cost effectiveness.

1. Introduction

Bacterial meningitis, pneumonia and otitis media caused by *Streptococcus pneumoniae* (*S. pneumoniae*) are serious but preventable health problems in young children. Pneumococcal conjugate vaccines (PCVs) have been proven safe and effective in children less than 5 years old to prevent both invasive (e.g., meningitis, bacteremia) and non-invasive (e.g., pneumonia, otitis media) pneumococcal diseases [1–3]. Moreover, clinical studies in the United States and Europe have demonstrated that vaccinating young children with PCV can lead to a significant decline in the incidence of pneumococcal disease among unvaccinated populations, notably older children, adults and the elderly [4–6]. Although PCV has been available for more than a decade, its use has been limited in many areas due to high cost.

Abbreviations: PCV, pneumococcal conjugate vaccine; EPI, Expanded Program on Immunization; AOM, acute otitis media; MoPH, Ministry of Public Health; SE, standard error; VE, vaccine efficacy; IPD, invasive pneumococcal disease; RCT, randomized controlled trial; THB, Thai Baht; QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio.

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The cost-effectiveness of PCV has been documented in many high-income countries, and the governments in these settings have adopted the vaccine as part of their national immunization programs [7–13]. However, few economic evaluations have been conducted in low- or middle-income settings, where the burden of pneumococcal disease is at least as high [14–16]. In recent years, many low-income countries, especially in Africa, have introduced PCV programs with substantial support from the GAVI Alliance, a broad partnership that works to improve access to immunization [17]. Most middle income countries such as Thailand, which are not eligible for GAVI support and therefore face potentially substantial financial barriers to PCV implementation, have not yet implemented PCV programs. Cost-effectiveness studies are especially important to inform decision-making in these settings.

This study was conducted at the request of policy makers in Thailand to inform decisions about the adoption of PCV as part of this country's Expanded Program on Immunization (EPI). It was believed that if the vaccine is included in the EPI, its coverage would be almost 100%. Given that Thailand achieves 99% coverage with DTaP 3 dose vaccine [18], such an assumption is not unrealistic. This economic evaluation considered costs and impact of offering 10-valent PCV (PCV10), which covers 10 of approximately 90 *S. pneumoniae* serotypes, or recently licensed 13-valent PCV (PCV13), which covers 3 additional serotypes, compared to the current situation without a PCV program.

2. Methods

A model-based economic evaluation was performed to estimate costs as well as outcomes of vaccination with PCV10 and PCV13 compared to 'no vaccination'. Because there are different options for vaccination schedules [19], this study considered two commonly recommended regimens: two-dose primary series at 2 and 4 months of age plus a booster dose at age 13 months (2 + 1) and three-dose primary series at 2, 4 and 6 months of age plus a booster dose at age between 12 to 15 months (3 + 1). The study adopted a societal viewpoint using a life-time horizon with 3% discounting for both costs and outcomes beyond one year, as recommended in the by the Thai Health Technology Assessment guideline [20].

2.1. Model structure and assumptions

A Markov model was constructed based on the natural history of disease related to *S. pneumoniae* infection (Fig. 1). The model consisted of three major health states: healthy, *S. pneumoniae* infection and death. For *S. pneumoniae* infection, the model accounts for four health conditions based on their association with high case fatality or permanent disability (e.g., epilepsy, neurodevelopmental impairment or chronic lung disease): pneumococcal meningitis, pneumococcal bacteremia, all-cause pneumonia and all-cause acute otitis media (AOM). A one-year cycle was deployed in the model, and it was assumed that more than one infection is possible during a lifetime but each Markov cycle allows for only one infection.

2.2. Model input parameters

2.2.1. Epidemiological data

Estimated age-specific incidences of pneumococcal diseases in Thailand are presented (Supplementary Table 1). Pneumococcal bacteremia incidence was based on findings from active surveillance for bacteremia requiring hospitalization in two rural Thailand provinces [21] and does not include outpatient cases. All-cause meningitis and pneumonia incidence were derived from national surveillance conducted by the Bureau of Epidemiology, Ministry of Public Health (MoPH) [22]. For this model, all hospitalized meningitis cases reported to the national surveillance system were assumed to be caused by bacteria. The proportion of pneumococcal meningitis cases among all bacterial meningitis (mean = 14.27%, standard error (SE) = 3) was derived from hospital databases [23,24]. AOM incidence was obtained from the Thailand Burden of Disease Project [25].

Table 1 illustrates probabilities of hospitalization and developing complications from pneumococcal disease. Mortality rate and case fatality data were acquired from the Burden of Disease Project and literature review, utilizing data from Thailand or the East Asia region whenever available [23–28].

2.2.2. Direct effects (vaccine efficacy)

For a 3 + 1 dosing schedule, vaccine efficacy (VE) against vaccine-type invasive pneumococcal disease (IPD) was considered 89% based on a 2009 meta-analysis of randomized controlled trials (RCTs) [29]. This figure was used to estimate the efficacy of PCV10 and PCV13 against vaccine-type IPD (Table 1) by assuming the same overall efficacy against vaccine-type IPD, accounting for the additional serotype coverage [30–33]. Because sufficient data on serotype coverage were not available for pneumonia and AOM, VE against all-cause pneumonia and AOM for PCV10 and PCV13 were extrapolated from the efficacy of PCV7 against all-cause pneumonia (6%) [3] and AOM (6%) [29]. It was assumed that the efficacy of PCV10 and PCV13 against pneumonia and AOM increased proportionally with the increase in serotype coverage.

VE for a 2 + 1 schedule was modified to account for reduced immunogenicity for serotypes 6B and 23F [34] compared to the 3 + 1 schedule; a 20% reduction in efficacy against these serotypes was assumed. Serotypes 6B and 23F accounted for approximately 40% of PCV7 serotypes in Thai children [30–32]. As a result, an overall reduction of 8% in VE for the 2 + 1 schedule was estimated using the following formula:

$$VE_{2-1} = VE_{3-1}x(1 - 0.08)$$

2.2.3. Indirect effects (herd protection)

This model accounted for the indirect effect of the vaccine to prevent disease in unvaccinated populations (Supplementary Table 2). The percentage reduction in IPD incidence among unvaccinated populations was based on survey data after mass vaccination in the United States [4] with the adjustment for differences in serotype distribution between Thailand and the United States [35]. The indirect effect for IPD was based using the following formula:

$$\%\ \text{IPD fall in Thailand} = \%\ \text{IPD fall in the United States} \times \text{Serotype coverage in Thailand/Serotype coverage in the United States}$$

Because the indirect effects can occur in every population cohort ranging from aged 16–99 years, we manually calculated the indirect effects in each age group using the static model.

The indirect effect for pneumonia was estimated for unvaccinated populations, assuming that the protective effect would be equivalent to the decrease in IPD incidence among the same groups and adjusted for proportion of hospitalized pneumonia caused by *S. pneumoniae*. To estimate the proportion of hospitalized pneumonia cases caused by *S. pneumoniae*, we used data from Prapasiri et al. [26], who found that 11.76% (SE = 2.35) of bacteremic pneumonia cases in two Thai provinces were *S. pneumoniae*. The calculation of indirect effect of vaccine was base on the following formula:

$$\%\ \text{Hospitalized pneumonia fall in Thailand} = \text{Proportion of pneumococcal pneumonia} \times \%\ \text{IPD fall in Thailand}$$

Table 1
Input parameters used in the model.

Parameter description	Distribution	Mean	SE	References
Epidemiological parameters				
Proportion of bacterial meningitis due to *S. pneumoniae*	Beta	0.14	0.03	Meta analysis [23,24]
Epilepsy after pneumococcal (Pnc.) meningitis	Beta	0.10	0.06	[28]
Hearing loss after Pnc. meningitis	Beta	0.03	0.03	[28]
Neurodevelopmental impairment after Pnc. meningitis	Beta	0.34	0.09	[28]
Death after Pnc. meningitis	Beta	0.03	0.03	[28]
Death after Pnc. bacteremia	Beta	0.08	0.04	[28]
Necrotizing pneumonia after Pnc. pneumonia[a]	Beta	0.18	0.05	[27]
Death after hospitalized pneumonia	Beta	0.01	0.00	[22]
Hearing loss after AOM	Beta	0.05	0.00	[25]
Risk ratio of mortality compared to general population				[25]
Epilepsy		1.01–1.14[b]		
Hearing loss		1.00–1.01[b]		
Neurodevelopmental impairment		5.16–7.17[b]		
Chronic lung		1[b]		
Baseline vaccine parameters				
Vaccine efficacy (PCV7; 3 + 1 schedule)				
IPD caused by vaccine serotype	Normal	89.00%	3.57%	[29]
Clinical pneumonia	Beta	6.00%	2.30%	[3]
AOM	Normal	6.00%	1.53%	[29]
Vaccine serotype coverage in Thais				
PCV7 serotype coverage in aged <5	Normal	67.60%	5.36%	Meta analysis [30–33]
PCV10 serotypes coverage in aged <5	Normal	70.60%	5.66%	Meta analysis [30–33]
PCV13 serotypes coverage in aged <5	Normal	86.80%	4.03%	Meta analysis [30–33]
PCV7 serotypes coverage in aged ≥5	Normal	38.09%	2.29%	Meta analysis [30–33]
PCV10 serotypes coverage in aged ≥5	Normal	43.71%	3.00%	Meta analysis [30,31,33]
PCV13 serotypes coverage in aged ≥5	Beta	60.19%	4.69%	[30]
Serotypes coverage US				[35]
PCV7 serotypes coverage in aged 10 to 39	Not varied	71.30%		
PCV7 serotypes coverage in aged 40 to 64	Not varied	65.40%		
PCV7 serotypes coverage in aged ≥65	Not varied	69.70%		
% IPD fall among unvaccinated group in US				[4]
% fall among who aged 20 to 39	Beta	40.00%	4.59%	
% fall among who aged 40 to 64	Beta	14.00%	4.59%	
% fall among who aged ≥65	Beta	29.00%	3.57%	
Cost parameters (THB)				
Vaccine costs				
PCV10 cost per dose	Not varied	1440		GlaxoSmithKline (Thailand)
PCV13 cost per dose	Not varied	1930		Pfizer (Thailand) Limited
Delivery cost per dose	Not varied	5% of vaccine price		[37]
Direct medical costs				
Cost per episode				
Meningitis aged ≤14	Gamma	63,775	20,830	[24]
Meningitis aged 15 to 59	Gamma	59,210	15,570	[24]
Meningitis aged ≥60	Gamma	31,980	15,260	[24]
Bacteremia aged ≤14	Gamma	14,120	4587	[24]
Bacteremia aged 15 to 59	Normal	22,120	743	[24]
Bacteremia aged ≥60	Gamma	22,440	5372	[24]
Hospitalized pneumonia aged ≤14	Normal	9099	46	[24]
Hospitalized pneumonia aged 15 to 59	Normal	23,952	122	[24]
Hospitalized pneumonia aged ≥60	Normal	31,948	278	[24]
Non-hospitalized pneumonia aged ≤14	Normal	39	2	[36]
Non-hospitalized pneumonia aged 15 to 59	Normal	103	5	[36]
Non-hospitalized pneumonia aged ≥60	Normal	98	5	[36]
AOM aged ≤14	Normal	350	7	[36]
AOM aged 15 to 59	Normal	520	7	[36]
AOM aged ≥60	Normal	764	17	[36]
Cost per year				
Epilepsy aged ≤14	Gamma	3962	475	[36]
Epilepsy aged 15 to 59	Normal	1600	21	[36]
Epilepsy aged ≥60	Gamma	1672	85	[36]
Hearing loss aged ≤14	Gamma	896	385	[36]
Hearing loss aged 15 to 59	Gamma	838	48	[36]
Hearing loss aged ≥60	Gamma	1312	123	[36]
Neurodevelopmental impairment aged ≤14	Gamma	3582	2333	[36]
Neurodevelopmental impairment aged 15 to 59	Gamma	936	72	[36]
Neurodevelopmental impairment aged ≥60	Gamma	5811	2892	[36]
Chronic lung aged ≤14	Gamma	1404	1404	[36]
Chronic lung aged 15 to 59	Normal	3306	62	[36]
Chronic lung aged ≥60	Normal	3636	31	[36]
Direct non-medical costs[c]				Primary data collection
Meningitis (per episode)		15,485		
Bacteremia (per episode)		9987		
Hospitalized pneumonia (per episode)		5674		
Non-hospitalized pneumonia (per episode)		527		
AOM (per episode)		527		

Table 1 (*Continued*)

Parameter description	Distribution	Mean	SE	References
Epilepsy (per year)		4489		
Hearing loss (per year)		868		
Neurodevelopmental impairment (per year)		17,548		
Chronic lung (per year)		7133		
Age-specific productivity loss (per day)				[38]
15–29	Not varied	196		
30–39	Not varied	409		
40–59	Not varied	571		
60–69	Not varied	246		
70–79	Not varied	98		
Utility parameters (using HUI3)				Primary data collection
Meningitis	Beta	0.96	0.00	
Bacteremia	Beta	0.99	0.00	
Pneumonia	Beta	0.99	0.00	
AOM	Beta	1.00	0.00	
Epilepsy	Beta	0.64	0.07	
Hearing loss	Beta	0.55	0.06	
Neurodevelopmental impairment				
Mild mental retardation	Beta	0.69	0.07	
Severe mental retardation	Beta	0.10	0.11	
Mental retardation + epilepsy	Normal	0.00	0.09	
Chronic lung disease	Beta	0.59	0.06	

[a] Assuming all necrotizing pneumonia cases would develop chronic lung disease.
[b] Risk ratio of mortality varied by age
[c] Including travel costs, foods, accommodation, informal care and special education, each component is gamma distributed.

2.2.4. Costs and outcomes

The cost analysis was performed based on a societal perspective, and included both direct medical and direct non-medical costs (Table 1). Direct medical costs for outpatient and inpatient care were obtained from the Thailand's Centre for Health Equity Monitoring [36] and the Central Office for Healthcare Information [24], respectively. The cost of the vaccination program included the vaccine cost and delivery cost [37]. Direct non-medical costs, such as costs for transportation, meals, accommodation, facilities, productivity loss [38] by parents or caregivers for hospital visits or providing informal care, were derived from face-to-face interviews with caregivers of 192 ill children aged 5–14 years in seven public hospitals in five provinces throughout Thailand. All cost parameters are presented in 2010 Thai Baht (THB) (THB 31 = US$ 1).

Outcomes were measured in quality-adjusted life years (QALYs) using the Health Utilities Index Mark 3 [39] (Table 1). Utility measures were derived from interviews with the aforementioned 192 caregivers and the results previously described [40].

2.3. Uncertainty analyses

2.3.1. One-way sensitivity analysis

One-way sensitivity analysis was performed to examine the uncertainty surrounding each parameter individually (e.g., discounting rate at 0% and 6% per annum, disease incidence, vaccine efficacy, vaccine serotype coverage, percentage incidence reduction among unvaccinated groups, utility and cost). The impact of serotype replacement and indirect vaccine effects were also examined. The former was done by adjusting the serotype coverage parameter whereas the latter was explored by varying the

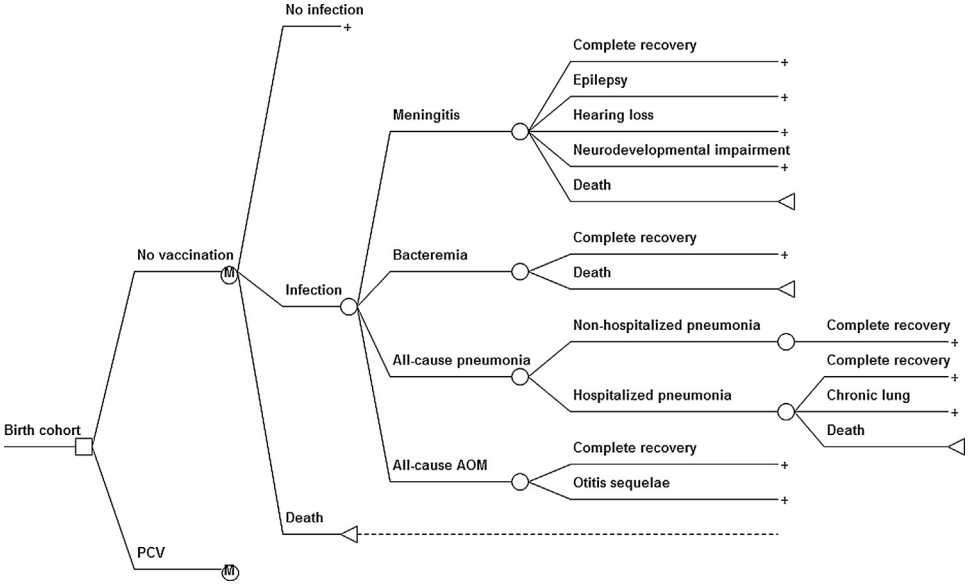

Fig. 1. Markov model used for assessing costs and outcomes of pneumococcal conjugate vaccine (PCV) vaccination compared to 'no vaccination'. The structure of the 'PCV' node is identical to the 'no vaccination' node and is thus omitted.

disease incidence reduction among unvaccinated groups in the United States [4]. For pneumonia incidence, there were two data sources in Thailand. We used data from Thailand's national surveillance (Bureau of Epidemiology, MoPH) [22] as the base-case and data from an active, population-based surveillance system operated collaboratively by MoPH and the International Emerging Infections Program (IEIP, US Centers for Disease Control and Prevention) [41] in the sensitivity analysis. We also assessed the effect of two different durations of vaccine protection: 5 and 10 years.

This analysis used the cost-effectiveness ceiling threshold of one per-capita gross domestic product or THB 100,000 (US$ 3226) per QALY gained as recommended by the Subcommittee for Development of the National List of Essential Drugs 2007 [42]. The Subcommittee sets the threshold for considering new medicines and vaccines for public reimbursement. For PCV vaccination scenarios determined to be not cost-effective at the current price, we examined the maximum cost of the vaccine that would make it cost-effective as well as cost-saving in the Thai setting. Cost-saving implies that no additional budget would be required for vaccination, because resources saved from averted pneumococcal disease could be used to cover vaccination costs.

2.3.2. Probabilistic sensitivity analysis

Probabilistic sensitivity analysis was conducted to examine the effect of all parameter uncertainty simultaneously using a Monte Carlo simulation using Microsoft Office Excel 2007. The simulation was run for 1000 iterations to yield a range of possible values for total costs, health outcomes, and incremental cost-effectiveness ratios (ICERs) in THB per QALY gained. The probability distributions were determined according to the range of each input parameter value. The normal distribution was used as a default. The beta distribution was used when parameter values ranged between zero and one, such as in probability and utility parameters. The gamma distribution was used when parameter values ranged between zero and positive infinity, such as costs parameters.

3. Results

Compared to 'no vaccination', the 3 + 1 dose schedule of PCV10 and PCV13 would prevent an estimated 4262 and 5241 episodes of pneumococcal disease in the vaccinated population, respectively (Fig. 2). In addition, 4510 and 6211 episodes of pneumococcal disease would be averted in unvaccinated populations due to indirect effects. It was estimated that 369 and 495 pneumococcal deaths would be avoided by introducing PCV10 and PCV13, respectively.

Table 2 shows the ICERs of different PCV vaccination schedules with and without inclusion of indirect vaccine effects. Without the indirect effects of vaccine, the 2 + 1 dose schedule produced ICERs of THB 1,368,072 and THB 1,490,305 per QALY gained for PCV10 and PCV13, respectively. The 3 + 1 dose schedule without accounting for indirect effects produced ICERs of THB 1,677,379 for PCV10 and THB 1,830,716 for PCV13. When the indirect effects of vaccination were included in the analysis, ICERs of PCV vaccination decreased by more than half. In one-way sensitivity analysis, the important determinants were discount rate, the change in duration of vaccine protection (5 vs. 10 years) and the incidence of pneumonia for all age groups. A 10-year protection duration including indirect effects, ICERs of PCV10 decreased to THB 287,353 and THB 363,248 for the 2 + 1 and 3 + 1 dose schedules, respectively; for PCV13, the corresponding ICERs were THB 290,420 and THB 367,339. When we used pneumonia incidence from active, population-based surveillance [41] and included indirect effects, the ICERs were reduced by almost 50% for the 3 + 1 schedule to THB 360,891 (PCV10) and THB 371,723 (PCV13) as well as by approximately 50% for the 2 + 1 schedule to THB 287,353 (PCV10) and THB 290,420 (PCV13). The model was less sensitive to variations in direct medical and non-medical costs and serotype replacement.

At current pricing, neither PCV10 nor PCV13 would be cost-effective compared to 'no vaccination' at a ceiling threshold of THB 100,000 per QALY gained, with or without inclusion of indirect vaccine effects (Fig. 3). Including the indirect vaccine effects, PCV13 had a higher probability of being cost-effective compared to 'no vaccination' at a ceiling threshold between THB 600,000 and THB 750,000, depending on dosing schedule (Fig. 3A and 3B). Compared to PCV10, PCV13 had a higher probability of being cost-effective at a ceiling threshold between THB 550,000 and THB 600,000.

Without indirect vaccine effects, PCV10 yielded a higher probability of being cost-effective compared to 'no vaccination' at a ceiling threshold between THB 1,450,000 and THB 1,750,000, and PCV13 had a higher probability of being cost-effective compared to PCV10 at a ceiling threshold between THB 2,050,000 to THB 2,550,000 (Fig. 3C and D).

Threshold analysis demonstrated that using the 2 + 1 dosing schedule and considering indirect vaccine effects, PCV10 and PCV13 costs would have to be 75% lower (to THB 373 and THB 494), to be cost-effective; 92% cost reduction for both PCV10 and PCV13 (to THB 121 and THB 165) would be needed for either vaccine to be cost-saving (Fig. 4). Using a 3 + 1 dosing schedule, PCV10 and PCV13 costs would have to be 79% lower (to THB 304 and THB 403), to be cost-effective, and 93% lower (to THB 99 and THB 134), respectively, to be cost-saving.

When indirect vaccine effects were excluded, the maximum vaccine costs for both PCV10 and PCV13 to achieve cost-effective ranged from THB 107 to THB 162, and to be cost-saving, maximum costs ranged from THB 14 to THB 21.

4. Discussion

This study indicates that, at current pricing, neither PCV10 nor PCV13 would be considered cost-effective in Thailand at either dosing schedule examined, using Thailand's standard ceiling threshold to assess health interventions. This finding results largely from the relatively high cost of the vaccine (per dose), which is equivalent to 5–6 times Thailand's daily minimum wage. Our findings also reveal that the vaccine can become cost-effective or even cost-saving if vaccine costs were reduced by around 70–90% of current market prices.

Our findings stand in contrast to previous studies conducted in Argentina and Singapore which found PCV to be cost-effective [43,44]. The differences may be explained by differences of model structure and input parameters, especially epidemiological and economic data that vary across settings. In addition, the VE estimate used in our model was lower than that used in other studies. In this study, VE against vaccine-type IPD (89%) was derived from a systematic review and meta-analysis of RCTs [29], while other studies used 97% as reported from a single RCT conducted in the United States [1]. Difference in country specific serotype coverage may also have influenced the results. PCV10 serotype coverage for IPD among children aged less than 5 years is 75%, 81%, and 71% in Argentina, Singapore and Thailand, respectively [30–32,43,45]. This study also assumed a vaccine protection duration of 5 years, which is in line with several other economic evaluations of PCV studies [9,46], whereas some studies assumed protection lasted 10 years [7,47,48]. Our decision to use a 5-year protection duration was based on an immunogenicity study of PCV9 in South Africa [49], although this study did not follow participants beyond 5–6 years. Recognizing the limited data available, we applied a conservative assumption for the duration of vaccine protection. Furthermore, lower treatment costs in Thailand compared to other settings [12,13,43,44], contributed

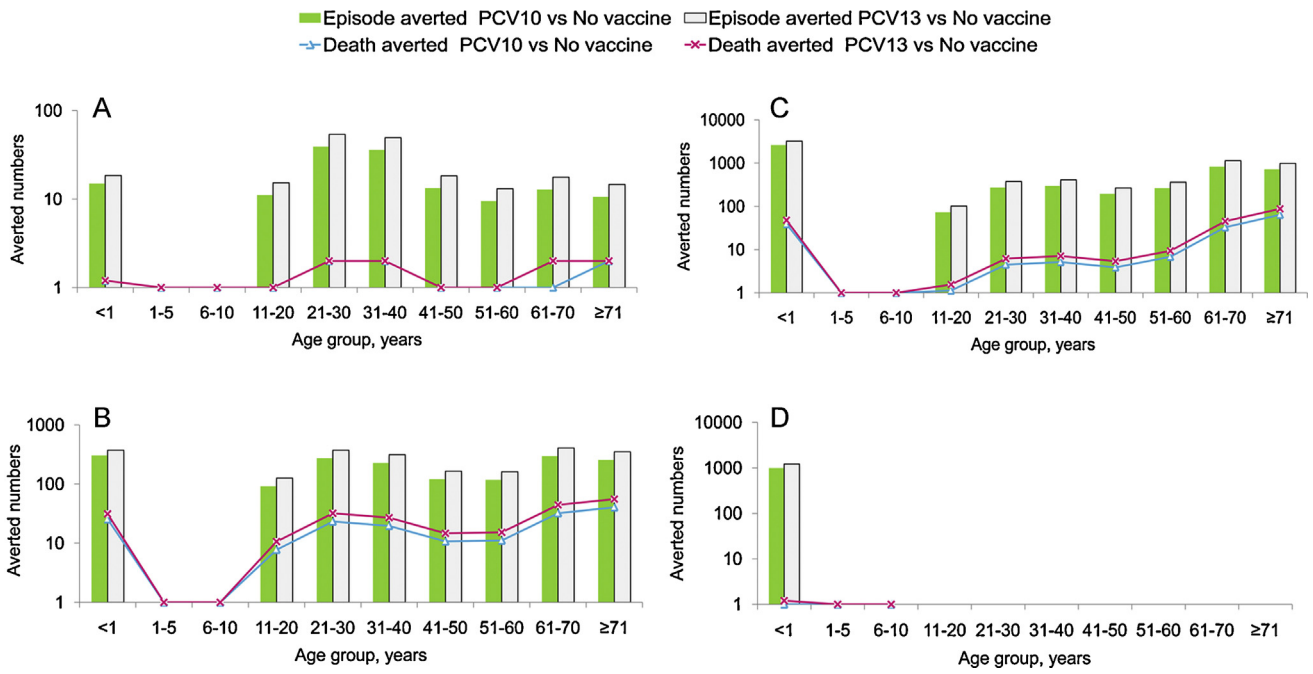

Fig. 2. Predicted numbers of life-time pneumococcal disease cases and deaths averted due to vaccination with 10- and 13-valent pneumococcal conjugate vaccines (PCV10 and PCV13) by clinical syndrome and age at entry to the cohort. (A) pneumococcal meningitis; (B) pneumococcal bacteremia; (C) all-cause pneumonia; (D) all-cause acute otitis media.

to the different conclusions about vaccine cost effectiveness in this study.

The model was very sensitive to pneumonia incidence. The ICERs decreased significantly when the pneumonia incidence was based on active, population-based surveillance compared to Thailand's national surveillance system. However, even using the higher pneumonia incidence rate, PCV was not considered cost-effective for Thailand in our model.

4.1. Strengths and limitations

Parameters used in this model were obtained from high quality studies, including systematic reviews and meta-analyses. All parameters were contextualized for Thailand; thus, applying results of this study to other settings should be performed with caution. Our study examined two PCV formulations (10- and 13-valent) and two dosing schedules (2 + 1 and 3 + 1). Although

Table 2
Incremental cost effectiveness ratios (ICER, in THB/QALY) classified by vaccination schedules and inclusion of indirect vaccine effects.

	PCV10 vs. No vaccine	PCV13 vs. No vaccine
2 + 1 schedule with indirect effects		
Incremental cost (THB)	4178	5593
Incremental LYs	0.00674	0.00898
Incremental QALYs	0.00804	0.01061
Episode averted	0.01867	0.02501
Death averted	0.00200	0.00275
ICER per QALY gained (THB/QALY)	519,399	527,378
3 + 1 schedule with indirect effects		
Incremental cost (THB)	5658	7576
Incremental LYs	0.00726	0.00967
Incremental QALYs	0.00870	0.01147
Episode averted	0.02030	0.02723
Death averted	0.00217	0.00299
ICER per QALY gained (THB/QALY)	650,087	660,662
2 + 1 schedule without indirect effects		
Incremental cost (THB)	4492	6026
Incremental LYs	0.00212	0.00261
Incremental QALYs	0.00328	0.00404
Episode averted	0.00469	0.00577
Death averted	0.00007	0.00009
ICER per QALY gained (THB/QALY)	1,368,072	1,490,305
3 + 1 schedule without indirect effects		
Incremental cost (THB)	6001	8048
Incremental LYs	0.00229	0.00282
Incremental QALYs	0.00358	0.00440
Episode averted	0.00508	0.00625
Death averted	0.00008	0.00010
ICER per QALY gained (THB/QALY)	1,677,379	1,830,716

LY = life year, QALY = quality-adjusted life year.

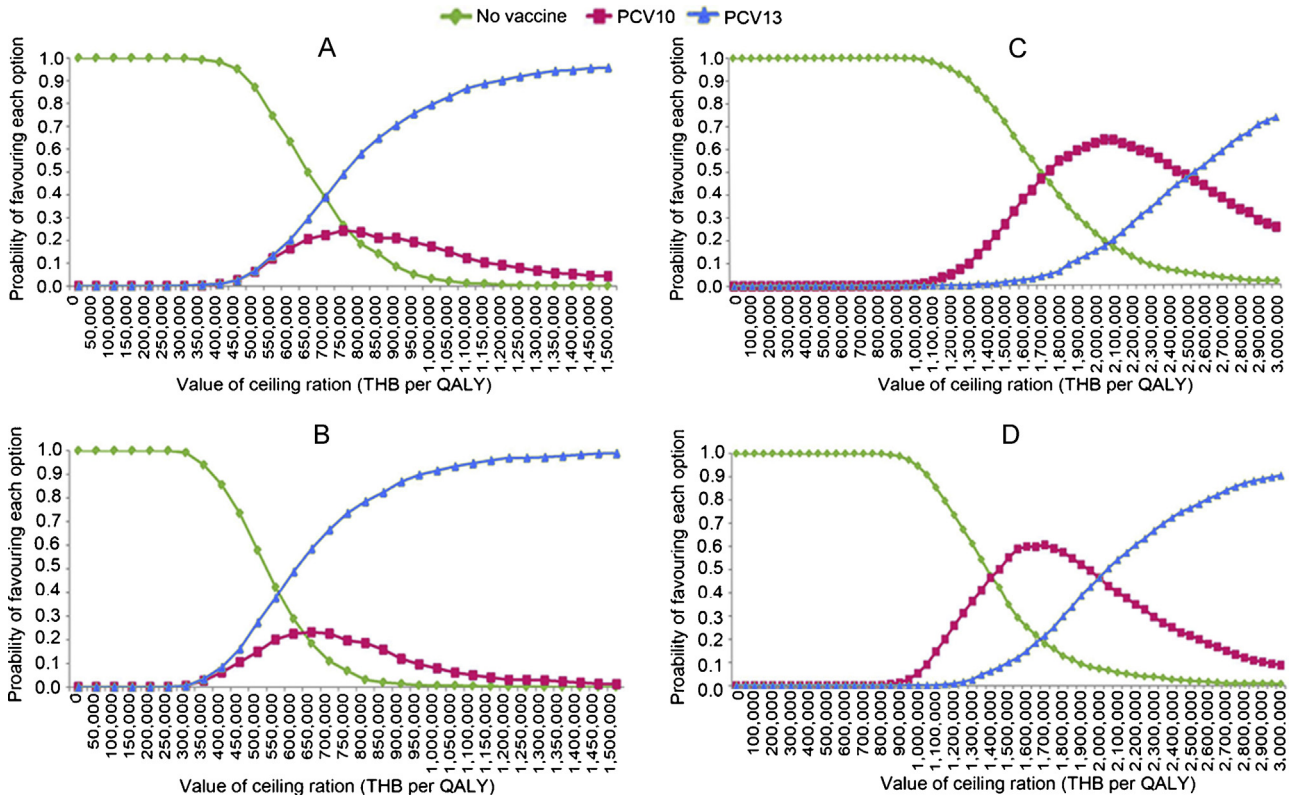

Fig. 3. Cost-effectiveness acceptability curves for 10- and 13-valent pneumococcal conjugate vaccines (PCV10 and PCV13), and 'no vaccination'. (A) 3 + 1 schedule with indirect vaccine effects; (B) 2 + 1 schedule with indirect vaccine effects; (C) 3 + 1 schedule without indirect vaccine effects; (D) 2 + 1 schedule without indirect vaccine effects.

this study adopted a static modeling rather than dynamic one, it included indirect effect of vaccination that protects infection in population who are not vaccinated. The use of static model also facilitates transparency of this study because many Thai decision makers and academics are more familiar with Markov, and the use of dynamic model in this study will require a number of assumptions given that this study considers four health conditions.

Nonetheless, this study has some limitations. First, due to the lack of local data on indirect vaccine effects, the model made assumptions based on findings from the United States [4]. Data from the United States showed a significant decline in IPD incidence among unvaccinated populations aged 20 years and above only. This ignored herd protection among young children (1–4 years) and teenagers, which could not be assessed in the United States, because children in this age group (1–4 years) were vaccinated as part of catch-up vaccination efforts. Second, IPD incidence rates used in this model were likely underestimates, because the available studies were conducted in public health facilities (i.e. government hospitals and health centers); thus, patients without access to public hospitals or at private hospitals were not included. Additionally, it has been shown that antibiotic use before blood culture collection

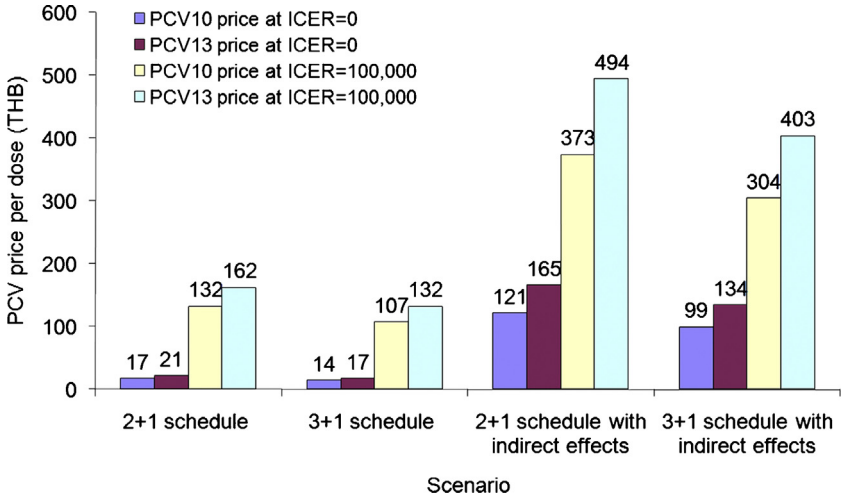

Fig. 4. Threshold analysis for maximum per-dose price for 10- and 13-valent pneumococcal conjugate vaccines (PCV10 and PCV13) to achieve cost-effective (incremental cost-effectiveness ratio (ICER) = THB 100,000) or cost-saving (ICER = THB 0). Current price per dose: THB 1440 for PCV10; THB 1930 for PCV13.

in Thailand leads to underestimation of IPD incidence in hospital-based studies [21]. Perhaps more importantly, IPD rates cited for this analysis did not include outpatients because most of them were suspected and not confirmed cases. Including outpatient IPD cases in the model inputs would have resulted in lower ICERs. Lastly, the ceiling threshold used in this analysis is based on the preference of decision maker in Thailand. Decision makers in different settings may have their own preference regarding health investment, we encourage readers to compare the results to any threshold they consider it appropriate.

4.2. Implications

In summary, based on a societal perspective with a ceiling threshold of THB 100,000 per QALY, PCV10 and PCV13 would not be considered cost-effective, whether or not indirect vaccine effects were included in the model. Therefore, it cannot be recommended that PCV be included in Thailand's EPI until prices decline to recommended values. Reduction in vaccine cost, which seems possible given the widespread introduction of PCV in many countries, could improve the feasibility of introduction in Thailand, which could result in substantial public health impact. Based on analyses that include indirect vaccine effects, PCV would become cost-effective at a price per-dose between THB 304 (PCV10, 3 + 1 schedule) and THB 494 (PCV13, 2 + 1 schedule) and cost-saving at a per-dose price between THB 99 and THB 165.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2013.03.047.

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RESEARCH ARTICLE Open Access

Variation of health-related quality of life assessed by caregivers and patients affected by severe childhood infections

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Abstract

Background: The agreement between self-reported and proxy measures of health status in ill children is not well established. This study aimed to quantify the variation in health-related quality of life (HRQOL) derived from young patients and their carers using different instruments.

Methods: A hospital-based cross-sectional survey was conducted between August 2010 and March 2011. Children with meningitis, bacteremia, pneumonia, acute otitis media, hearing loss, chronic lung disease, epilepsy, mild mental retardation, severe mental retardation, and mental retardation combined with epilepsy, aged between five to 14 years in seven tertiary hospitals were selected for participation in this study. The Health Utilities Index Mark 2 (HUI2), and Mark 3 (HUI3), and the EuroQoL Descriptive System (EQ-5D) and Visual Analogue Scale (EQ-VAS) were applied to both paediatric patients (self-assessment) and caregivers (proxy-assessment).

Results: The EQ-5D scores were lowest for acute conditions such as meningitis, bacteremia, and pneumonia, whereas the HUI3 scores were lowest for most chronic conditions such as hearing loss and severe mental retardation. Comparing patient and proxy scores ($n = 74$), the EQ-5D exhibited high correlation ($r = 0.77$) while in the HUI2 and HUI3 patient and caregiver scores were moderately correlated ($r = 0.58$ and 0.67 respectively). The mean difference between self and proxy-assessment using the HUI2, HUI3, EQ-5D and EQ-VAS scores were 0.03, 0.05, -0.03 and −0.02, respectively. In hearing-impaired and chronic lung patients the self-rated HRQOL differed significantly from their caregivers.

Conclusions: The use of caregivers as proxies for measuring HRQOL in young patients affected by pneumococcal infection and its sequelae should be employed with caution. Given the high correlation between instruments, each of the HRQOL instruments appears acceptable apart from the EQ-VAS which exhibited low correlation with the others.

Keywords: Infection, Chronic conditions, Child, Health-related quality of life, Utility, Proxy

Background

Measuring health-related quality of life (HRQOL) is increasingly used to quantify the effect of a health condition on an individual's life, and to assess the impact of health care interventions. Economic evaluations measure HRQOL in terms of utility, which can be subsequently incorporated along with changes in life expectancy in the calculation of Quality-Adjusted Life Years (QALYs) to compare health outcomes across health interventions in different diseases and disabilities to inform resource allocation. Utility scales usually range from 0 to 1, where full health is assumed to have the value 1 and death the value 0. Some HRQOL measures such as the Health Utilities Index Mark 2 (HUI2), and Mark 3 (HUI3), and EuroQoL Descriptive System (EQ-5D) allow negative scores that express health states considered worse than death.

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There are difficulties and limitations in assessing HRQOL in young children. Firstly, children's growth and development changes rapidly, which may affect the baseline measure of particular health dimensions such as self-care, usual activity or communication ability [1,2]. At present, there are no standard instruments for measuring health status in this population. While the HUIs and EQ-5D, generic health status instruments are recognised as valid and reliable for eliciting health status in adults and children aged over four years (for the HUIs and through proxy-assessment) or 14 years (for the EQ-5D) [3-7], and are widely used in cost-utility analysis (CUA) [1,8], their application for younger age-groups is still controversial [1]. Furthermore, HRQOL obtained using different instruments can differ substantially even when measured in the same person [9,10] a phenomenon that is particularly evident in young children. While some variation in HRQOL scores obtained from different instruments is inevitable, these can be tested in target populations in order to explore the extent of variation between them. Instruments that provide widely differing outcomes might then be considered less appropriate for use in these populations.

A second challenge to the use of HRQOL instruments with young children, is that these should ideally be completed by the target population, posing substantial challenges in very young responders. A review found that only 2% of studies where children were the primary beneficiaries of the intervention estimated HRQOL scores directly from this age-group [1]. This is expected given the greater difficulties children might face in accurately describing their health condition during and after illness episodes. In addition, some of the questions might be too complex for young children to answer. As a result, proxy-assessment, where children's health status is obtained through their caregivers, physicians, or adult patients with similar health conditions, is applied [11-14]. However, self- and proxy-assessed HRQOL scores may vary, even when using the same tools [12,13].

Based on this review, two potential sources of variation are present when assessing HRQOL in young children: 1) variation due to the choice of instrument; 2) variation between the measures obtained from patients directly as opposed to their carers. The agreement between self-reported and proxy measures of health status in ill children is not well established and there are no clear guidelines as to whether this is acceptable practice [12,13,15,16]. Where the use of a proxy is not appropriate, better guidance is needed on the most appropriate tools for health status measurement in young children.

This study explores the use of instruments for HRQOL measurement in young children affected by infectious diseases in Thailand, and is a part of a CUA of 10- and 13-valent pneumococcal conjugate vaccines. Assessment using various HRQOL instruments by the caregivers and affected children (who are able to rate their health status) can provide the necessary data to address the above knowledge-gap.

The specific objectives of this study are to 1) quantify the variation in scores derived from young patients and their carers using different HRQOL instruments in different health conditions; 2) provide recommendations as to whether it is appropriate to measure HRQOL of paediatric patients using their caregivers' assessments; 3) where proxy assessment is not appropriate, identify which instrument is most suitable for use in very young children.

Methods

Study design and sample

The health conditions to be assessed in this study were selected by a consortium of experts in paediatric infectious disease, paediatric neurology, epidemiology, vaccinology, and health economics. The list of conditions aimed to include the most common severe pneumococcal infections and their sequelae that are likely to have the highest impact on HRQOL. The final list included: 1) meningitis 2) bacteremia, 3) pneumonia, 4) acute otitis media (AOM), 5) hearing loss, 6) chronic lung disease, 7) epilepsy, 8) mild mental retardation (MMR), 9) severe mental retardation (SMR), and 10) mental retardation combined with epilepsy (MR + epilepsy).

We conducted a hospital-based cross-sectional survey from August 2010 to March 2011 in seven public tertiary hospitals in different parts of Thailand. The hospitals were selected based on having a high number of bacterial meningitis cases which was a relatively rare condition but one with a high burden of disease. This study was approved by the ethics committee of Queen Sirikit National Institute of Child Health, Nopparat Rajathanee Hospital, Maharat Nakhon Ratchasima Hospital, Udonthani Hospital, Chiangrai Regional Hospital, Hatyai Hospital, and Faculty of Medicine, Prince of Songkla University. We calculated the sample size based on a attempt to detect a mean difference of 0.05 of the maximum of various scales for HRQOL for patient-caregiver pairs with and an estimated standard deviation (SD) of paired response difference of 0.03 [17], a power of 80% with a significance level of 0.05, at least six pairs were required for each health condition.

Health personnel from the study sites helped in the identification of eligible patients and their caregivers. Pneumococcal bacteremia, pneumococcal pneumonia and bacterial meningitis cases were identified in the paediatric wards. The case definition for these cases conformed with the clinical criteria defined by the Case Definitions for Infectious Conditions in Thailand [18] or the International Classification of Diseases and Related

Health Problems (10th edition). AOM, hearing loss, chronic lung disease, epilepsy, MMR, SMR and MR + epilepsy cases were identified in the paediatric clinics. Relevant outpatient cases were classified into each health condition according to physicians' diagnosis, regardless of diagnostic method. We selected all cases who met the criteria during the data collection period.

Patients aged between five and 14 years in the selected hospitals who were diagnosed with any single one of the selected health conditions were enrolled. All school age patients aged 7 years and above who were able to communicate were invited along with their caregivers to directly participate in the study. For patients aged under seven years and for patients who refused or were unable to answer a series of questions, such as those with mental retardation (MR), only caregivers were invited to participate. Caregivers were excluded if they were unable to answer the questions or unwilling to participate in the study.

Consent was sought from a parent or guardian of the identified patients prior to interviews and reviews of paediatric medical records. The participants were interviewed by interviewers using the Thai version of HUIs and EQ-5D questionnaires. Although these instruments can routinely be completed independently by patients, in the study both patients and caregivers were interviewed face-to-face by well-trained interviewers reading out the structured questionnaires and themselves completing the forms.

Study instruments

The HUI2, HUI3 and EQ-5D were selected as they have been widely used in HRQOL measurement in children and Thai versions have already been validated and approved by the Health Utilities Inc and the EuroQol group, respectively. In addition, responses can be converted into utility scores. The EQ-VAS is an integral component of the EQ-5D questionnaire; however, we examine it here independently of the primary descriptive system. From our literature review, all of these scales were reported to have minimal problem of floor and ceiling effects with the exception of an important ceiling effect in the case of EQ-5D [19-23].

The EQ-5D includes five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) with three ordered levels of severity for each dimension. The self-administered version of EQ-5D is considered suitable for people aged 14 years and above. An EQ-5D youth (EQ-5D-Y) version for children aged between seven to 12 years has been developed but has not been adapted to the Thai context. The EQ-VAS is a standardised extension to the EQ-5D descriptive system. It is a rating scale with a vertical 20 cm Visual Analogue Scale (VAS) with the end points labelled best imaginable health state at the top and worst imaginable health state at the bottom having numeric values of 100 and 0, respectively. The standard version was used for all subjects.

The HUI2 comprises seven dimensions (sensation, mobility, emotion, cognition, self-care, and pain and fertility) with four or five ordered levels of severity for each dimension. The HUI3 was developed to address concerns surrounding certain definitions in the HUI2 [24], and is comprised of eight dimensions (vision, hearing, speech, cognition, pain, emotion, ambulation, and dexterity) with five or six ordered levels of severity for each dimension. Of the seven dimensions in HUI2, the fertility dimension was excluded, whereas the sensation dimension was split into vision, hearing and speech. We used the validated Thai version 'HUI23' [25], which includes all 41 questions that comprise HUI2 (37 questions) and HUI3 (33 questions), and from which each instrument can be used by selecting the relevant components. The HUIs have been considered suitable for people aged five years and above through proxy-assessment.

Data analysis

A Thai algorithm was used to calculate the EQ-5D scores [26] but a Canadian scoring function of HUIs was used for HUI23 due to the lack of local data [27]. The correlation between scores from different instruments was calculated for patients and for caregivers, and the correlation between scores from patients and caregivers was calculated for different instruments. To determine whether there were systematic differences in scores between instruments, we calculated for each health condition and overall HRQOL the mean score and its 95% confidence interval (CI) using each of the HRQOL instruments in both paediatric patients where possible, and in their caregivers. ANOVA was used to analyze the source of variability of the scores. Differences in scores between caregivers and patients were tested using paired t-tests for the 28 condition-instrument combinations. All statistical analyses were carried out in the open source R software package [28].

Results

In total 173 cases were identified. None of the caregivers refused to participate giving a 100% response rate. The number of respondents by health conditions is shown in Table 1. A total of 74 paediatric patient-caregiver complete sets participated in this study. Additionally, 99 caregivers participated with a corresponding patient that was either too sick (all cases of MR and the majority of meningitis, pneumonia and AOM, $n = 53$) or were too young (aged less than 7 years, $n = 46$) to complete the questionnaire. The overall mean patient age was 10 (SD = 3). Males accounted for 62%. Among

Table 1 Number of assessors by health conditions

Health conditions	Total 173 cases	
	Assessed by caregivers and paediatric patients	Assessed by caregivers alone
Acute		
Meningitis	7	12
Bacteremia	9	7
Pneumonia	8	16
AOM	7	11
Sequalae		
Hearing loss	15	7
Chronic lung disease	12	4
Epilepsy	16	4
MMR	0	8
SMR	0	11
MR + epilepsy	0	18
Total	**74**	**99**

173 caregivers, the mean age was 40 years (SD = 11) and males accounted for only 13%. The duration for completing the HUI23 was approximately eight minutes in both patients and caregivers, significantly longer than for the EQ-5D + VAS which took approximately three minutes.

Table 2 shows correlation coefficients among different instruments in the same subjects (both the patient and caregiver) and between the same patient-caregiver pair using the same instrument (highlighted in the bold). Most values indicated relatively high or moderate correlation except the correlation coefficients between the EQ-VAS and HUIs, both within the same person and between patient and caregiver in the same pair.

The HRQOL scores obtained from all caregivers are shown in Figure 1. The EQ-5D scores are the lowest for seven of 10 health conditions i.e., meningitis, bacteremia, pneumonia, AOM, chronic lung disease, epilepsy and MMR, whereas the HUI3 gave the lowest scores for three health conditions i.e., hearing loss, SMR and MR + epilepsy. The HRQOL scored by paediatric patients themselves are shown in Figure 2. Similarly, the EQ-5D scores were lowest among four of the seven health conditions in which patients could respond i.e., meningitis, bacteremia, pneumonia and epilepsy. Likewise, the HUI3 scores were lowest in the remaining three conditions. We ran a factor analysis for the mean of each measure on each health condition. Two factors were identified in both caregiver and patient data sets. In both groups, the first factor included meningitis, bacteremia, pneumonia, chronic lung disease and epilepsy. The second factor had less consistent components. The total variances of these means explained by the two factors were 94% in caregivers and 98% in patients.

Table 3 illustrates the source of variation in HRQOL scores in the two data sets. Using data from the complete sets, variation within the same patient-caregiver pair was small and not significant ($P = 0.59$). Variation contributed by difference in the health conditions and instruments were highly significant in both data sets. When accounting for interaction between the health conditions and instruments, the P was small indicating that both health conditions and instruments were not acting independently from each other.

Table 4 shows the breakdown of differences within caregiver-patient sets by health condition and instruments. HRQOL reported by paediatric patients were slightly and non-significantly higher than those

Table 2 Matrix of scores obtained in paediatric patients and caregivers using 4 HRQOL instruments ($N = 74$)

	Scores from caregiver			Scores from patient			
	HUI3	EQ-5D	EQ-VAS	HUI2	HUI3	EQ-5D	EQ-VAS
Scores from caregiver							
HUI2	0.84	0.63	0.43	**0.58**	0.57	0.56	0.20[a]
HUI3		0.69	0.50	0.58	**0.67**	0.59	0.24
EQ-5D			0.55	0.40	0.44	**0.77**	0.49
EQ-VAS				0.11[a]	0.20[a]	0.40	**0.50**
Scores from patient							
HUI3				0.89			
EQ-5D				0.59	0.58		
EQ-VAS				0.11[a]	0.16[a]	0.37	

Values in bold correspond to the correlation coefficients of the scores between the patients and the caregivers using the same instruments. [a]The correlation is found to be non-significant ($P > 0.05$).

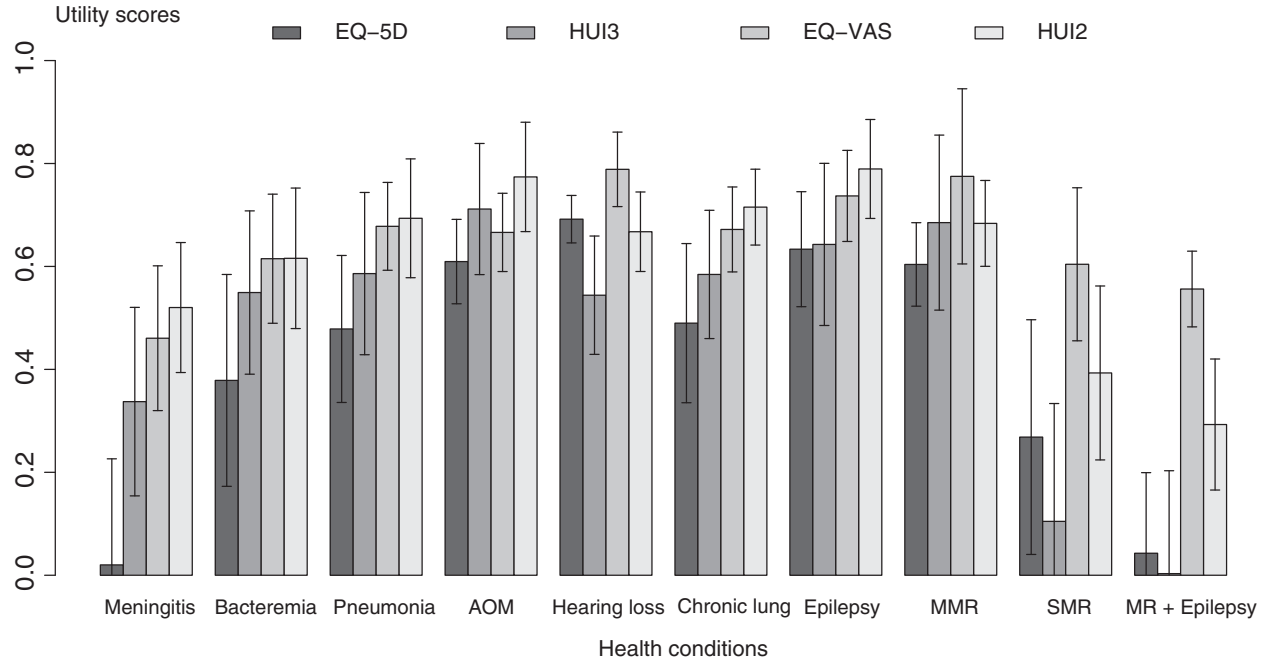

Figure 1 Mean scores and 95% CI obtained in caregivers using 4 HRQOL instruments (proxy-assessment).

reported by caregivers. The only significant difference detected within the pairs was for hearing loss using HUI3 and chronic lung disease using EQ-5D.

Discussion

This is the first study considering methodological aspects of children's HRQOL instruments in the Thai context and results of this study can be useful for guiding future economic evaluations or outcome studies in this and other settings. In this analysis, we address two major methodological issues concerning the use of caregivers as proxies for children's HRQOL measures, and the use of different HRQOL instruments across health conditions in young patients.

The variation in HRQOL derived from patients compared to their caregivers

We observed disparity in HRQOL derived from young patients and caregivers using all instruments, and the mean of differences exceeded 0.03, a difference that has been considered to be clinically significant by previous investigators [7,9,29]. Likewise, the data in Table 4

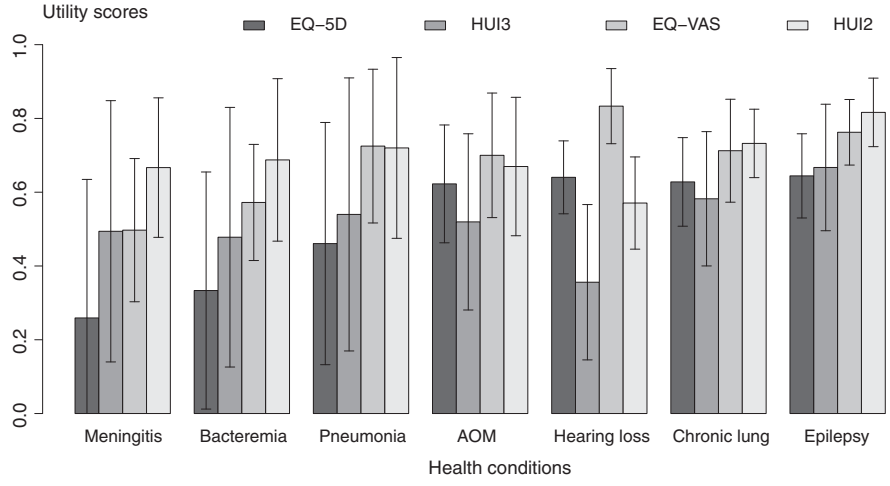

Figure 2 Mean scores and 95% CI obtained in paediatric patients using 4 HRQOL instruments (self-assessment).

Table 3 Comparison of mean scores by sources

	Df	SS	MS	F	P-value
From caregivers and patients complete sets					
Assessor	1	0.02	0.02	0.28	0.59
Health condition	6	4.02	0.67	9.57	<0.001
Instrument	3	3.85	1.28	18.31	<0.001
Health condition : instrument	18	2.99	0.17	2.49	<0.001
Residuals	581	40.66	0.07		
From sets with caregivers only					
Health condition	9	15.29	1.70	27.38	<0.001
Instrument	3	3.51	1.05	16.92	<0.001
Health condition : instrument	27	3.12	0.12	1.86	<0.01
Residuals	652	40.47	0.06		

suggest that the difference between patients and caregivers was in the majority of health conditions of a magnitude which would be regarded as clinically meaningful though not statistically significant (except for hearing loss and chronic lung disease using particular instruments). The largest gap was found in hearing loss. Health conditions relating to sensory impairment such as hearing loss might be more challenging in proxy-assessment than objective measures such as mobility.

The variation in HRQOL scores derived from patients compared to their caregivers was also associated with HRQOL instruments. The HUIs and EQ-5D scores had good correlation within patient-caregiver pairs, a finding that is also compatible with other studies [14,30,31]. The degree of caregiver-patient correlation in the HUI3 was higher than in the HUI2 in our study. The EQ-VAS in both patients and caregivers had the lowest correlation with other measures. This may be because the EQ-VAS involves a different task (valuation of health state) whereas for the other three measures the respondents were asked to describe their own or the child's health state.

The use of different HRQOL instruments across health conditions in young patients

As would be expected, all instruments offered different HRQOL scores for the same health condition. For both self- and proxy-assessment, the EQ-VAS and HUI2 gave

Table 4 Mean of difference of scores between caregivers and paediatric patients

			Mean of difference			
Health conditions		***N***	**HUI2**	**HUI3**	**EQ-5D**	**EQ-VAS**
Meningitis		7	−0.07	−0.07	−0.27	0.05
	(95%CI)		(−0.17 to 0.03)	(−0.21 to 0.07)	(−0.58 to 0.05)	(−0.09 to 0.20)
Bacteremia		9	0.05	0.13	0.08	0.01
	(95%CI)		(−0.15 to 0.24)	(−0.18 to 0.44)	(−0.13 to 0.29)	(−0.19 to 0.21)
Pneumonia		8	−0.08	−0.02	−0.05	−0.05
	(95%CI)		(−0.22 to 0.07)	(−0.13 to 0.10)	(−0.15 to 0.05)	(−0.28 to 0.17)
AOM		7	0.05	0.07	−0.08	−0.06
	(95%CI)		(−0.09 to 0.19)	(−0.09 to 0.24)	(−0.20 to 0.04)	(−0.23 to 0.11)
Hearing loss		15	0.14	0.24	0.08	0.01
	(95%CI)		(−0.01 to 0.28)	(0.03 to 0.46)[a]	(−0.03 to 0.19)	(−0.12 to 0.14)
Chronic lung		12	0.00	0.03	−0.11	−0.03
	(95%CI)		(−0.11 to 0.12)	(−0.09 to 0.14)	(−0.22 to −0.00)[a]	(−0.16 to 0.09)
Epilepsy		16	−0.01	0.00	−0.00	−0.02
	(95%CI)		(−0.08 to 0.07)	(−0.11 to 0.12)	(−0.06 to 0.06)	(−0.10 to 0.06)
Overall		**74**	**0.03**	**0.05**	**−0.03**	**−0.02**
	(95%CI)		**(−0.02 to 0.07)**	**(−0.00 to 0.11)**	**(−0.07 to 0.02)**	**(−0.06 to 0.02)**

[a]Statistically significant ($P < 0.05$) different utility score for caregivers compared with patients.

the highest scores whereas the EQ-5D and HUI3 tended to provide the lowest. The EQ-5D yielded the lowest HRQOL scores compared to other instruments in acute diseases, whereas the HUI3 provided the lowest score in most of chronic conditions. These findings are consistent with two other studies [10,32]. Our study, however, found that for epilepsy the HRQOL score was the lowest using the EQ-5D, as opposed to HUI3 in another study [10]. It is noteworthy that the Thai algorithm used for EQ-5D was derived from the Time Trade-Off (TTO) technique, whereas HUI scoring function was obtained from the Standard Gamble (SG) technique and VAS. This difference might influence the results because previous studies indicated that TTO produced lower utility scores than SG in Asian and other population groups [33-36]. Moreover, the absence of a Thai specific scoring function for HUIs could have affected the results as people in different countries are likely to have different health state preferences [32].

The EQ-5D in particular may not be sufficiently sensitive for measuring HRQOL in patients with sensory impairment as it does not include a sensory dimension [32,37-39]. SG and TTO have been used to measure utility directly in hearing impaired persons [40]. The SG and TTO, however, are time-consuming and conceptually challenging. Furthermore, the HUI3 has proven to be valid and acceptable for measuring HRQOL in hearing impaired populations [10,32,37-39,41]. For health conditions associated with sensory impairment, therefore, self-reported assessment of health status using the HUI3 is the optimal choice. The EQ-VAS score obtained from patients and caregivers is similar, yet correlation between scores rated by this and other instruments was low. Furthermore, given the general difficulties in using the EQ-VAS in people who may not understand its quantitative properties [33,42,43], it may not be appropriate for very young patients. This was supported by a prior study showing that 13% of adult patients found it difficult to use [43].

In addition, the degree of correlation between instruments is used to examine their agreement (convergent validity). The HUIs and EQ-5D scores had a moderate to high correlation within the same subject, confirming findings from previous studies [44-46]. The HUI2 and HUI3 had very high correlation; this is mainly because there is much duplication in these tools (30 of 40 questions in HUI23 are identical). The HUI3 is claimed to be superior to the HUI2 as it was developed to improve structural independence so that each domain would yield specific information [24,47].

Study limitations

In addition to the limitation of incomplete pairs of patient-caregiver sets, another methodological concern is the fact that subjects were recruited at tertiary hospitals where patients are likely to be in an acute phase of their illness and the impact on certain HRQOL dimensions such as mobility may not be readily apparent. We argue that this did not introduce a substantial bias since patients in most of our pre-specified conditions are usually hospitalized. The shortcoming may be more serious in health states associated with chronic disability as patient and proxy assessment of their HRQOL once back home may be different from when they are hospitalized [48]. Lastly, although this study selected patients with a single condition, there may have been co-morbidities that were undiagnosed during data collection that may have influenced HRQOL scores.

Conclusions

Our data imply that use of caregivers as proxies for measuring HRQOL in young patients affected by pneumococcal infection and its sequelae should be employed with caution. Given the high correlation between instruments, each of the HRQOL instruments appears acceptable apart from the EQ-VAS which exhibited low correlation with the others. For conditions associated with sensory impairment we would recommend the use of HUI3 due to its explicit inclusion of this dimension.

Abbreviations

HRQOL: Health-related quality of life; QALYs: Quality-adjusted life years; HUI2: Health Utilities Index Mark 2; HUI3: Health Utilities Index Mark 3; EQ-5D: EuroQoL Descriptive System; VAS: Visual Analogue Scale; TTO: Time Trade-Off; SG: Standard Gamble; CUA: Cost-utility analysis; AOM: Acute otitis media; MR: Mental retardation; MMR: Mild mental retardation; SMR: Severe mental retardation; MR + epilepsy: Mental retardation combined with epilepsy; CI: Confidence interval; SD: Standard deviation; *r*: Correlation coefficient.

Competing interests

The authors declare that they have no completing interests.

Authors' contributions

WK, VS, VC, JC and YT contributed to conception and study design. WK and VC analyzed and interpreted data. WK drafted the manuscript. All authors contributed to the analysis and revised the manuscript. All authors read and approved the final manuscript.

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Assessing key model parameters for economic evaluation of pandemic influenza interventions: the data source matters

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Background In our previous systematic review of economic evaluations of pandemic influenza interventions, five model parameters, namely probability of pandemic, duration of pandemic, severity, attack rate, and intervention efficacy, were not only consistently used in all studies but also considered important by authors.

Objectives Because these parameters originated from sources of varying quality ranging from experimental studies to expert opinion, this study aims to analyze the variation in values used according to sources of information across studies.

Methods An analysis of estimated values of key parameters for economic modeling was performed against their different data sources, following the standard hierarchy of evidence.

Results A lack of good-quality evidence to estimate pandemic duration, pandemic probability, and mortality reduction from antiviral treatment results in a large variation of values used in economic evaluations. Although there are variations in quality of evidence used for attack rate, basic reproduction number, and reduction in hospitalizations from antiviral treatment, the estimated values do not vary significantly. The use of higher-quality evidence results in better precision of estimated values compared to lower-quality sources.

Conclusion Hierarchies of evidence are a necessary tool to identify appropriate model parameters to populate economic evaluations and should be included in methodological guidelines. Knowledge gaps in some key parameters should be addressed, because if good-quality evidence is available, future economic evaluations will be more reliable. Some gaps may not be fulfilled by research but consensus among experts to ensure consistency in the use of these assumptions.

Keywords costs and cost analysis, disease outbreaks, economic evaluation models, human influenza, model parameters, review.

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Background

The H5N1 and pH1N1 outbreaks that occurred in recent years directed international attention toward the cost-effectiveness of interventions aiming to prevent and control pandemic influenza. As a result, and part of its Public Health Research Agenda for Influenza, the World Health Organization (WHO) commissioned the Health Intervention and Technology Assessment Program (HITAP) of Thailand to conduct a systematic review of preparedness strategies and interventions against pandemic influenza, published in early 2012.[1] By offering a comprehensive framework for efficient allocation of resources – a tool that was lacking until then – the study intended to serve as a reference for the future revision of the WHO pandemic preparedness and response guidance.[2]

In our study, we searched relevant databases as well as screened references and contacted authors up to September 2011. Eligible papers were full and partial economic evaluations including both costs and outcomes, while editorials, reviews, and papers on economic impact or complications were excluded. We selected a total of 44 evaluations for the review. Although in general the methods applied were appropriate, we detected important shortcomings in the quality of evidence used. There were also considerable variations in drug regimens and vaccination protocols. In summary, pharmaceutical interventions ranged from cost-saving to high cost-effectiveness ratios. Combinations of pharmaceutical and non-pharmaceutical interventions were cost-effective compared with vaccines and/or antivirals alone. Reduction in contacts, prevention with antivirals together with school closure demonstrated to be especially

cost-effective for all countries. In contrast, quarantine for household contacts was cost-ineffective in all settings. Finally, we provided recommendations on practical issues necessary to improve the quality and generalizability of economic evaluation studies in the future. In particular, we underlined the importance of five model parameters (i.e., probability of pandemic, duration of pandemic, severity, attack rate, and intervention efficacy/effectiveness) that were not only consistently employed in all evaluations but also considered important by study authors.

In this study, our purpose is to describe and analyze the variation in key parameter values employed according to sources of information across studies. These key parameters originate from different sources of varying quality ranging from experimental studies to expert opinion. An investigation into this variation is warranted, with the aim to promote the reaching of consensus on certain important parameters used for future economic evaluations and identify future priority research areas.

Methods

We conducted a descriptive analysis of five key parameters for economic modeling of pandemic influenza interventions. The identified parameters were cross-tabulated against the different data sources, following the hierarchy developed by Cooper *et al.*[3] In this hierarchy, different data sources are assessed according to their level of quality: a) clinical effect sizes, b) adverse events and complications, c) baseline clinical data, d) resource use, e) costs, and f) utilities (only in cost utility analyses). Parameter sources are given a rank from 1–6 and 9 in descending order, with rank 1 applied to parameters derived from the best quality sources. In summary, in the case of clinical effect sizes/adverse events and complications, rank 1 is given to meta-analyses of randomized controlled trials (RCTs) or RCTs that directly evaluate comparator interventions and quantify final outcomes; rank 2 is given to similar designs but measuring surrogate outcomes or using placebo as a comparator while measuring final outcomes for each intervention; rank 3 is applied to meta-analyses or RCTs that use placebo as comparator and measure surrogate outcomes; rank 4 is given to observational studies; rank 5 to non-analytic studies; and, finally, rank 6 and 9 are given to expert opinion and cases where the source is not clear, respectively. In the case of baseline clinical data, rank 1 is given to purposely conducted case series/analyses of dependable databases including patients from the study setting; rank 2 is given to similar studies that were conducted recently; rank 3 is given to similar studies conducted recently in a different setting; rank 4 is given when these studies are old or the estimates are derived from RCTs; rank 5 is given to estimates retrieved from other economic evaluations; and ranks 6 and 9 are given in the same fashion as for clinical effect sizes/adverse events and complications.

Results

Key parameters related to baseline clinical data

Figure 1 illustrates the variation of means of the parameters for attack rate, basic reproduction number (R_0), pandemic probability, and pandemic duration. The graph clearly demonstrates a lack of high-quality evidence for pandemic probability and pandemic duration, because authors of all reviewed papers derive these parameters from previous economic evaluations, expert opinion, or unclear sources.

For pandemic duration, there is only one study using data from a previous economic evaluation of antiviral stockpiling in Singapore, which estimates pandemic duration at 12 weeks.[4] In six studies that estimate pandemic duration from expert opinion, the value varies from 15 to 43 weeks. Regarding pandemic probability, although most studies apply the common belief that a pandemic is expected to occur every 30 years, there is one study where the estimate is unexpectedly five years.[5]

In the cases of attack rate and R_0, authors of the reviewed studies select evidence from a wide array of data sources ranging from recent cases series/analyses of reliable administrative databases to expert opinion. Although higher-quality sources tend to provide less variation in estimates, there are not considerable differences in absolute values used.

Key parameters related to clinical effect sizes

As for pharmaceutical interventions, there is a knowledge gap in the value of antiviral efficacy measured as mortality reduction, with all six studies using parameters derived from expert opinion or unclear sources (Figure 2). This is not the case for the estimates of antiviral efficacy measured as reduction in hospitalizations, where authors employ a broader range of data sources. In the studies, the absolute values are also similar. For vaccine efficacy, the variations in estimates observed are large, especially evident in seven studies where authors use expert opinion or estimated from other sources, for example one study based on previous pandemics[6], one study based on seasonal influenza[7], and five additional studies where the source of the estimates is unclear.[5,8–11]

To assess the effect of the 2009 pandemic on the quality of evidence used in economic evaluation studies, Figure 3 compares the ranking of each parameter in studies conducted before and after the 2009 pandemic. Even though the number of studies is small, the 2009 pandemic seems to provide a positive benefit to the quality of evidence used for two of the parameters, namely attack rate and R_0, but not for the other parameters.

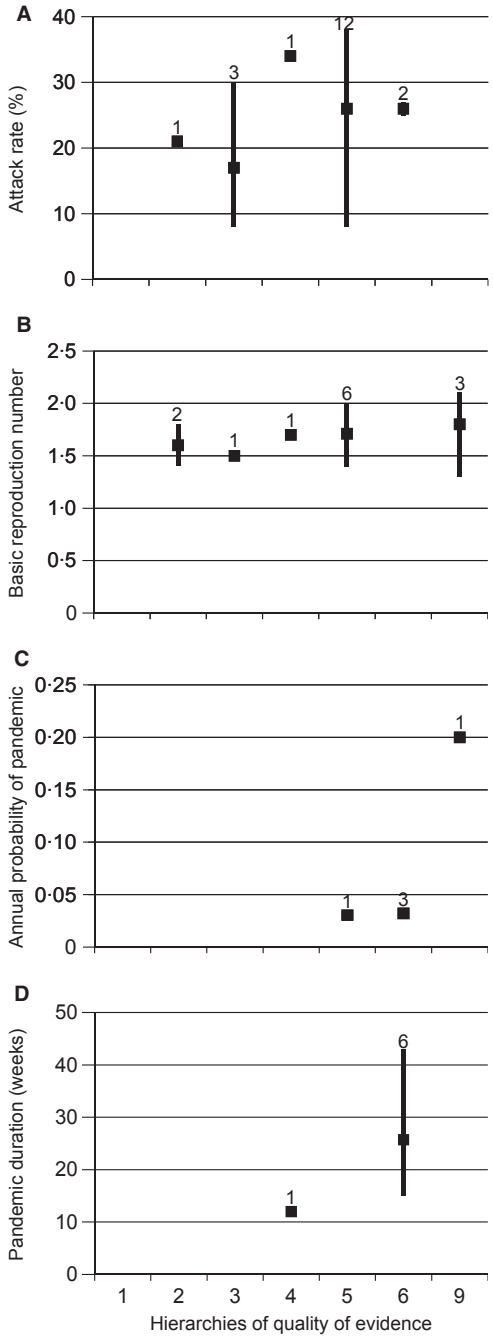

Figure 1. Hierarchy of quality of evidence for pandemic duration, probability of pandemic, basic reproduction number, and attack rate parameters. Vertical lines represent the range of values. Square boxes represent average values. The numbers above each line are the number of studies. The hierarchy of evidence is based on Cooper *et al.*[3]

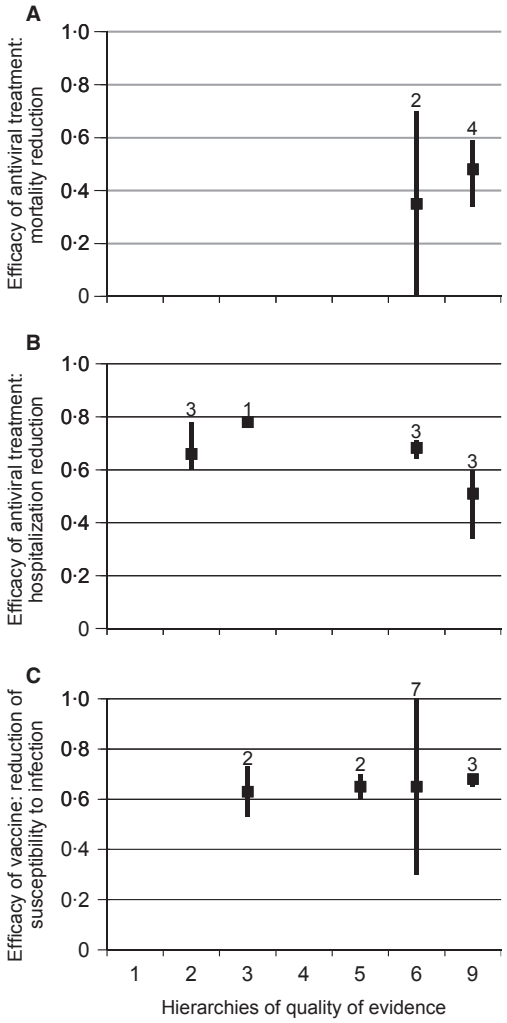

Figure 2. Hierarchy of quality of evidence for intervention efficacy parameters. Vertical lines represent range of values. Square boxes represent average values. The numbers above each line are the number of studies. The hierarchy of evidence is based on Cooper *et al.*[3]

Discussion

From our analysis, we identified an important knowledge gap in three key parameters necessary for economic evaluation studies of pandemic influenza preparedness strategies and interventions. This includes pandemic duration, pandemic probability, and mortality reduction from antiviral treatment. Because there is no high-quality evidence for these parameters, resulting both in a large variation of estimated values used and a high impact on economic evaluation results, this will ultimately hinder cross-study comparisons of economic information to guide policy decisions.

In the cases of attack rate, R_0, and reduction of hospitalizations from antiviral treatment, there are not large variations in values used. This may be because there is already high-quality evidence available and that most experts are aware of the existing evidence. For example, because there were two studies conducted by Khazeni *et al.*[12] and Tuite *et al.*[13] that analyzed information from U.S. and Canadian administrative databases[14] to estimate R_0, and economic

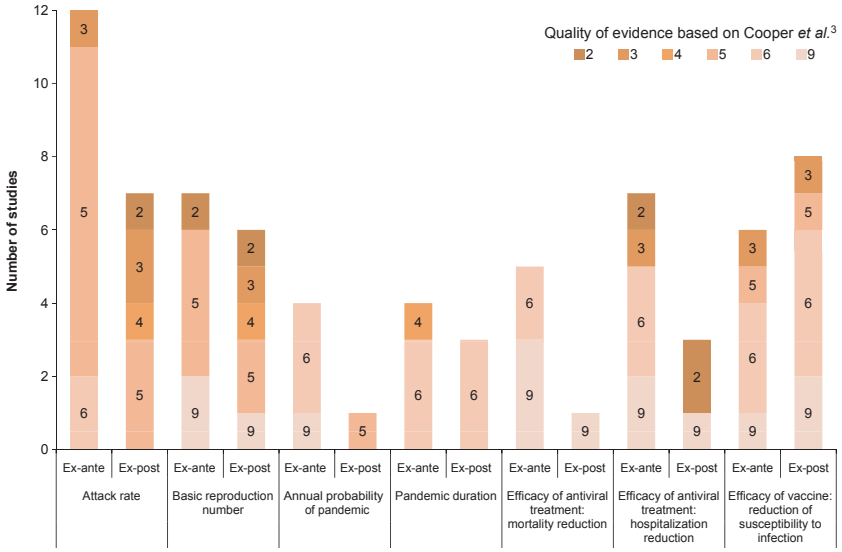

Figure 3. Comparison of number of studies according to quality of evidence between ex-ante and ex-post studies. Ex-ante = before the 2009 H1N1 pandemic; Ex-post = after the 2009 H1N1 pandemic. The hierarchy of evidence is based on Cooper *et al.*[3]

evaluations conducted after that year employed an estimate that did not differ significantly from the results of those two studies. Even in three other studies published more recently in 2009[15], 2010[16], and 2011[17], which derived the value of R_0 from the authors' own assumptions, we found these estimates comparable to the results from the two studies mentioned above.[13,14]

There are some limitations in this study. As this study was derived from a systematic review completed in September 2011, studies published later are not included. Nonetheless, an update of our search strategy in MEDLINE/PubMed covering from September 2011 to September 2012 indicates that, although the scope of settings and interventions has broadened, there are few eligible additional economic evaluations[18–21] and most of the studies are cost analyses.[22–25] We believe that our results are still valid even though these new studies are not included. Moreover, we only reviewed economic evaluation studies and, therefore, can only capture the data sources selected by these studies. If there is better-quality evidence available but not used in these reviewed studies, it is not included in our analysis. Lastly, we employed a hierarchy of evidence developed for health economic evaluations of general diseases. However, pandemic influenza is not a disease where the past is a reliable guidance for the future. Hence, the hierarchy may not always be relevant for all parameters. For example, results from genetic studies that are not population-based may be more reliable in giving an indication of how a pandemic flu strain may drift and attenuate over time than observational studies of the past pandemic.

Recommendations

Firstly, we found that hierarchies of evidence are a necessary tool to help identify appropriate model parameter estimates to populate economic evaluations. Research funders and health economic evaluation methodological guideline developers should request that researchers select the highest quality data sources as possible according to standard hierarchies of evidence.

Secondly, we also identified a knowledge gap in some key parameters that should be addressed by funders of responsible agencies, who should include them in future research programs. This is because future economic evaluations will tend to have less variation in values of parameters used (e.g., the case of R_0), if good-quality evidence is available and utilized.

Finally, it may not be possible to fill some evidence gaps (i.e., pandemic probability and duration) by research and these will need to be addressed by reaching consensus among experts to ensure a better consistency in the use of these assumptions, so that future economic evaluations can be comparable and meaningful for guiding resource allocation decisions.

Acknowledgements

The authors would like to thank the researchers who provided information on grey literature, especially those who shared their papers. In addition, we are grateful to the WHO Global Influenza Program for funding the previous systematic review on which this paper is based and for inviting us to publish in this supplement.

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Conflict of interest

The authors have declared that no competing interests exist.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Hierarchies of data sources according to quality of evidence (adapted from Cooper *et al.*).

Table S2. Model parameters of infectivity and disease severity values with quality of evidence (QoE) ranking of reviewed studies.

Table S3 Model parameters of intervention effectiveness values with quality of evidence (QoE) ranking of reviewed studies.

Table S4 Model parameters of pandemic duration and probability values with quality of evidence (QoE) ranking of reviewed studies.

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FULL-LENGTH ORIGINAL RESEARCH

Economic evaluation of HLA-B*15:02 screening for carbamazepine-induced severe adverse drug reactions in Thailand

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Summary

Purpose: There is strong evidence of an association between the presence of the human leukocyte antigen (HLA)-B*15:02 and two severe adverse drug reactions—Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)—in patients taking carbamazepine (CBZ), a common treatment for patients with epilepsy and neuropathic pain. As a result, there are calls for all patients that are due to undergo CBZ therapy to be screened for this genetic marker before commencing their therapy. This study aims to determine the value for money of HLA-B*15:02 screening compared to the following: (1) administering CBZ therapy without conducting patient screening, and (2) not prescribing CBZ but alternative drugs that are less likely to result in severe reactions, but that come at a higher cost.

Method: An economic evaluation was carried out by using a decision tree and Markov models to examine the cost-utility of providing HLA-B*15:02 screening for all patients with either newly diagnosed epilepsy or neuropathic pain in the Thai setting. All transitional probabilities were derived from the national and international literature. The majority of the data on direct medical care costs were collected from 10 community, provincial, and regional hospitals throughout Thailand. Direct non-medical cost and health-related quality of life (HRQoL) data were obtained from interviews that were conducted with 33 patients, some of whom had experienced severe drug reactions.

Key Findings: The incremental cost-effectiveness ratio (ICER) of adopting a universal HLA-B*15:02 screening policy was estimated at 222,000 Thai baht, THB/quality-adjusted life year (QALY) gained for epilepsy patients and 130,000 THB/QALY gained for patients with neuropathic pain. Furthermore, we found that 343 patients need to be tested for HLA-B*15:02 allele to prevent one case of SJS/TEN.

Significance: Universal HLA-B*15:02 screening represents good value for the money in terms of preventing SJS/TEN in CBZ-treated patients with neuropathic pain at the Thai ceiling ratio of 120,000 THB/QALY gained. However, the prevalence of CBZ-induced SJS/TEN in the Thai population and the positive predictive value (PPV) are major factors that influence the cost-effectiveness of HLA-B*15:02 screening. Therefore, an active surveillance system to make a more accurate assessment of the prevalence CBZ-induced SJS/TEN in the Thai population would enhance the generalizability of the results.

KEY WORDS: Cost-utility analysis, HLA-B*15:02, Stevens-Johnson syndrome, Toxic epidermal necrolysis.

According to national and global pharmacovigilance systems, the most common adverse drug reactions (ADRs) are cutaneous. The most severe life-threatening forms of cutaneous ADRs are Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), two related acquired bullous disorders of the skin that, in the majority of cases, are caused by reactions to certain drugs, such as sulfonamide-antibiotics, antiepileptic agents—especially carbamazepine (CBZ), allopurinol, and oxicam-type nonsteroidal antiinflammatory drugs (NSAIDs) (Harr & French, 2010). Incidence rates for SJS/TEN vary according to ethnicity, and the highest rates are seen among Han Chinese, Malays, and Thais (Lim et al., 2008).

CBZ is the primary treatment choice for patients with epilepsy and neuropathic pain according to current Thai

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clinical practice guidelines (National Drug Committee, 2008; Thai Association for the Study of Pain, 2008; The Epilepsy Society of Thailand, Prasat Neurological Institute, 2011). As such, many doctors are forced to make a difficult choice—they can either prescribe patients CBZ treatment, with the knowledge that it brings with it high risk of SJS/TEN (Health Product Vigilance Center, 2011a), or they can prescribe a less effective and more expensive treatment. Evidence suggests that host genetics play an important role in determining the probability of developing SJS/TEN reactions to certain drugs (Chung et al., 2004; Hung et al., 2005; Chantarangsu et al., 2009; Chen et al., 2011). In 2004, HLA-B*15:02 was the first genetic marker identified for predicting CBZ-induced SJS/TEN in Taiwanese patients.

Since the initial discovery of HLA-B*15:02 and CBZ-induced SJS/TEN, this association has been confirmed in a number of other Asian populations. For instance, in South East Asian populations and Southern Chinese populations, where HLA-B*15:02 carriers are relatively common (>10% for carriers in the population and >5% for minimal allele frequency), this association was also demonstrated. However, in countries where the proportion of the population who are HLA-B*15:02 carriers is low, such as Japan and Korea, the association has not been found (McCormack et al., 2011). This is also true for European nations, where carriers of HLA-B*15:02 are also relatively rare (McCormack et al., 2011). As a result of these studies, the U.S. Food and Drug Administration (FDA) now recommends that HLA-B*15:02 screening be conducted for all patients of Asian descent before undergoing CBZ treatment. Moreover, the screening for HLA–B*15:02 is covered under the National Health Insurance system in Taiwan (Chantratita et al., 2011).

At present in Thailand, allele-specific genotyping for HLA-B*15:02 is currently available through nine regional centers of the laboratory network of the National Institute of Health (NIH) at the Department of Medical Sciences (DMSc) and at a number of medical school laboratories. Despite the availability, a universal HLA-B*15:02 screening policy for patients due to undergo CBZ therapy is not yet in place in Thailand. To decide whether screening should be conducted universally, an economic evaluation study is required to help policy makers assess the value for money of universal HLA-B*15:02 screening compared to (1) the current practice, in which patients receive no HLA-B*15:02 screening before undergoing CBZ treatment, and (2) prescribing drugs other than CBZ that have a lower risk of triggering severe reactions but are more expensive. The results of the study will be submitted to the Subcommittee for Development of the Benefit Package and Service Delivery (SCBP)—the coverage decision authority responsible for issuing recommendations on whether HLA-B*15:02 screening should be offered to individuals who are eligible under the health benefit package of the Universal Coverage Scheme (UC).

Methods

Overview of potential strategies

Current practice

In Thailand, patients with either newly diagnosed epilepsy or neuropathic pain commonly commence their treatment with CBZ because it is an effective and inexpensive drug (1.39 Thai baht [THB] per tablet) (Center of Essential Information for All Health Officers, 2011) that is widely available at all types of hospital throughout the country. However, these patients usually commence their CBZ without first undergoing screening for HLA-B*15:02. The standard World Health Organization (WHO)–recommended defined daily dose for CBZ is 1 g for both patients with epilepsy and neuropathic pain (The WHO Collaborating Centre for Drug Statistics Methodology, 2012). Although the majority of patients with epilepsy require life-long treatment, clinicians have indicated that this is likely to be unnecessary for most patients in the Thai setting (Rattanavipapong et al., 2012a), where the average treatment duration for epilepsy is about 4 years. These findings are similar to those found in Taiwan (Hu et al., 2011). However, we did assess the value for money of providing lifetime treatments for patients with epilepsy. For patients with neuropathic pain, the average treatment duration in the Thai setting was found to be 2 years (Rattanavipapong et al., 2012a).

*Universal HLA-B*15:02 screening*

Because CBZ-induced SJS/TEN has been found to be associated with the presence of the HLA-B*15:02 allele (Locharernkul et al., 2008; Tassaneeyakul et al., 2010), the provision of HLA-B*15:02 screening prior to starting treatment with CBZ should serve as a useful pharmacogenetic test. At present, screening is available to anyone who can afford it (at a cost of 1,000 THB, according to the DMSc price). However, there are growing calls for HLA-B*15:02 screening to be publicly funded and alternative treatment options offered for those who test positive for HLA-B*15:02.

*Prescribing alternative drugs without screening for HLA-B*15:02*

To prevent CBZ-induced SJS/TEN, patients can be prescribed alternative drugs at the outset of treatment, thereby removing the need for HLA-B*15:02 screening. As recommended by the Thai Clinical Practices Guidelines and an expert consultation meeting, sodium valproate (VPA) and gabapentin (GBP) are suitable alternative treatments for patients with epilepsy and neuropathic pain, respectively (Rattanavipapong et al., 2011; The Epilepsy Society of Thailand, Prasat Neurological Institute, 2011). The standard dosage regimen for VPA is 1.5 g per day at a cost of 12.66 THB per 500 mg tablet (Center of Essential Information for All Health Officers, 2011; The Epilepsy Society

of Thailand, Prasat Neurological Institute, 2011; The WHO Collaborating Centre for Drug Statistics Methodology, 2012). The standard dosage regimen for GBP is 1.2 g a day at a cost of 8 THB per 300 mg tablet (Thai Association for the Study of Pain, 2008; Center of Essential Information for All Health Officers, 2011; Moore et al., 2011; Rattanavipapong et al., 2012a).

Analyses and model

Model-based economic evaluations consisting of a decision tree and a Markov model were constructed for the Thai context using the societal perspective. Two separate models were constructed—one for patients with newly diagnosed epilepsy and one for patients with newly diagnosed neuropathic pain. These models were used to evaluate the costs and consequences of each strategy, by following the same adult cohort (made up of individuals aged 20 years or older) for all strategies. The lifetime time horizon was used with a cycle length of 1 year. The primary outcomes of interest were lifetime costs, quality-adjusted life-years (QALYs) gained, and the incremental cost-effectiveness ratio (ICER) in THB per QALY gained.

The decision tree model (Fig. 1) imitated the three potential strategies for treating patients with epilepsy or

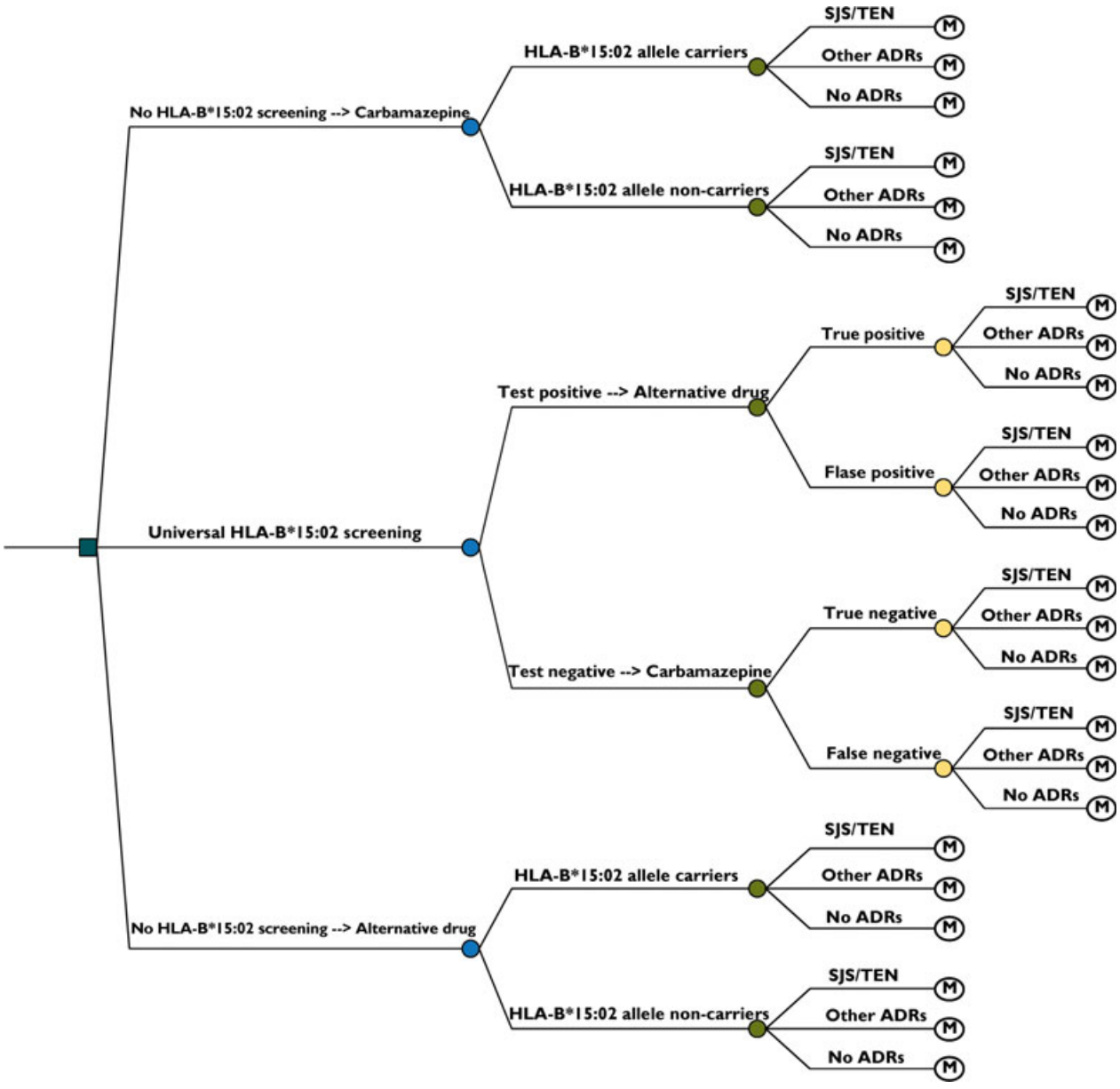

Figure 1.
Decision tree model showing the three practical strategies for epilepsy or neuropathic pain treatment with carbamazepine.
Epilepsia © ILAE

neuropathic pain. In the first strategy, patients started CBZ without HLA-B*15:02 screening (reflecting current practice). In the second strategy, all patients were tested for the HLA-B*15:02 allele, and patients who tested positive for HLA-B*15:02 allele were prescribed the alternative drugs, whereas patients who tested negative received CBZ. In the third strategy, patients were given alternative drug treatments and did not undergo HLA-B*15:02 screening. For all patients—whether they received CBZ or alternative drugs—there were three possible outcomes: (1) the development of SJS/TEN, (2) the development of other ADRs without SJS/TEN, and (3) no development of ADRs.

A Markov model (Fig. 2) was used to predict the lifetime costs and outcomes of each outcome that occurred after taking CBZ or alternative drugs. As shown in Figure 2A, there are four possible health scenarios for patients who develop SJS/TEN: (1) patients develop SJS/TEN, which may or may not lead to complications during hospitalization; (2) patients recover but experience sequelae such as blindness; (3) patients recover without any complications; and (4) patients die from SJS/TEN or other causes, such as diseases and accidents. Patients who develop other ADRs could move to a state of recovery or death in the next cycle, as shown in Figure 2B, whereas patients who do not develop any ADRs could remain in this state or could die from other causes, as shown in Figure 2C. All parameters used in the analysis are presented in Table 1 and discussed further in the model parameter sections. The Monte Carlo simulation was used to model costs and outcomes over a lifetime period. All costs and outcomes occurring after 1 year were discounted at a rate of 3%, as recommended in the health technology assessment guidelines of Thailand (Permsuwan et al., 2008).

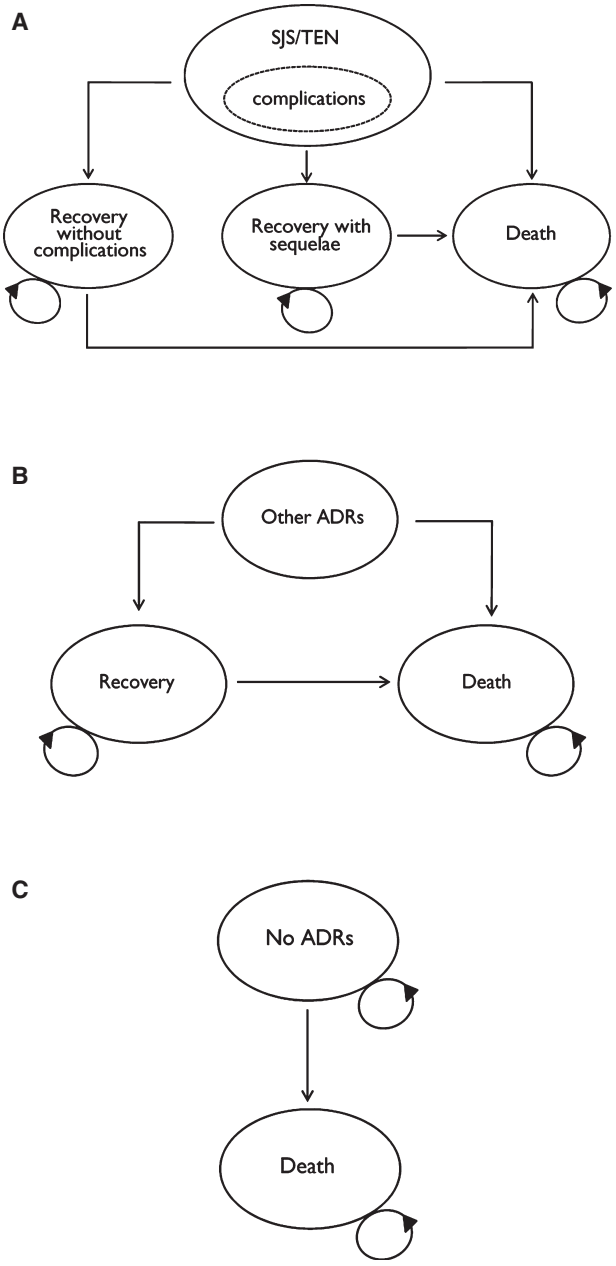

Figure 2.
(**A**–**C**) Markov model representing the three events that could occur for patients after treatment by carbamazepine or alternative drugs. Each event shows all health states in each cycle. It is possible to transit to another health state with transitional probability as shown by the arrows. (**A**) Patients who developed SJS/TEN after receiving drugs. (**B**) Patients who developed other ADRs after receiving drugs. (**C**) Patients who did not developed any ADRs after receiving drugs.
Epilepsia © ILAE

Model parameters

Health state transitional probabilities

Transitional probabilities between health states were obtained from published studies and primary data. The prevalence of HLA-B*15:02 allele carriers in the Thai population was derived from our own meta-analysis of national studies (Kupatawintu et al., 2010; Romphruk et al., 2010). We conducted an analysis of the Health Product Vigilance Center (HPVC) database of the Thai Food and Drug Administration (TFDA) from 2006 to 2011 (Health Product Vigilance Center, 2011b), to acquire the probability of patients developing SJS/TEN, sequelae, or other ADRs from either CBZ or alternative drugs. The age-adjusted mortality rate for the general population was taken from the Thai Burden of Disease and Injury Study in Thailand (The Thai Working Group on Burden of Disease and Injuries, 2004).

Intervention effectiveness

The PG 1502 test (PharmiGene, Inc., Taipei, Taiwan) was used to detect the presence of the HLA-B*15:02 allele; this has been approved by Taiwan's Department of Health as a recommended in vitro diagnostic (IVD) test. The sensitivity of the test was 100%, and the specificity was 98.7%,

Table 1. Input parameters used in the model

Parameters	Distribution	Mean	SE
Epidemiologic parameter and transitional probabilities			
Prevalence of HLA-B*15:02 allele in the Thai population (Kupatawintu et al., 2010; Romphruk et al., 2010)	Beta	0.155	0.003
Probability of CBZ-induced SJS/TEN in patients testing positive for HLA-B*15:02 allele (PPV) (Tassaneeyakul et al., 2010)	Beta	0.019	0.019
Probability of CBZ-induced SJS/TEN in patients testing negative for HLA-B*15:02 allele (1-NPV) (Tassaneeyakul et al., 2010)	Beta	0.0004	0.0004
Probability of patients developing sequelae	Beta	0.570	0.060
Probability of CBZ-induced other ADRs	Beta	0.032	0.032
Probability of VPA-induced other ADRs	Beta	0.004	0.004
Probability of GBP-induced other ADRs	Beta	0.025	0.025
Probability of death due to CBZ-induced SJS/TEN	Beta	0.002	0.002
Costing parameters (THB per year)			
Epilepsy			
Direct medical cost			
Treatment with CBZ[a]	Normal	4,094	38
Treatment with VPA[b]	Normal	15,477	20
CBZ-induced SJS/TEN[a]	Normal	25,868	192
VPA-induced SJS/TEN[b]	Normal	25,666	189
Treatment of other ADRs (Kankeawlar & Phurmsuwan, 2006)	Gamma	2,319	2,319
Follow-up of sequelae (Thavorncharoensap et al., 2008)[c]	Gamma	1,505	1,505
Direct non-medical cost			
Treatment with CBZ or VPA[a]	Normal	6,431	23
CBZ-induced SJS/TEN[a]	Normal	20,812	199
VPA-induced SJS/TEN[b]	Normal	21,020	202
Treatment of other ADRs (Kankeawlar & Phurmsuwan, 2006; Rattanavipapong et al., 2012b)	Gamma	1,870	1,870
Follow-up of sequelae (Rattanavipapong et al., 2012b)[c]	Gamma	794	794
Neuropathic pain			
Direct medical cost			
Treatment with CBZ[a]	Normal	5,387	36
Treatment with GBP[b]	Normal	14,576	33
CBZ-induced SJS/TEN[a]	Normal	26,970	322
GBP-induced SJS/TEN[b]	Normal	26,885	305
Treatment of other ADRs (Kankeawlar & Phurmsuwan, 2006)	Gamma	2,319	2,319
Follow-up of sequelae (Thavorncharoensap et al., 2008)[c]	Gamma	1,505	1,505
Direct non-medical cost			
Treatment with CBZ or GBP[a]	Normal	3,527	28
CBZ-induced SJS/TEN[a]	Normal	37,230	226
GBP-induced SJS/TEN[b]	Normal	37,608	231
Treatment of other ADRs (Kankeawlar & Phurmsuwan, 2006; Rattanavipapong et al., 2012b)	Gamma	1,870	1,870
Follow-up of sequelae (Rattanavipapong et al., 2012b)[c]	Gamma	794	794
Utility parameters			
Epilepsy			
No ADRs [a]	Beta	0.68	0.003
Develop SJS/TEN[a]	Beta	−0.08	0.002
Recover from SJS/TEN without complication	Beta	0.52	0.003
Recover from SJS/TEN with sequelae (Teerawattananon et al., 2007)[d]	Beta	0.30	0.200
Develop other ADRs[e]	Beta	0.46	0.003
Neuropathic pain			
No ADRs[a]	Beta	0.63	0.003
Develop SJS/TEN[a]	Beta	−0.18	0.002
Recover from SJS/TEN without complication	Beta	0.65	0.003
Recover from SJS/TEN with sequelae (Teerawattananon et al., 2007)[d]	Beta	0.30	0.200
Develop other ADRs[e]	Beta	0.58	0.003

THB, Thai baht; PPV, positive predictive value; NPV, negative predictive value; N/A, not applicable; CBZ, carbamazepine; VPA, sodium valproate; GBP, gabapentin; ADRs, adverse drug reactions; DMSc, the Department of Medical Sciences, Ministry of Public Health.

[a]Analysis of primary data using bootstrap method.

[b]Analysis of primary data collected by the authors.

[c]Because no data are available on the costs of treating SJS/TEN with sequelae, the costs of treating patients with psoriasis, which normally involves the skin, were used instead.

[d]The utility of patients with complete vision impairment was used in this study because there were no available data on the utility of patients with SJS/TEN with sequelae.

[e]Utility of patients with other ADRs is assumed to be 10% lower than the utility of recovered patients from SJS/TEN without complication.

as specified by the manufacturer (Tassaneeyakul et al., 2010). On the basis of previous research, the prevalence rate for CBZ-induced SJS/TEN in the Thai population was set at 0.27%; the positive predictive value (PPV) and negative predictive value (NPV) of HLA-B*15:02 screening were set at 1.92% and 99.96%, respectively (Tassaneeyakul et al., 2010). The PPV was used to indicate the probability of CBZ-induced SJS/TEN occurring in patients who tested positive for the HLA-B*15:02 allele; 1-NPV (0.04%) was used to indicate the probability of CBZ-induced SJS/TEN occurring in patients who tested negative for the HLA-B*15:02 allele.

Cost and utility parameters

Costs and health-related quality of life (HRQoL) data were collected from Thai patients who had been treated with CBZ from 10 community, provincial, and regional hospitals. The case groups comprised patients who were diagnosed by specialists as having CBZ-induced SJS/TEN and who met the inclusion criteria. To minimize recall bias, only patients who had started CBZ treatment for epilepsy or neuropathic pain treatment between 2006 and 2010, when they were 20 years old or older, were included in the dataset. However, patients with conditions that can act as underlying etiologic conditions for SJS and TEN, such as graft-versus-host disease, human immunodeficiency virus (HIV) infection, tuberculosis, and systemic lupus erythematosus (SLE), were excluded from the study. For the control group, patients who had not developed any adverse drug reactions from CBZ were individually matched with patients who had developed SJS/TEN in terms of age, gender, disease, CBZ starting time, and treatment settings. Following this, 15 patients who had developed SJS/TEN were identified as suitable for inclusion in the case (5 of whom had epilepsy) and 18 patients were identified as suitable for the control group (5 of whom had epilepsy). Ethics committee approval was given and the patients gave informed consent.

In the model, costs were defined as (1) direct medical costs—the cost of treating the disease and any ADRs, the cost of follow-up, the cost of screening, outpatient fees, and blood testing fees—all of which were collected from hospital databases, and (2) direct non-medical costs—travel and food costs for patients and their caregivers, personal facility costs, and opportunity costs incurred by patients (e.g., patient time spent on visits to healthcare facilities). These were defined based on information provided during detailed face-to-face interviews with patients. Indirect costs were excluded in order to avoid double-counting, since the effectiveness outcome or QALYs already take into account morbidity and mortality effects (Riewpaiboon, 2008). The medical records of all patients were reviewed to identify the level of health care resource utilization; costs were estimated using a standard costing menu and reference price (Center of Essential Information for All Health Officers, 2011; Riewpaiboon, 2011). All costs were converted to 2011 values using the Thai consumer price index (Bureau of Trade & Economic Indices, 2011). For international comparison, costs were converted into international dollars using the purchasing power parity (PPP) conversion rate, where a PPP 2011 dollar is worth 17.505 THB (The World Economic Outlook Database, 2012).

The mean direct medical costs per year of SJS/TEN treatment induced by CBZ and alternative drugs were 25,868 THB (SE = 192) and 25,666 THB (SE = 189), respectively, in the epilepsy model, versus 26,970 THB (SE = 322) and 26,885 THB (SE = 305), respectively, in the neuropathic pain model. The direct non-medical costs of SJS/TEN treatment induced by CBZ and alternative drugs were 20,812 THB (SE = 199) and 21,020 THB (SE = 202), respectively, in the epilepsy model, versus 37,230 THB (SE = 226) and 37,608 THB (SE = 231), respectively, in the neuropathic pain model.

The QALYs gained from the interventions were measured as health outcomes. The HRQoL results were obtained from face-to-face patient interviews using the EQ-5D-TH questionnaire (The EuroQol Group, 1990; Brooks, 1996; Tongsiri, 2009). All patients were asked about their health state preferences, and these data were then converted to utility scores, which were in turn multiplied by life expectancy to generate QALYs. Detailed information about the means and standard errors of each health state are presented in Table 1. The mean utility score of patients with epilepsy was 0.68 (SE = 0.003), whereas the mean utility score of patients with neuropathic pain was 0.63 (SE = 0.003). The mean utility scores of patients who developed SJS from CBZ decreased dramatically to −0.08 (SE = 0.002) in patients with epilepsy, and −0.18 (SE = 0.002) in patients with neuropathic pain.

The bootstrap method was used to analyze the primary data from both the dataset and control group. This method was chosen because of its suitability for studies with small sample sizes and large variability. The bootstrap technique creates a new sample by randomly sampling individuals with replacements from the original sample, and then computing bootstrap replicates of statistical quantities, such as the sample mean, standard error, and confidence intervals; in most cases, this is based on at least 1,000 bootstrap samples. As a result, the bootstrap method uses simulated data to create large sample sizes, which provides more accurate and reliable estimates (Campbell & Torgerson, 1999; Grunkemeier & Wu, 2004; Walters & Campbell, 2005; Sharma & Kim, 2012). According to the Central Limit Theorem, the sampling distribution will show normal distribution because the sample size is sufficient (Briggs et al., 2006).

Uncertainty analyses

Probabilistic sensitivity analyses (PSAs) were conducted to offset the effect of parameter uncertainty. The input variables were assigned a probability distribution to reflect the

feasible range of values that each input parameter could attain (Briggs, 2000). Consequently, one value from each parameter was taken out and calculated for cost and effectiveness. This process was repeated 1,000 times, and the range of possible values was given as a cost-effectiveness acceptability curve. This analysis used the cost-effectiveness ceiling threshold of 120,000 THB per QALY gained, as recommended by the Health Economic Working Group under the Subcommittee for Development of the National List of Essential Drugs (The Health Economic Working Group, 2012).

In addition, a threshold analysis was performed for the sake of generalization. The results of different levels of selected parameters—prevalence of the presence of the HLA-B*15:02 allele in the Thai population, PPV, NPV, cost of VPA, cost of HLA-B*15:02 screening, and duration of epilepsy treatment—were assessed to evaluate their potential benefits in other settings.

Results

Costs

The lifetime costs of each option are presented in Figure 3. Overall, the average lifetime cost for the current treatment policy tends to be lower than the other two strategies, by approximately 42,100 THB for epilepsy patients, and 18,600 THB for patients with neuropathic pain. The average lifetime cost of providing universal HLA-B*15:02 screening before prescribing CBZ to patients with epilepsy and neuropathic pain was about 50,200 and 22,700 THB, respectively. The average lifetime cost of prescribing drugs other than CBZ to all patients who would currently receive CBZ treatment was nearly 83,700 for epilepsy patients and 35,800 for patients with neuropathic pain.

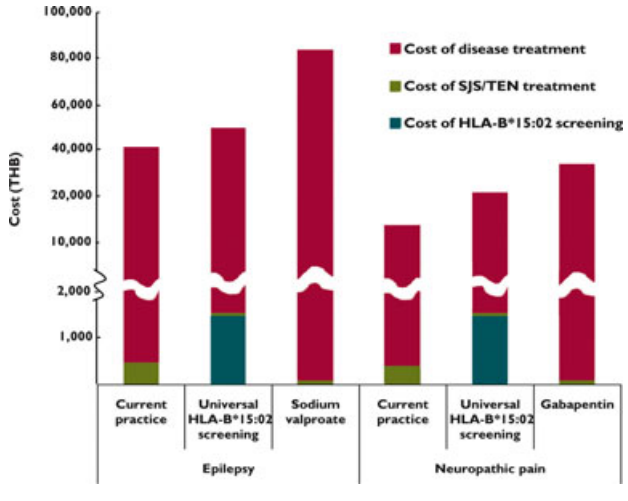

Figure 3.
The lifetime costs of each strategy categorized by disease.
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As Figure 3 shows, the cost of treating epilepsy according to the current policy is almost the same as the cost of providing universal HLA-B*15:02 screening before prescribing CBZ. However, current practice accounts for most of the cost of SJS/TEN treatment, a cost that can be avoided with the implementation of prospective HLA-B*15:02 screening. Because the cost of prescribing VPA is nine times higher than CBZ, the cost of treating epilepsy represented a sizeable proportion of the total costs in cases where VPA rather than CBZ was prescribed. For patients with neuropathic pain, a similar pattern was observed.

An analysis was conducted on the number needed to screen (NNS), which showed that 343 patients need to be screened for HLA-B*15:02 allele to prevent one case of SJS/TEN. As a result, the cost of preventing one case of SJS/TEN was calculated as 375,200 THB (the cost providing HLA-B*15:02 screening for 343 patients).

Health outcomes

It is estimated that without HLA-B*15:02 screening, 187 patients will develop SJS/TEN annually. Universal HLA-B*15:02 screening or treatment with alternative drugs can reduce this number to approximately 23 patients per year. When the provision of universal HLA-B*15:02 screening is compared with current practice, the number of life years saved and QALYs gained is insignificant for patients with both epilepsy and neuropathic pain, reflecting the fact that SJS/TEN is a rare condition. A similar finding is observed when comparing universal HLA-B*15:02 screening and providing alternative drugs (Table 2).

Cost-utility analysis

Table 2 shows the average lifetime costs and the QALYs gained for each of the three strategies compared in this study. Compared to current practice, universal HLA-B*15:02 screening incurs higher costs but results in slightly more QALYs gained. The ICER of the universal HLA-B*15:02 screening strategy was estimated at 222,000 THB/QALY gained for epilepsy patients and 130,000 THB/QALY gained for patients with neuropathic pain. Compared to universal HLA-B*15:02 screening, the policy of providing alternative drugs without screening yielded only marginal benefits but did result in a significantly higher ICER of 32,522,000 THB/QALY gained for epilepsy patients and 35,877,000 THB/QALY gained for patients with neuropathic pain.

Uncertainty analysis

A probabilistic sensitivity analysis was undertaken, and the results are presented in Figure 4. The line graph illustrates the probabilities of the three strategies being cost-effective at different ceiling ratios. The results reveal that the probability of universal HLA-B*15:02 screening being cost-effective at the Thai ceiling ratio of 120,000 THB/QALY gained for epilepsy and neuropathic pain models, is

Table 2. Life time costs and health outcomes of each strategy using societal perspective[a]

Options	Costs (THB)	Incremental LYs (days)	Incremental QALYs (days)	ICER (THB per QALY gained)
Epilepsy model				
Current practice	42,000	–	–	–
Universal HLA-B*15:02 screening	50,000	0.07	13.44	222,000
Alternative drugs	84,000	0.11	0.38	32,522,000
Neuropathic pain model				
Current practice	19,000	–	–	–
Universal HLA-B*15:02 screening	23,000	0.05	11.53	130,000
Alternative drugs	36,000	0.03	0.13	35,877,000

THB, Thai baht as of 2011 value; LYs, life years; QALYs, quality adjusted life years; ICER, incremental cost-effectiveness ratio.
[a]The number presented in table was rounded to the nearest whole number.

16% (Fig. 4A) and 32% (Fig. 4B), respectively. It can be clearly seen that the cost-effectiveness of the screening rises in correlation with the increase of the ceiling threshold.

The probability of CBZ-induced SJS/TEN occurring in a person who tested positive for HLA-B*15:02 was sensitive to the result of the cost-effectiveness of universal HLA-B*15:02 screening. Because this parameter was obtained from only one paper, which was not based on a national survey, we conducted our own threshold analysis to determine the ICER for the range of prevalence of CBZ-induced SJS/TEN in the Thai population, the positive predictive value (PPV), and the negative predictive value (NPV). The results (Fig. 5) show the effect of the prevalence, PPV, and NPV values on ICERs. In the base case, universal HLA-B*15:02 screening in patients with neuropathic pain is found to be cost-effective at a rate of nearly 0.27% based on current evidence; conducting screening for patients with epilepsy is not found to be cost-effective. An increased prevalence of CBZ-induced SJS/TEN resulted in a reduction of ICERs for both patients with neuropathic pain and those with epilepsy. This particular information is useful because data on CBZ-induced SJS/TEN, PPV, and NPV values might change in the future, and this trend may be applicable to other relevant settings.

In addition, the reduced cost of VPA was also found to increase the value for money of HLA-B*15:02 screening. Screening becomes cost-effective if the cost of VPA decreases from 12.66 THB to 7.07 THB. However, a reduction in the cost of HLA-B*15:02 screening does not affect the value for money of the screening itself, because the screening cost is only a minor part of the total lifetime cost. This study also examined the effect of the duration of epilepsy treatment on the value for money of the proposed regimen. The durations assessed ranged from 4 years to lifetime, and the model found that the longer the duration of treatment, the lower the value for money of the screening.

In a voluntary reporting system, it is likely that the number of drug-induced ADRs is likely to be underestimated. To account for this, we performed an analysis that showed that the change of other CBZ-induced ADRs had a moderate effect on the ICER of screening in patients with epilepsy but exerted very little effect on patients with neuropathic pain. If the rate of other CBZ-induced ADRs is as high as 11.2% (the upper bound of its 95% confidential interval), the ICER drops to 143,000 THB/QALY. In contrast, if the rate of other CBZ-induced ADRs is as low as 0.1% (the lower bound of its 95% confidential interval), the ICER increases to 275,000 THB/QALY. Lastly, the analysis found that none of the other model parameters exerted an effect on the value for money of the gene screening. These include the direct non-medical costs and utility parameters data collected from a small number of samples.

Discussion

The findings of this study reveal that a significant decrease in the number of CBZ-related SJS/TEN cases is observed if either a universal HLA-B*15:02 screening policy or a policy of prescribing drugs other than CBZ is adopted for the treatment of epilepsy and neuropathic pain. In addition, universal HLA-B*15:02 screening was found to be preferable to alternative drug treatment because, although both policies generate similar health outcomes, the former is less expensive. Furthermore, our analysis of the NNS found that 343 patients need to be tested for the HLA-B*15:02 allele to prevent one case of SJS/TEN. As a result, the additional cost of preventing one case of SJS/TEN is assessed to be 375,200 THB (the cost of providing HLA-B*15:02 screening for 343 patients).

Using the cost-effectiveness ceiling threshold in Thailand, a program of universal HLA-B*15:02 screening represents good value for the money when conducted on patients with neuropathic pain, but not when conducted on patients with epilepsy. This is because the cost of alternative drug regimens is much higher for epilepsy (83,700 THB for lifetime treatment with VPA) than it is for neuropathic pain (lifetime treatment with GBP costs 35,800 THB). Moreover, with a universal screening policy, a significant proportion of patients with epilepsy who test positive for the HLA-B*15:02 allele will not develop SJS/TEN (98%), but will still switch to the more expensive treatment, as a precaution. It is interesting to note that our findings pose a significant

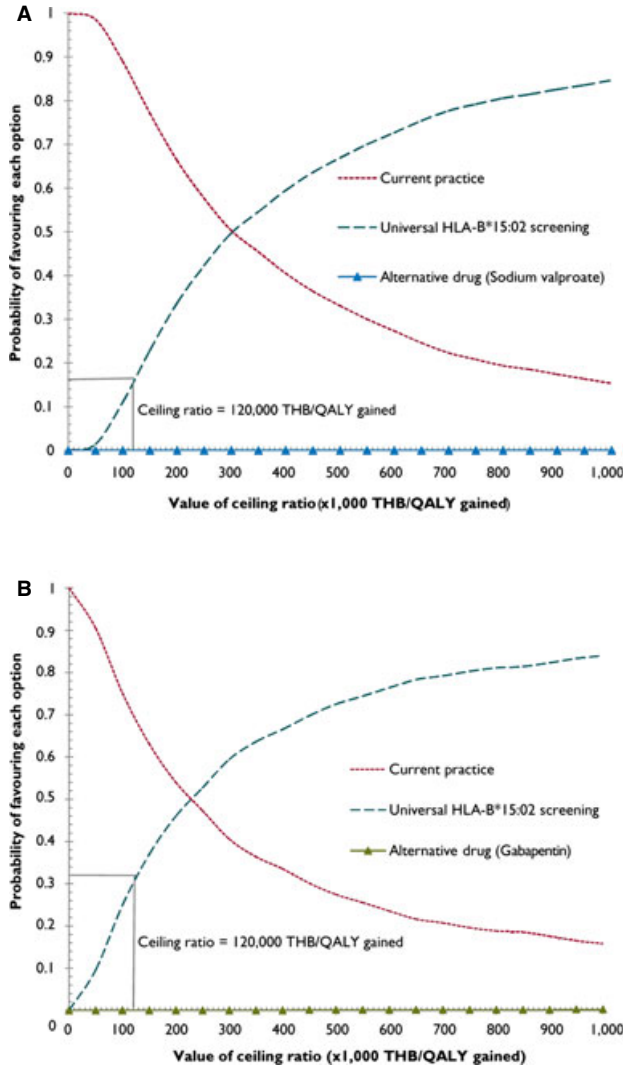

Figure 4.
(**A** and **B**) Cost-effectiveness acceptability curves demonstrate that the probability of three strategies for epilepsy and neuropathic pain treatment would be cost-effective at the different ceiling threshold values. (**A**) Probability of three strategies of epilepsy model being cost-effective at different ratio. (**B**) Probability of three strategies of neuropathic pain model being cost-effective at different ratio.
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challenge for policy implementation, since there are significant ethical issues involved with introducing HLA-B*15:02 screening for one group of patients and not for another when their risk level is identical. At this stage, no final decision has been made by the SCBP, and we believe that this evidence needs to be considered alongside other priorities, for example, equity grounds, ethical principles, and legal issues.

In 2012, a research study examining the cost-effectiveness of HLA-B*15:02 screening in newly diagnosed patients with epilepsy in Singapore from the perspective of the health care provider was published (Dong et al., 2012). The study used the HRQoL of burn patients as a proxy measurement for the HRQoL of SJS/TEN patients. They compared three similar treatment strategies, as we did in this study, and found that prescribing VPA without HLA-B*15:02 screening is not a cost-effective choice. However, in contrast to our findings, their study found that a universal HLA-B*15:02 screening would be cost-effective. This may be explained by the fact that a higher ceiling threshold (50,000 USD) and PPV (5.96%) were used in the Singapore study.

To the best of our knowledge, there is no published literature on the cost-utility analysis of HLA-B*15:02 screening for preventing CBZ-induced SJS/TEN in patients with neuropathic pain. The results of this study can be utilized as information to support decision making in other settings regarding the adoption of this pharmacogenetic test, given the increased concern over the safety of CBZ. On the other hand, if decision makers in other settings prefer local data, information derived from this study can also be employed for other economic evaluation studies. For example, data on the effect on HRQoL in patients with SJS/TEN has yet to be reported, and the primary data on HRQoL collected in this study could be used to assess the value for money of the test in other settings.

However, the results of this study should be interpreted with caution. First, because of the rarity of cases of SJS/TEN and the rigorous inclusion criteria, only a small number of patients were used in our evaluation, representing both cost and utility limitations. A larger number of patients with a wider variability in the severity of their SJS/TEN hypersensitivity would be more likely to ensure that the results accurately reflect the current situation among all patients. Second, no active surveillance system is in place to quantify the prevalence of CBZ-induced SJS/TEN in the Thai population, and this study employed data from only one study, which was conducted in a medical school in Bangkok. Therefore, further research on this topic would enhance the generalizability of the results and provide more valid and reliable evidence for applying the data to the study of the cost-effectiveness of HLA-B*15:02 screening policies for patients set to undergo CBZ treatment.

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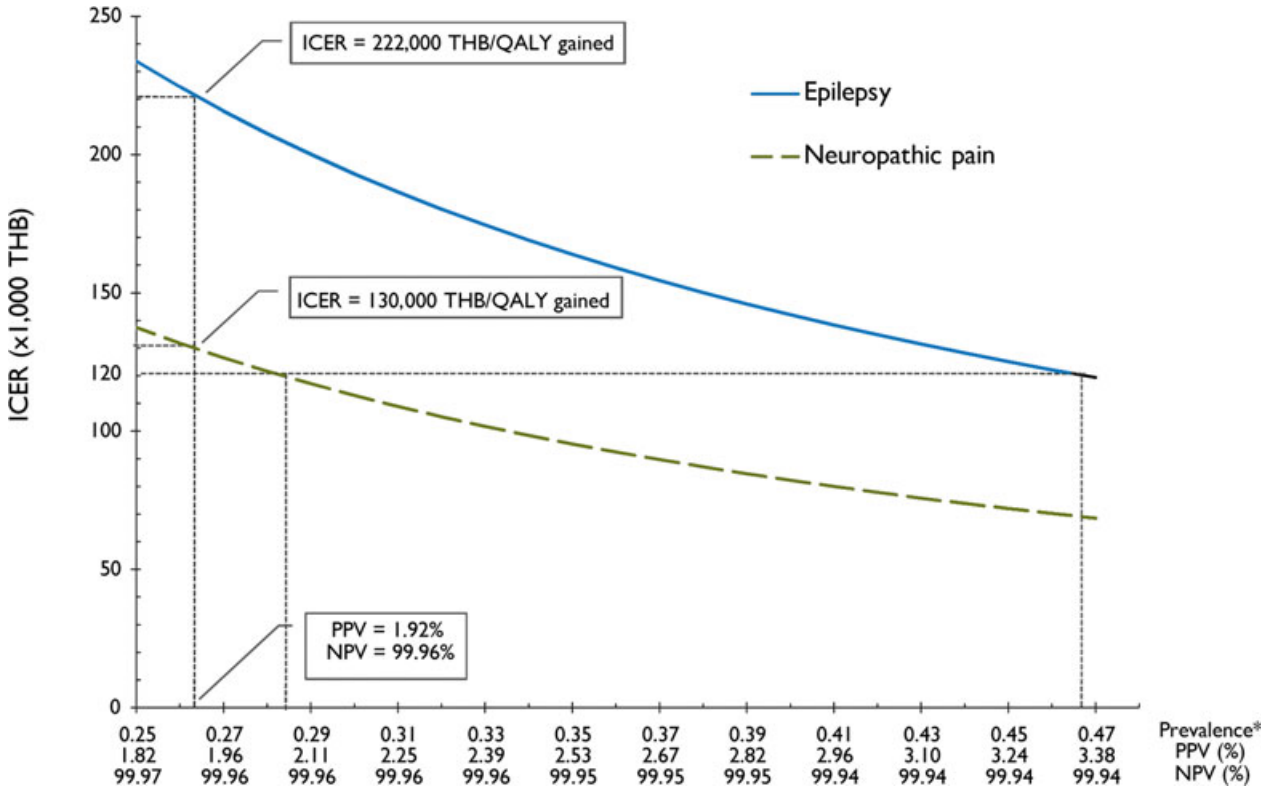

Figure 5.
Result of threshold analyses. *Prevalence of CBZ-induced SJS/TEN in the Thai population.
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express our appreciation for the standardized instrument used to measure HRQoL supported by the EuroQol Group. Finally, we acknowledge the input from all of the patients and health care professionals at the 10 hospitals that participated in this study.

Disclosure

Surakameth Mahasirimongkol is employed by DMSc, public health laboratory services under the Ministry of Public Health. He has received funding for research projects related to pharmacogenomics of severe cutaneous adverse drug reactions, but unrelated to the data presented in this article. The other authors declare no conflicts of interest. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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GLOBALIZATION AND HEALTH

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Health technology assessments as a mechanism for increased value for money: recommendations to the Global Fund

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Abstract

The Global Fund is experiencing increased pressure to optimize results and improve its impact per dollar spent. It is also in transition from a provider of emergency funding, to a long-term, sustainable financing mechanism. This paper assesses the efficacy of current Global Fund investment and examines how health technology assessments (HTAs) can be used to provide guidance on the relative priority of health interventions currently subsidized by the Global Fund. In addition, this paper identifies areas where the application of HTAs can exert the greatest impact and proposes ways in which this tool could be incorporated, as a routine component, into application, decision, implementation, and monitoring and evaluation processes. Finally, it addresses the challenges facing the Global Fund in realizing the full potential of HTAs.

Keywords: Global Fund, Health technology assessment, Cost-effectiveness analysis, Program evaluation, Global health

Introduction

The Global Fund, created in 2001 as a global financing mechanism, enables low-income countries (LICs) and middle income countries (MICs) to promote access to certain health interventions and technology for the prevention and treatment of HIV/AIDS, tuberculosis, and malaria. Given the commitment from its donors—amounting to almost $30.5 billion in pledges and $24 billion in contributions to date—as well as its scale of work in approximately 100 countries [1], the Global Fund has emerged as one of the most significant global health players over the last decade. Its total disbursements in 2009 constituted 3.29% of total health expenditure in LICs, 0.22% in low MICs and 0.07% in high MICs, while its contribution to individual countries ranged from 0.002% in Botswana to 53.4% in the Democratic Republic of Congo [2].

As a global health financier rather than a technical or implementing institution, the Global Fund does not operate directly within countries or implement its own programs [3]. Historically, the Global Fund has issued "calls for proposals" for applications through a rounds-based mechanism. As of August 2012, there have been 10rounds. At the time of writing, this system is in the process of being replaced by a funding model allowing for more flexible timing of grant applications. Global Fund affiliated partnerships—termed Country Coordinating Mechanisms (CCMs)—are tasked with developing proposals based on stakeholder consultations, local funding needs, and epidemiological context. The Global Fund notes that the applicant is responsible for "deciding their own priorities, strategies and programs." Proposals are submitted to the Secretariat, verified for eligibility, and reviewed for completeness by a Technical Review Panel (TRP), which in turn makes funding recommendations to the Global Fund Board. The TRP consists of representatives with an array of expertise, both scientific and programmatic, as well as program experience in HIV/AIDS, tuberculosis and/or malaria. The TRP terms of reference direct the panel to review grant applications against technical criteria including feasibility, value for money, and sustainability [3].

If a proposal is approved, funds can be disbursed under the supervision of the CCM to the Principal Recipients (PRs) and/or Sub-Recipient(s) (SRs) who are

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responsible for the program's implementation. In addition, a Local Fund Agent (LFA), an independent body contracted by the Global Fund Secretariat, is responsible for monitoring the PR's performance, grant implementation, and financial reports. Global Fund grants can be made for a period of up to five years, although funds are typically reviewed after two years, with continued funding conditional upon performance [3] and other factors [4].

As donor funding for global health declines due to the global recession, the Global Fund is experiencing increased pressure to optimize results and improve impact per dollar spent [1]. In its recent strategic plan [5] covering the 2012–2016 period, the Global Fund sets ambitious goals to increase impact by investing strategically in areas with high potential and offering strong value for money. Despite its clear objectives on "maximizing impact and value for money," there are still major challenges in the implementation of the plan. This paper reviews the current successes and impediments of Global Fund investment and examines how health technology assessment (HTA) can be used to provide guidance on the relative priority of health interventions (medications, devices, diagnostics, and other treatment modalities) subsidized by the Global Fund. In addition, this paper aims to identify areas where the application of HTA could have the greatest impact and to propose ways in which it could be incorporated, as a routine component, into application, decision, implementation, and monitoring and evaluation processes. Finally, it addresses the challenges facing the Global Fund in realizing the full potential of HTA.

The improved performance, transparency, and efficiency of the Global Fund

As of 2013, the Global Fund has disbursed a total of over $20 billion in 151 countries [6]. Its investments have likely contributed to the significant increase in the number of HIV/AIDS patients receiving antiretroviral treatment (from an estimated 300,000 in 2002to 5.25 million by 2009 [7]) as well as the number of insecticide-treated nets (ITNs) distributed in 35 high-burden African countries (from an estimated 10 million in 2004 to 35-44million per year between 2006 and 2008 [5]), as well as the detection rate of new smear-positive tuberculosis cases (from 36%– 44% in 2000 to 55%–67% in 2008 [8]).

The Global Fund is governed in a unique way, both at a board and implementation level. Leadership is sourced from within developing counties, the private-for-profit sector, and civil society. There is a strong commitment to increasing transparency and accountability, and as a result, the fund has improved the availability and accuracy of information related to the disbursement of funding and coverage of specific services, including the establishment of specific surveillance of the focal diseases, despite difficulties involving duplication of information systems in some recipient countries [7]. In addition, the Global Fund has pursued the principle of performance-based funding that is disbursement of funds has been largely correlated with grant performance; for example, the best performing programs receiving 79% of their grant sums compared to 38% for the worst performers [9].

Although there is an argument that performance-based funding systems might place LICs at a disadvantage due to their comparatively poor access to resources and capacity, at least three studies have rejected this hypothesis [2,10,11]. These studies reveal that when taking other factors into consideration, grants in LICs have tended to out-perform their more resource-rich counterparts. Lu and colleagues [10] reported that an increase in per-capita income from $1000 to $2000 is associated with a substantial reduction in disbursement of 2-year grant sums (an indicator of both expenditure and performance, in view of the Global Fund's incremental disbursement system). Radelet and Siddiqi [11] demonstrated a similarly strong negative relation between the income and achievement of programmatic targets. The authors concluded that poor nations, including so-called fragile states, had proven themselves capable of effectively utilizing increased funding flows from the Global Fund. Moreover, the most important finding is a significant negative association between grant implementation rates and income per person, suggesting that LICs are more likely to disburse grants from the Global Fund than countries with higher per capita income.

Although the Global Fund has dedicated itself to increasing prevention and control of AIDS, tuberculosis, and malaria, it has also made significant investments in improving the health systems of LICs [12]. Flexibility of the financial support from the Global Fund allows recipient countries to strengthen their health systems through a number of approaches, ranging from health worker training sessions and salary support to improved workforce retention and electronic health records systems. Such efforts may not only facilitate the success of AIDS, tuberculosis, and malaria programs, but also ensure that scarce health system resources are not diverted to these three diseases at the expense of other health needs. In 2009, 35% of its funding contributed directly to supporting human resources, infrastructure and equipment, and monitoring and evaluation in health systems [13]. AIDS treatment programs themselves benefit from investment in health systems, as healthcare workers benefit directly from improved systems and increased access to antiretroviral treatment results in fewer patient admissions to hospital, which then helps

free up health workers and related resources to that they can be devoted to other health needs [13].

The impediments and challenges

As with a number of global health initiatives, including the GAVI Alliance, the policies and priorities of the Global Fund are defined at a global level. Although the Global Fund works to maintain relatively high levels of national ownership in its programming, evidence suggests that there remains misalignment between its policies and programs and those of national governments. As a result, services that are managed both by the government and the Global Fund are often badly coordinated and inefficiently managed, with duplication of tasks—including reporting, monitoring and evaluation, and funding/disbursement mechanisms—representing significant obstacles to efficiency [12,14]. Delays in disbursement of funds to the PRs and donor short falls in financial pledges have both emerged as significant challenges [1]. The significant fall in donor funding in the 2011–2013 funding round led directly to the cancelation of the eleventh call for proposals. As a result of these issues, efficiency improvement has been defined as a central tenet of the Global Fund strategic plan for 2012–2016.

Several studies have identified efficiency shortfalls within the Global Fund. At a macro-level, Zhao et al. [15] reviewed performance indicators for Global Fund malaria programs and identified an over reliance on input indicators—especially those related to training activities—at the expense of outcome or impact indicators, which are better suited to measuring disease reduction. This tendency to set inappropriate indicators may distort performance ratings and, consequently, grant funding [15]. This has been seen in Timor-Leste, where effective strategies for controlling malaria receive less funding than behavioral change activities, despite the fact the former approach has been found to be more effective in disease prevention [16]. For instance, both ITN distribution programs (which have been found to be very effective in preventing malaria in high transmission areas [17]) and case management (improved diagnosis), another highly effective intervention, were clearly underfinanced, receiving less than 1% of the total grant support [16], in favor of behavioral change programs.

This situation is repeated across HIV and tuberculosis programs. Effective and efficient prevention and control depend on implementing the right mix of interventions for each setting and assuring the necessary coverage of those interventions. Bridge et al. [18] found that less than half HIV proposals funded by the Global Fund included harm reduction activities, even though many studies confirm that these activities offer good value for money [19,20]. Moreover, although there is strong evidence that male circumcision can reduce HIV transmission in men by up to 60% [21], we found that no Global Fund proposals included circumcision initiatives. At the same time, many interventions that aim to influence knowledge, attitudes, and beliefs and influence psychological and social correlates of risk have received significant support from the Global Fund [22], despite the fact that the impact of these programs—including whether they bring about sustained long-term behavior change—remains uncertain [23]. Korenromp et al. [24] suggest that the Global Fund could significantly enhance the impact of its tuberculosis investment by reevaluating its investment across regions, for instance by prioritizing investment in Africa, and by screening and treating tuberculosis in populations with high levels of HIV infection. A recent report developed by the Value for Money Working Group (2013) reaffirmed the limitations of the Global Fund's investments in the TB, HIV/AIDS and Malaria programs and it also provided suggestions to improve funding strategies.

Aside from the issue of effectiveness, an increasing amount of information on resource use and health consequences, i.e. cost-effectiveness, has been amassed in recent years. Global health professionals no longer focus only on effective prevention and treatment; instead, more sophisticated models that examine cost-effectiveness and comparative effectiveness as a way of improving public health without requiring significantly more funding are at the centre of most public health initiatives. The differences in cost-effectiveness between interventions can be staggering, particularly when considering initiatives that require implementation at scale. For instance, despite massive increases in access to HIV treatment, WHO and UNAIDS estimate that, as of 2011,there are still as many as 15 million people around the world in need of antiretroviral therapy. To treat populations of this scale, the difference in cost-effectiveness between the most cost-effective treatment option and the least can be as much as 1,400 fold (Disease Control Priorities in Developing Countries Project) [25]. Even differences in intervention implementation can result in significant variation. A 2011 paper by Amole et al. [26] found that some Global Fund recipient countries are not currently optimizing their HIV treatment by selecting the most cost-effective antiretroviral regimen and implementation strategy (i.e. treating population who is most likely to further transmit HIV infection to other populations). Adjusting the current make-up of antiretroviral drug purchases in sub-Saharan Africa and India could yield over $300 million in savings over the next five years and expand the provision of quality services in resource limited settings.

Despite the Global Fund's explicit commitment to implementing cost-effective and proven initiatives, it is clearly failing to fund programs that fulfill these criteria to the extent that it should. This may be because the Global Fund provides support to countries based on

requests received from CCMs, who themselves may not have a clear idea about a country's needs or the most cost-effective strategies that can be implemented to meet those needs. As a funding organization, the Global Fund has little in-house technical capacity and little direct engagement with countries to which they provide funding. There is no systematic support to PRs on whether proposed interventions are among the most effective and cost-efficient for achieving the desired outcome in a given context. Although the TRP has been set up to provide funding recommendations to the Board of the Global Fund for making final decisions, it is difficult for the TRP to assess technical soundness and value for money or to make rational recommendations on strategic investments based only on the data presented in the applications, especially when the information is weak, patchy, or inconsistent, and where funding is limited to specific time periods. Moreover, an absence of guideline on what information should be used in order to assess value for money and a lack of HTA capacity of the TRP secretariat prohibit the use of value for money information in TRP review process.

Furthermore, it is widely accepted that the impact and cost-effectiveness of interventions depends to a large extent on the strength of the health system within which they are delivered. A lack of absorptive capacity at all levels of grant implementation has been identified in many settings and may explain the slow progress in grant implementation outside of a robust health system [16,27]. Previous research on this subject reveals that inadequate institutional capacity and high staff turn-over negatively impacts organizational capacity, which can lead to poor performance in both project implementation and monitoring and evaluation [28-33]. Therefore, the Global Fund needs to ensure that relevant infrastructure, e.g. laboratory for HIV and CD4 test, is built before investment in commodities, e.g. antiretroviral drugs, are made. On the other hand, HTA focus on effectiveness (real-work effect) of investment rather than efficacy (potential effect in idea situation) so that weakness at system level can be taken into account appropriately in decision making process.

The situation can also be applied to the substantial investments in health information systems for improving healthcare services and enhancing management, monitoring and evaluation of the fund itself. Until now, very few studies have addressed this issue [34,35]. As a result, HTA on health information systems should be one of priority areas given that there is very little evidence of a comprehensive plan by the Global Fund in this area or attempts to standardize on a small number of well-established systems or to initiate any evaluations of such systems.

Potential applications of HTA within the Global Fund

As is made clear in The Global Fund strategy 2012–2016, the organization must make the transition from an emergency funder to a long-term, sustainable financing mechanism. To this end, it needs to develop new risk-management approaches, strengthen internal governance, institute a new grant-approval process, strengthen decision making by middle management, and improve its focus on results [5]. Although this report does not provide direction on certain critical issues that will define the future success and impact of the Global Fund, it suggests that the Global Fund could achieve better value for money with better technical evaluation and management.

A 2011 report [36] by the Results for Development Institute on behalf of the Global Fund's Market Dynamics Committee makes several recommendations for the optimization of product selection, including that the Global Fund commission global value for money guidance on specific products: *"An experienced independent expert body such as the National Institute for Health and Clinical Excellence (NICE) could be commissioned to conduct robust comparative cost-effectiveness analyses of two or more WHO-recommended products and provide that information to the Global Fund and its recipients."* This is not the first time that academics have urged the Global Fund to consider the use of HTA to improve its cost-effectiveness [25]. The application of an HTA to a health initiative is a multidisciplinary activity that systematically examines the costs and benefits as well as the organizational implications and social consequences of the application of a health policy and/or technology. HTAs often function as a "bridges" between evidence and policy-making, providing health policy-makers with accessible, useable, and evidence-based information that can help guide their decisions regarding the appropriate use of technology [37].

HTAs not only generate a wide range of policy-relevant information that can aid decision making, but also empower stakeholders that are involved in the decision making process. This is because HTAs, as tools in a priority setting approach, are often designed according to a set of questions that themselves encourage a critical evaluation of the relevant social and financial factors [38]. This kind of evaluation can help decision makers unpack evidence and assess the relative importance of both process values (such as transparency, accountability, participation, legality, faithfulness to constitutional provisions, and respect for international obligations) and content values (such as clinical effectiveness, value for money, equity, solidarity, and feasibility). HTAs are particularly suitable for global organizations because they take into account the kinds of values that vary across settings as a result of differing social factors, including politics, culture, social demographics, religion, and levels of economic development.

Figure 1 is a modified version of the Global Fund's model of performance-based funding. It presents a method for enhancing the efficiency of Global Fund projects, through the use of HTA. HTAs can enhance value for money at all stages of the Global Fund process, from

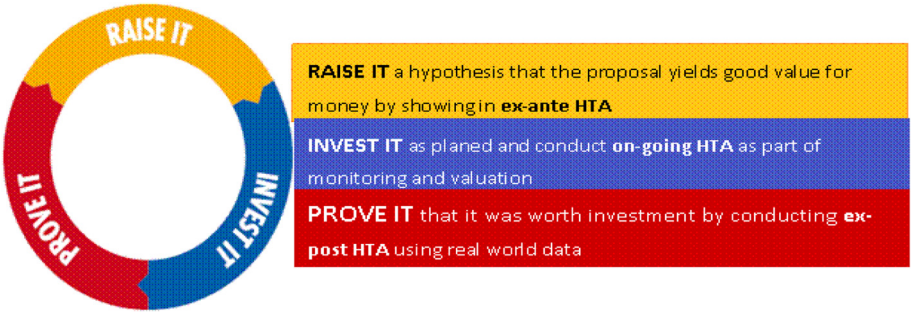

Figure 1 Potential use of Health Technology Assessment (HTA) to enhance value for money of Global Fund initiatives.

proposal development to final evaluation. For instance, with the inclusion of an HTA, proposals are far more likely to take into account cost and efficiency, among other factors, resulting in a much higher quality, rigorous, and evidence-based proposal. The higher the quality of the proposal submitted to the Global Fund, the more likely the donors will be to respond to the sustained level of demand for resources. In other words, the higher the quality of the proposal, the greater the impact obtained from investment. However, this task is not simple. Proposal development requires an increased focus on intervention or mixes of interventions that are locally appropriate, including assessments of affordability and cost-effectiveness in the given context. Cost-effectiveness information may be derived from the existing literature, including the Disease Control Priorities in Developing Countries project [17], as well as from the Global Fund's value for money guidance—a collective set of comparable cost-effectiveness information of various interventions implemented in various settings. This supports the claim of Korenromp et al. [24] that proactive approaches from the Global Fund to inform demand on the kinds of initiatives that yield good value for money (and those that do not) would result in larger numbers of lives saved than might be the case with the prevailing funding model, which relies heavily on country demand.

We suggest not only that cost-effective interventions be selected correctly from *the value for money guidance*, but also that HTA be applied to at least some aspects of a proposal before implementation. These ex-ante HTAs would use existing evidence and assumptions to estimate the likely costs and impacts of the proposed program (Table 1). Having HTA as a pre-condition may well drive local data generation through countries' initiative and also by the Global Fund. Relevant stakeholders should work with HTA experts to ensure the local relevancy of the assessment, as well as to strengthen the absorptive capacity of the grant recipients by facilitating the consideration of important parameters (factors) affecting the potential success of grant implementation. The results of these ex-ante HTA can then also be used as a baseline for conducting monitoring and evaluation once the program is implemented. An ex-ante assessment can be used as a requirement for a CCM that does not select the cost-effective interventions in its proposal to demonstrate that the selected intervention(s) is at least as cost-effective in a given context if not more so than those reported in *the value for money guidance*. It is also expected that this approach will help create shared priorities of the Global Fund and its recipients.

HTAs are not only recommended at the pre-implementation stage, they are also effective monitoring and evaluation tools. Even though interventions may be primarily designed to take into account context-specific issues, it is essential that examinations be carried out to determine whether they work well and remain efficient in practice, particularly when implemented together with other interventions within and outside Global Fund programs. Unlike ex-ante assessments, on-going HTAs can take into account primary research and focus on context-dependent issues, e.g. willingness of target populations to participate in the program, adherence to intervention protocol by providers and end-users, or other sectors' responses to the program (Table 1). These kinds of HTAs should also pay particular attention to the key surrogate outcome indicators identified in the ex-ante assessment. It is also possible that results from the ex-ante assessment be used as benchmarks for the assessment at this stage.

Lastly, it is advised that HTA be included as part of the final report that all CCMs submit to the Global Fund when a particular program comes to an end. This should help the Global Fund incorporate feedback mechanisms regarding the requirements, constraints, and potential of the PR and SRs, who will ultimately determine if the Global Fund will achieve its goals. Collective information on the value for money of various programs implemented in different settings (*value for money guidance*) will be a valuable resource for the Global Fund and other development agencies in making future resource allocation decisions. An equally important implication is that ex-post HTA can provide information to various responsible authorities in recipient countries to encourage them to continue financing programs that are proven to be good value for money. As sustainability is a serious concern for all

Table 1 Examples of ex-ante and ex-post health technology assessments

A case study of ex-ante assessment of the feasibility and value for money of the maternal and child health voucher scheme in Myanmar [39]	A case study of an on-going HTA of HIV prevention for the most-at-risk population in Thailand [40]
An ex-ante assessment was conducted as part of a collaborative study undertaken by Myanmar's Ministry of Health, WHO, and the Thai Ministry of Public Health between March 2010 and September 2011. The aim of the assessment was to collect information to guide the formulation and implementation of a demand-side financing mechanism for maternal and child health (MCH) services in Myanmar. The main objective of the MCH voucher scheme is to eliminate the financial barriers to maternal and child health care among poor households by providing support in the form of four antenatal visits, delivery by skilled birth attendants, postnatal care, transportation, food, and lodging. Using both qualitative and quantitative methods, including an economic evaluation, this collaborative research demonstrates that the use of demand-side financing for MCH services in Myanmar appears to be feasible and represents good value for money. The evidence suggested that the initiative was likely to garner support from community leaders and civic groups, and be accepted by target populations and health workers, because it removes many of the impediments that people currently Figure 1 Potential use of Health Technology Assessment (HTA) to enhance value for money of Global Fund initiatives. Teerawattananon et al. Globalization and Health 2013, 9:35 Page 5 of 9 http://www.globalizationandhealth.com/content/9/1/35 encounter when trying to access MCH services. Some of the most common barriers that people face when trying to access these services are the long distances between the residence of the mother and the nearest health facility, and the related high travelling costs (particularly in rural areas), the high cost of medicines (which for many is unaffordable). In Myanmar, where the average number of pregnancies per year is 900,000, it is estimated that introducing the MCH voucher scheme would increase ANC coverage from 68% to 93% and delivery by skilled-birth attendants from 50% to 71%. The ex-ante assessment found that the MCH voucher scheme was likely to save a significant number of lives of mothers and infants, for whom the cost of ANC is currently prohibitive. The assessment also found that this could be done at a reasonable cost. The incremental costeffectiveness ratio (ICER), which in this case is the additional cost per life-year saved from introducing the MCH voucher scheme compared to the status quo, ranged from 376,548 to 452,110 kyats (475 kyats = 1 international dollar, in 2010). This represents good value for money, especially given the ceiling threshold of 1 time of GDP per capita of 413,800 kyats. The results of this study were presented to senior decision makers in Myanmar in March 2011 resulting in an agreement being reached to implement the MCH voucher scheme in one township commencing in November 2012 before scaling it up as a nationwide program.	Global Fund for a (Round 8) grant support of $75.46 million over five years, from July 2009 to May 2014. The three principal recipients (PRs) are the Thai Ministry of Public Health and two non-governmental organizations. This program aims to expand HIV preventive services for female sex workers (FSW), people who inject drugs (PWID), men who have sex with men (MSM), and migrant workers. Because there was concern among PRs about the sustainability of the program beyond the 5 years of the grant support, the Health Intervention and Technology Assessment Programme (HITAP) was invited by the Country Coordinating Mechanisms (CCM) to take part alongside PRs and Sub-PRs in an evaluation to assess the costs and cost-effectiveness of this ongoing program. The results of this study will be used to improve program performance and support policy decision making by the Thai government in terms of whether and how the program continues at the end of the period of Global Fund support. Using routine administrative data, program costs and outcomes in terms of population reached by CHAMPION were estimated in international dollars at I$2,333/ PWID, I$270/FSW, I$162/MSM, I$161/ migrant. These estimations were much higher than the cost per person in comparable programs for PWID in Bangladesh (I $727/PWID) and for FSW in India (I$129/FSW). The higher costs per person in Thailand may be explained by the shorter duration of the program (one and a half years for CHAMPION vs. three years for the Bangladesh project, and two years for the Indian project), which may have lead to higher fixed start-up costs that made up a significant proportion of the overall costs per person (a proportion which falls significantly for longer projects). Second, and more importantly, this higher cost may be due to Thailand's lack of a harm reduction policy and the presence of harsh criminal sanctions for PWID, which made it more difficult to recruit PWID to the CHAMPION scheme. In its conclusion, the study suggests an urgent need to improve program performance if CHAMPION is to offer value for money in the Thai setting.

parties involved in the delivery of external aid, and local governments are often in a difficult situation on whether to continue the support for initiatives previously funded by external donors, ex-post assessments can provide good opportunities to inform decision makers in recipient countries about the usefulness, value for money, and other implications the program might have if it is maintained.

Challenges of using HTA for the Global Fund

There are many challenges to overcome if HTAs are to help the Global Fund make a shift in funding projects that have a real impact.

Complexity of HTAs for the Global Fund

HTAs for the Global Fund need to be transparent, robust, and adaptable to local contexts. They also need to take into account the local factors that may influence the outcomes and impacts of investment. Unfortunately, typical HTAs tend to be articulated around a single or limited number of health interventions in a context-free environment [41]. Because Global Fund programs often relate to arrangements of health system and services, and encompass multiple interventions that are packaged together, HTAs for the Global Fund must allow for multiple interventions and outcomes being evaluated at the same time. Global Fund HTAs should also take care to

take into account the synergic effects of multiple intervention interactions on population health as well as on particular disease burdens. For example, HTAs could be used to assess the synergic effects of incorporating maternal and child health activities into Global Fund programs for HIV (which is an approach that has been recently signed off by the Global Fund Board).

Moreover, HTA should provide not only value for money information but also social, institutional and ethical implications including equity issues since different societies may have different social values toward health investment. For example, although expanding antiretroviral treatment to those eligible HIV patients but not on it would prove to be much more costly than investing in second or third line treatments for those failed from the first-line regime, decision makers in particular settings may opt to support a program to reach out the marginal groups due to equity consideration.

HTA facilities for the Global Fund

Since the Global Fund clearly states in its mission that it is a financing mechanism rather than an implementing institution, it is essential that the Global Fund maintain its role in promoting financial accountability and not develop its in-house HTA capacity. Indeed, not only would this go beyond the fund's specific remit, it would also create a conflict of interests in terms of eroding the separation between purchaser and provider. However, HTAs can be expensive. A review of HTA agencies found that the average cost per health technology assessment in ten different countries ranges from $3,000 to $650,000 [24]. As a result, independent contracting for the provision of technical support for HTAs might be effectively mobilized through the creation of global and/or regional HTA facilities. These HTA facilities would house the HTA research team, reducing costs through economies of scale, and would have the capacity to provide technical support to local staff in LICs and MICs as part of the Global Fund's capacity building and health system strengthening strategy. A global HTA facility could also be put in place to accredit regional and national HTA facilities to undertake HTA pertinent to a Global Fund program, while also serving as a hub for the collection of HTA-related information and advancing HTA methods for complex interventions (The Value for Money working group, 2013, [42-44]).

Increased investment in CCMs

Although implementation capacity is one factor that determines a country's readiness for funding, evidence demonstrates that CCMs only used about 1% of the Global Fund expenditure for administrative costs at their headquarters in 2009 [45]. A 2008 paper from the Center for Global Development notes that Local Fund Agents, tasked with overseeing CCMs, lack the expertise and capacity for program monitoring [46]. This lack of funding may be a limiting factor for thorough reviews and the incorporation of HTA into grant design and proposals. This warrants improved investment in CCMs and their partners to conduct monitoring and evaluations. Increasing the placement of HTA experts in CCMs and PRs, such as in ministries of health or ministries of finance, should be considered because these experts would bring HTA knowledge and insights to the country level and ensure the incorporation of cost-effectiveness into all steps of grant application and implementation.

Incentives for HTA

The Global Fund has enjoyed reputational benefits due to its promotion of performance-based financing. It is possible that the use of HTAs may help this reputation to grow. Firstly, the Global Fund would be able to make better-informed interventions, due to the evidence garnered by HTAs and by complying with the HTA-informed *value for money guidance*. The Global Fund is one of the largest suppliers of antiretroviral drugs in the world—as well a primary financier of other commodities, including ITNs [36]. Health technologies and medicines consume a significant portion of funds; currently almost 40% of Global Fund Grants are used for the procurement and management of pharmaceuticals and health technologies [47]. Under the current structure of the Global Fund, the interventions funded are selected by the PR and CCM during the proposal design process. There is no evidence that the Global Fund in any way limits the choice of interventions for which applicant countries may apply. For example, there are 92 antiretroviral drugs on the list in different forms and dosages, for a total of 309 unique items, subject to the Global Fund Quality Assurance Policy. There are 98 approved products for tuberculosis and 29 for malaria. Together, this set of over 430 possible options is not exhaustive and PR may purchase other items as long as the PR can determine that it would be compliant with the quality assurance standards [48]. Clearly, *the value for money guidance* issued on the back of an HTA can be a useful tool that PRs and CCMs can use to avoid investment in high-cost and low-impact options. In addition, *the value for money guidance* can be a resource for the Global Fund (at the global level) and PRs (at the local level) to negotiate prices with those in the industry, by using its evidence as their guidance.

Alternatively, efforts can also be made for improving the efficiency of performance-based payments, which currently rely on many input indicators rather than outcomes or impacts. The use of HTA data would allow the fund to set standard payments per unit of output (e.g.

number of condoms distributed) or outcome (e.g. % reduction of unsafe sex) which are closely linked to the final goals of the program (e.g. rate of HIV infection averted). This ceiling on standard payments would serve to drive substantial efficiency gains across the Global Fund's investment portfolio and exert pressure on other funders to decrease their own unit costs and improve efficiency. Countries that cannot meet the low-end unit costs set by the Global Fund would make up the difference from other sources, leading to enhanced cost sharing. With this option, the Global Fund can focus on providing effective coverage of proven interventions, an area where current monitoring and evaluation had identified significant shortfalls.

Conclusions

There is currently a new emphasis at the Global Fund and other global health initiatives to focus on ensuring the effective use of resources and on generating improved value for money. This timely report proposes that additional mechanisms, such as conducting HTAs before, during, and after grant implementation, can help improve the efficiency of Global Fund investment. Although some technical and management challenges merit further investigation, the costs of delaying the use of HTA evidence-informed investment in the Global Fund are high given the severe disproportion between the current resources available and the need for prevention and control of three major disease burdens worldwide.

Competing interests

With regard to ethical approval, this was not required because of the nature of our paper. Also, the authors have no conflict of interest to declare.

Authors' contributions

We confirm that all named authors meet the criteria of authorship. All authors equally contributed to the course of the review and provided critical comments to the manuscript.

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Economic Evaluation of 3-Drug Antiretroviral Regimens for the Prevention of Mother-to-Child HIV Transmission in Thailand

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Abstract

The current program for prevention of mother-to-child HIV transmission in Thailand recommends a 2-drugs regimen for HIV-infected pregnant women with a CD4 count >200 cells/mm^3. This study assesses the value for money of 3 antiretroviral drugs compared with zidovudine (AZT)+single-dose nevirapine (sd-NVP). A decision tree was constructed to predict costs and outcomes using the governmental perspective for assessing cost-effectiveness of 3-drug regimens: (1) AZT, lamivudine, and efavirenz and (2) AZT, 3TC, and lopinavir/ritonavir, in comparison with the current protocol, AZT+sd-NVP. The 3-drug antiretroviral regimens yield lower costs and better health outcomes compared with AZT+sd-NVP. Although these 3-drug regimens offer higher program costs and health care costs for premature birth, they save money significantly in regard to pediatric HIV treatment and treatment costs for drug resistance in mothers. The 3-drug regimens are cost-saving interventions. The findings from this study were used to support a policy change in the national recommendation.

Keywords

PMTCT, ARV, vertical transmission, mother-to-child transmission, HIV

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Background

Not long after starting the national program implementation for the prevention of mother-to-child HIV transmission (PMTCT) in Thailand in 1997, the country became recognized as one of the most successful developing countries in preventing vertical HIV transmission, with an estimate of more than 13 000 pediatric HIV infections averted during the past 2 decades.[1,2] Although the program includes voluntary counseling and HIV testing for all pregnancies, providing antiretroviral drugs (ARVs) for infected women and their newborns, and supporting infant formula feeding up to the age of 18 months, the ARV regimen used has still been the subject of consideration by national program managers.

The first recommended drug regimen was a short-course zidovudine (AZT).[3] In 2004, the national guidelines were changed by advocating a proven, better cost-effective regimen: a combination of AZT and single-dose nevirapine (sd-NVP).[4] The current guidelines established in 2007 proposed AZT+sd-NVP for HIV-infected pregnant women with a CD4 count of more than 200 cells/mm^3, and AZT+lamivudine+NVP (AZT+3TC+NVP) for those with a CD4 count of less than 200 cells/mm^3. The recent program assessment reported that the national rate of vertical HIV transmission was 5.4% compared with 33% without the PMTCT.[5]

Because of an increasing awareness of drug-resistant viruses among HIV-infected mothers exposed to sd-NVP and changes of practice in most developed countries where more highly effective combinations of 2 ARVs are commonly used for PMTCT, this study aims to assess the value for money of providing 3 ARVs compared with AZT+sd-NVP for PMTCT in Thailand. It is a collaborative research project involving the Department of Health (DOH), the Thai AIDS Society, and the Health Intervention and Technology Assessment Program, with the aim of providing evidence-based recommendations to the Advisory Committee on AIDS in Mother and Child, which develops the national guidelines for PMTCT, and the National Health Security Officer (NHSO), which provides financial support to the national PMTCT program.

Methods

This is a model-based health economic evaluation assessing the value for money of introducing 3 ARVs—AZT, 3TC, and efavirenz (AZT+3TC+EFV); and AZT, 3TC, and lopinavir/ritonavir (AZT+3TC+LPV/r)—in comparison to the current national protocol of a short-course AZT plus sd-NVP for HIV-infected pregnant women with a CD4 count >200 cells/mm^3. A decision tree was constructed to predict the costs and outcomes using the Thai governmental perspective (Figures 1 and 2). All costs were presented in Thai Baht as of 2009. Health outcomes were measured in terms of quality-adjusted life years (QALYs) gained from averting pediatric HIV infections. Input parameters were obtained from the national literature, if available, and international literature. A lifetime time horizon was applied with the use of a 3% discount rate as recommended in the national guidelines.[6]

Transitional Variables

Table 1 depicts the epidemiological parameters used in the model. Punsuwan[7] reported that from 14 provinces throughout the country, 92% of infected pregnant Thai women accepted ARV, either AZT+sd-NVP or AZT+3TC+NVP, as part of PMTCT. This report assumed the same acceptance rate for infected mothers receiving either the AZT+sd-NVP or the 3-ARV regimens because the latter has never been implemented in the country. Adherence to infant formula feeding was derived from the DOH, which reveals a rate of 98%.[8]

A clinical study in Thailand revealed that the HIV transmission rate of the intrapartum and peripartum period was 18.9%.[9] A meta-analysis suggested that the transmission rate via breastfeeding was 9.3%.[10] The DOH reported that the transmission rate was reduced to 3.5% with AZT+sd-NVP and formula feeding.[5] Meanwhile, 3-ARV regimens for pregnant women with

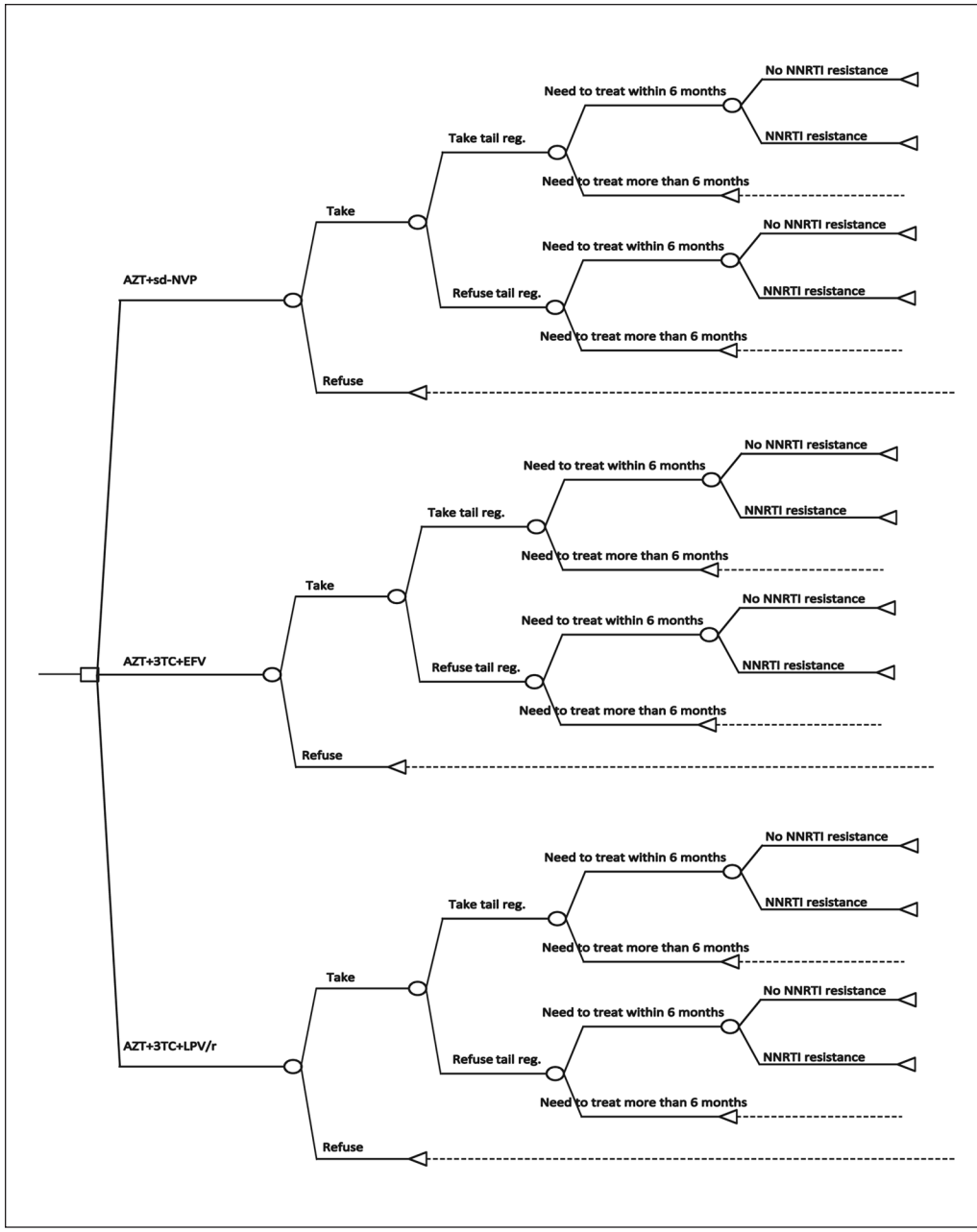

Figure 1. The decision tree model representing the consequences from different treatment regimens in pregnant women.
Abbreviations: AZT, zidovudine; sd-NVP, single-dose nevirapine; EFV, efavirenz; LPV/r, lopinavir/ritonavir; tail reg, AZT+lamivudine; NNRTIs, nonnucleoside reverse transcriptase inhibitors.

CD4 > 200 cells/mm^3 have never been implemented in Thailand before. Their effectiveness was identified through a systematic review of the Medline database using MeSH terms as follows: ["HIV Infections"(Mesh)] OR HIV) AND ["Anti-Retroviral Agents"(Mesh)] OR ["Antiretroviral Therapy, Highly Active"(Mesh)] OR (Antiretroviral Therapy) OR (Antiretroviral drug)) AND

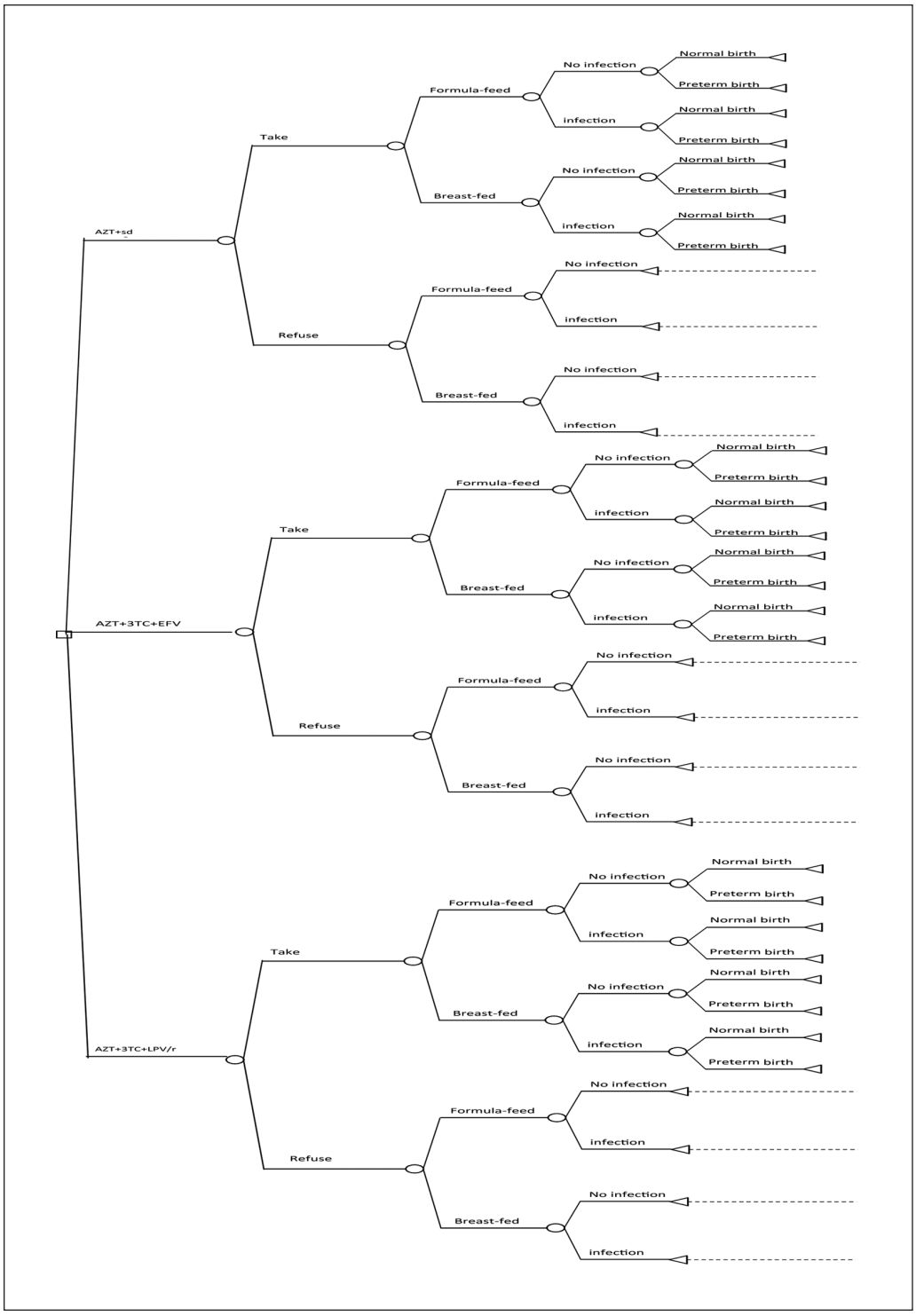

Figure 2. The decision tree model representing the consequences from different treatment regimens in newborns.

Abbreviations: AZT, zidovudine; sd-NVP, single-dose nevirapine; EFV, efavirenz; LPV/r, lopinavir/ritonavir; tail regimen, AZT+lamivudine.

Table 1. Input Parameters Used in Decision Models.

Model Inputs	Annual Transitional Probabilities	Reference Number
Intrapartum and peripartum HIV transmission rate	18.9	9
HIV transmission rate via breast-feeding	9.3	10
Vertical HIV transmission rate of AZT and sd-NVP regimen	3.5	5
Vertical HIV transmission rate of 3-ARV regimens	1.3	11-14
Acceptance rate of AZT and sd-NVP and 3-ARV regimen	0.92	7
Acceptance rate of infant formula feeding	0.98	8
Acceptance rate of receiving tail regimen	0.66	17
Probability of HIV-infected mothers needing ARV treatment within 6 months after delivery	0.18	15
Probability of development of ARV resistance in infected mothers not exposed to sd-NVP	0.25	15
Probability of development of ARV resistance in infected mothers exposed to sd-NVP, who received tail regimen and needed ARV treatment within 6 months after delivery	0.27	16
Probability of development of ARV resistance in infected mothers who did not receive tail regimen and needed ARV treatment within 6 months after delivery	0.41	15
Probability of premature delivery in mothers exposed to AZT	0.14	18
Probability of premature delivery in mothers exposed to EFV	0.19	18
Probability of premature delivery in mothers exposed to LPV/r	0.23	18

Abbreviations: AZT, zidovudine; sd-NVP, single-dose nevirapine; ARV, antiretroviral drug; EFV, efavirenz; LPV/r, lopinavir/ritonavir; tail regimen, zidovudine+lamivudine.

(Mother to child) OR (Mother-to-child) OR (Vertical transmission) AND (antenatal) OR (peripartum). The review identifies 4 relevant studies[11-14] in which their pool data suggested 1.3% of HIV transmission rate using any 3-ARV regimen.

Taking into account the development of drug resistance reported in the national and international literature, it was found that 41% of infected mothers who were exposed to sd-NVP without tail regimen and who needed ARV treatment within 6 months failed to respond to nonnucleoside reverse transcriptase inhibitors (NNRTI)-based treatment,[15] whereas only 27% of mothers exposed to sd-NVP with tail regimen were detected with NVP-resistant variants, using a standard genotyping technique, and were likely not to respond to the NNRTI-based treatment.[16] This study used findings from Thailand, which revealed that 66% of HIV-infected pregnant women exposed to sd-NVP received tail regimen within 7 days after delivery.[17] Other studies in Zambia, Kenya, and Thailand reported that only 18% of HIV-infected mothers exposed to sd-NVP needed ARV treatment within 6 months; this figure was assumed in this study for infected mothers needing ARV treatment regardless of whether or not they received tail regimen.[15] For HIV-infected mothers who needed ARV treatment for longer than 6 months, only 25% failed to respond to NNRTI-based treatment[15] and, therefore, required more expensive protease inhibitor (PI)-based treatment. For drug adverse side effects, a meta-analysis conducted in 2006 reported that the use of ARV for PMTCT increased the risk of premature births by 14% for single-drug regimens, 19% for combination non-PI-based regimens, and 23% for combination PI-based regimens.[18]

Outcome Variables

The utility data were derived from a Thai study, which measured 932 infected adults from 16 community hospitals throughout the country using EQ-5D.[19] The study reported utility weights

Table 2. Cost Parameters Used in Decision Models.

Cost Parameters	Thai Baht	Reference
Drug cost of AZT and sd-NVP regimen	2415	—[a]
Drug cost of AZT+3TC+EFV regimen	6609	—[a]
Drug cost of AZT+3TC+LPV/r regimen	12 411	—[a]
Drug cost of tail regimen (AZT+3TC, 7 days)	280	—[a]
Cost of premature birth	17 500	23
Cost of formula feeding	10 250	—[b]
Lifetime treatment cost of HIV infection in mothers not exposed to sd-NVP	212 200	21
Lifetime treatment cost of HIV infection in mothers exposed to sd-NVP	437 800	21
Lifetime treatment cost of pediatric HIV infection	764 200	22

Abbreviations: AZT, zidovudine; sd-NVP, single-dose nevirapine; 3TC, lamivudine; EFV, efavirenz; LPV/r, lopinavir/ritonavir.
[a]Cost of antiretroviral drugs were obtained from the National Health Security Office.
[b]Cost of formula feeding was obtained from the Department of Health.

of 0.860 for asymptomatic HIV infection and 0.759 for AIDS. Using the life table from the Burden of Disease study in Thailand[20] and the above utility data, QALYs gained from 1 pediatric, averted HIV infection was estimated at 16 years, compared with 67 years for those without HIV vertical transmission.[20] Also, a reduction of 0.05 QALYs is expected for each premature birth.[20]

Cost Variables

The program costs consisted of (1) costs of ARV and infant formula feeding, (2) costs of treatment of premature birth, (3) costs of treatment of pediatric HIV infection, and (4) costs of treatment of drug resistance among mothers. The costs of ARVs were obtained from the NHSO, and the costs of formula feeding were derived from the DOH. The lifetime treatment costs of HIV infection in mothers with and without exposure to sd-NVP were obtained from an economic evaluation study comparing EFV-based treatment and NVP-based treatment in Thailand.[21] The lifetime treatment costs of pediatric HIV infection were estimated from another economic evaluation study in HIV vaccine for the Thai population.[22] It was assumed in this study that the costs associated with the health services for premature births are similar to the costs for low birth weight as reported in a study by Neramitpitagkul et al,[23] which analyzed data from the Central Office for Healthcare Information, a national center that gathers information from 95% of the public and private hospitals in the country (Table 2).

Uncertainty Analysis

A 1-way sensitivity analysis was conducted to assess uncertainty surrounding the key input parameters. First, the vertical HIV transmission rate of the AZT+sd-NVP regimen was assessed and ranged from 1.3% to 5.3% as reported in a clinical trial in Thailand[24] and in the national program evaluation conducted by the DOH,[5] respectively. Second, the transmission rate of the 3-ARV regimens ranged from 1.0% to 1.6% based on a 95% confidence interval obtained from our meta-analysis. Third, the probability of the development of ARV resistance in infected mothers exposed to sd-NVP, receiving tail regimen, and needing ARV treatment within 6 months after delivery was assumed to range from 18% to 75%, based on the results of the subgroup analysis of the same article used for base-case analysis.[25] Fourth, because there was no probability of the development of ARV resistance in infected mothers exposed to 3-ARV regimens, this study

Table 3. Cost (2009 Thai Baht) and Outcome in Each Regimen.

Regimen	Cost of ARVs and Formula Feeding	Cost of Treatment of Premature Birth	Cost of Treatment of Pediatric HIV Infection	Cost of Treatment of Drug Resistance in Mothers	Total Program Cost	Quality-Adjusted Life Year (QALYs)	Incremental Cost-effectiveness Ratio per QALY (ICER)
AZT+sd-NVP	12 400	2300	12 300	36 600	63 600	64.549	—
AZT+3TC+EFV	16 300	3100	9600	21 300	50 300	65.560	−13 200
AZT+3TC+LPV/r	21 500	3700	9600	21 300	56 100	65.560	−7400

Abbreviations: ARV, antiretroviral; QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; AZT, zidovudine; sd-NVP, single-dose nevirapine; 3TC, lamivudine; EFV, efavirenz; LPV/r, lopinavir/ritonavir.

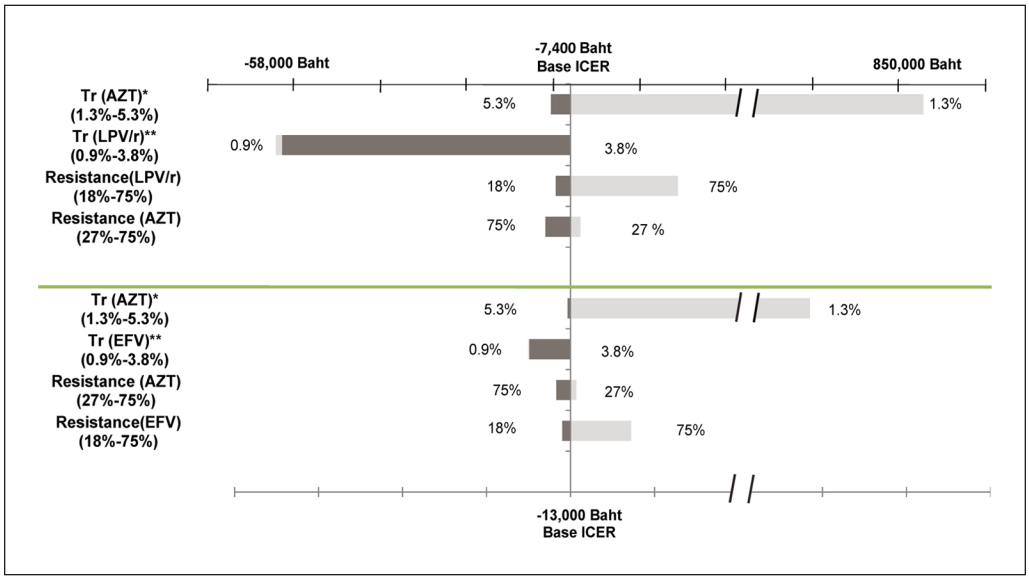

Figure 3. Tornado diagram from 1-way sensitivity analysis (bars above the green line are results comparing AZT+sd-NVP with LPV/r-based treatment, bars below the green line are results comparing AZT+sd-NVP with EFV-based treatment.
Abbreviations: AZT, zidovudine; sd-NVP, single-dose nevirapine; EFV based, AZT+lamivudine+efavirenz; LPV/r based, AZT+lamivudine +lopinavir/ritonavir; tail reg, AZT+lamivudine; ICER, incremental cost-effectiveness ratio.

assumed similar rates of ARV resistance (18% and 75%) in the uncertainty analysis. Finally, the acceptance rate of receiving tail regimen ranged from 39% to 100%.

Results

Table 3 shows that AZT+3TC+EFV has the lowest total program costs, followed by AZT+3TC+LPV/r, and AZT+sd-NVP. It is noteworthy that, although AZT+sd-NVP offers the lowest PMTCT cost and treatment cost related to premature birth, it causes the highest treatment costs for pediatric HIV infection and ARV resistance in mothers. Meanwhile, the 3-ARV regimens yield a similar health gain at 65.56 QALYs compared with 64.55 QALYs for AZT+sd-NVP. Thus, the 3-ARV regimens do save costs compared with AZT+sd-NVP. In addition, approximately 1 QALY is gained as a result of using the 3-ARV regimens.

The results from the 1-way sensitivity analysis are shown in the tornado diagram in Figure 3. It was found that the effectiveness of ARV regimens is among the most important parameters determining the value for money of the PMTCT, following the probability of development of

ARV resistance in infected mothers exposed to sd-NVP, receiving tail regimen, and needing ARV treatment within 6 months after delivery. The acceptance rate of tail regimen plays a minimal role in the cost-effectiveness determination.

Discussion

This study demonstrated that the combinations of 3 ARVs for PMTCT were cost-effective compared with AZT+sd-NVP, under the Thai health care setting. This is because the 3-drug regimens saved more treatment costs of pediatric HIV infection and long-term consequences of ARV resistance in mothers. These savings outweigh the higher drug costs of 3TC, EFV, and LPV/r and the treatment costs of premature births, which are adverse effects of using the 3-drug regimen. As a result, it is recommended that the national protocol for PMTCT for HIV-infected pregnant women with a CD4 count greater than 200 cells/mm^3 be changed to the 3-drug regimen (at the time when this study was conducted, the cutpoint for antiretroviral treatment was 200 cells/mm^3).

After WHO launched the recommendation of PMTCT guidelines late in the year 2009,[26] we identified 3 economic evaluation studies related to drug regimens for PMTCT. These included studies conducted in Tanzania,[27] Nigeria,[28] and Zimbabwe.[29] All studies did not focus on populations with high CD4 levels but considered all HIV-infected pregnant women. These studies came to the same conclusion, showing that using 3-drug regimens are cost-effective. A higher adherence to ARVs and formula feeding was observed in this study because Thailand has good health care infrastructure and a high utilization rate of maternal and child health services. In addition, the costs of LPV/r and EFV used in this study are likely to be lower than those available in other settings because they are under the recent government use licenses, which result in a significant reduction of the drug costs.[30] Thus, adopting results from this study should be done with caution.

There are some limitations to this study. First, this model did not account for all possible costs of the program. These include (1) the cost of adverse effects of EFV and LPV/r during pregnancy, (2) the treatment cost of long-term side effects of using PI-based regimens in mothers and children who were exposed to sd-NVP and developed ARV resistance, (3) the treatment cost of ARV resistance in partners of mothers exposed to sd-NVP and who developed ARV resistance, and (4) the treatment cost of ARV resistance in pediatric HIV-infected babies delivered from mothers exposed to sd-NVP. Second, because this study adopted the government's perspective, it omitted direct nonmedical costs, such as the transportation cost of patients, and indirect costs, for example, the cost of sick leave. It is expected that 3-drug regimens will be cost-effective if the societal perspective is used. Third, this model did not take account of health outcomes in terms of QALYs gained from avoiding ARV resistance in both mothers and infants. If included, this could lead to higher cost savings for the use of 3-ARV regimens. Fourth, this study assumed no different adverse effects between the two 3-ARV regimens despite the fact that there was concern over reports of neural tube defects in infants with mothers exposed to EFV.[26,31] Fifth, this study was conducted at the time when the national guidelines for HIV/AIDS treatment referred to the cutpoint of 200 cells/mm^3. In 2012, the guidelines were revised,[32] indicating the new cutpoint of 350 cells/mm,^{3} and these would affect the cost and outcome of the programs. However, we strongly believe that the study conclusion remains valid.

Finally, this is a computer simulation study and may not reveal possible barriers of implementing 3-ARV regimens for PMTCT. Therefore, a feasibility study that assessed the technical and practical barriers of introducing a 3-drug regimen (AZT+3TC+LPV/r) for PMTCT was carried out in 46 public hospitals in 4 provinces throughout Thailand. It was found that it is feasible to replace AZT+sd-NVP with the combination of 3 ARV drugs. During July and November 2009, 33 HIV-infected pregnant women were identified in those hospitals under study, and 100% of them accepted the use of the 3-ARV regimen, with high adherence. Using newly developed

health education materials to inform HIV-infected mothers about the benefits and risks of the 3-ARV regimens, it was demonstrated that the protocol of the 3-ARV drug regimen is simple and feasible in the Thai health care setting.

Final Remark

The findings of this study were presented to the Advisory Committee on AIDS in Mother and Child and the Subcommittee of HIV/AIDS System Development of the NHSO in September and November 2009, respectively. Decision makers decided to adopt the new ARV protocol using AZT+3TC+LPV/r as the new national regimen for HIV-infected pregnant women with a CD4 count >200 cells/mm^3. The reasons why AZT+3TC+LPV/r was selected as the national regimen—because of the concerns among health professional over the potential adverse effects, that is, neural tube defect in infants born from mothers exposed to EFV—were not included in the economic model.

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