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ORIGINAL ARTICLE

Randomized Controlled Trial and Meta-analysis of Oral Decontamination with 2% Chlorhexidine Solution for the Prevention of Ventilator-Associated Pneumonia

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OBJECTIVE. To determine the effectiveness of oral decontamination with 2% chlorhexidine solution for the prevention of ventilator-associated pneumonia (VAP).

DESIGN. Randomized controlled trial and meta-analysis.

SETTING. A tertiary care university hospital in Bangkok, Thailand.

PARTICIPANTS. Adult patients who received mechanical ventilation and who were hospitalized in intensive care units and general medical wards.

METHODS. The patients were randomized to receive oral decontamination with 2% chlorhexidine solution or normal saline solution 4 times per day until their endotracheal tubes were removed. The outcome measures were the development of VAP and oropharyngeal colonization with gram-negative bacilli. Meta-analysis was performed by combining the results of the present study with those from another randomized controlled trial that also used a 2% chlorhexidine formulation for oral decontamination.

RESULTS. The characteristics of the patients in the chlorhexidine group ($n = 102$) and the normal saline group ($n = 105$) were not significantly different. The incidence of VAP in the chlorhexidine group was 4.9% (5 of 102), and the incidence in the normal saline group was 11.4% (12 of 105) ($P = .08$). The rate of VAP in the chlorhexidine group was 7 episodes per 1,000 ventilator-days, and the rate in the normal saline group was 21 episodes per 1,000 ventilator-days ($P = .04$). Irritation of the oral mucosa was observed in 10 (9.8%) of the patients in the chlorhexidine group and in 1 (0.9%) of the patients in the normal saline group ($P = .001$). Oropharyngeal colonization with gram-negative bacilli was either reduced or delayed in the chlorhexidine group. Overall mortality of the patients did not differ significantly between the groups. Meta-analysis of 2 randomized controlled trials revealed an overall relative risk of VAP for patients in the chlorhexidine group of 0.53 (95% confidence interval, 0.31-0.90; $P = .02$).

CONCLUSION. Oral decontamination with 2% chlorhexidine solution is an effective and safe method for preventing VAP in patients who receive mechanical ventilation.

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Nosocomial pneumonia among patients receiving mechanical ventilation, also called ventilator-associated pneumonia (VAP), is an important nosocomial infection worldwide, which leads to increases in length of hospital stay, healthcare costs, and mortality.[1-5] The rate of VAP in Siriraj Hospital (Bangkok, Thailand) was 14 episodes per 1,000 ventilator-days, and 90% of the causative agents were gram-negative bacilli.[5] An episode of VAP in Siriraj Hospital increased the length of a patient's hospital stay by a mean of 13.2 days, increased the cost of antimicrobial therapy by a mean of $400, and contributed to a 20% increase in mortality.[5] Oral and dental colonization with pathogens in patients who received mechanical ventilation is associated with the development of VAP.[6,7] Therefore, oral decontamination with antibiotics and/or antiseptics has been attempted for the prevention of pneumonia in these patients.

A meta-analysis of good-quality randomized controlled trials[8-11] of oral decontamination with antibiotics for the prevention of pneumonia in patients who received mechanical ventilation revealed that topical antibiotic therapy was not an effective method of preventing VAP. Randomized controlled trials of oral decontamination showed that topical use of 0.12% or 0.2% chlorhexidine solution was effective for preventing pneumonia in patients who underwent cardiothoracic surgery.[8-17] The Centers for Disease Control and Prevention guideline for the prevention of healthcare-associated pneumonia published in 2004 made no recommendation on routine oral decontamination with chlorhexidine solution for

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the prevention of healthcare-associated pneumonia in critically ill patients and other patients who received mechanical ventilation and were at high risk for pneumonia.[18]

In 2006, we initiated a randomized controlled trial to determine the effectiveness and safety of using a higher concentration of chlorhexidine in solutions used for oral decontamination to prevent VAP. However, 3 meta-analyses published in 2007 revealed that oral decontamination with chlorhexidine solution reduced pneumonia in patients who received mechanical ventilation.[19-21] These meta-analyses included a randomized controlled trial published in 2006 that used 2% chlorhexidine solution for oral decontamination.[22] They found that 2% chlorhexidine oral decontamination was marginally effective for the prevention of pneumonia in patient who received mechanical ventilation, with a relative risk (RR) of 0.58 (95% confidence interval [CI], 0.31-1.09). Hence, we also performed a meta-analysis that included only the randomized controlled trials that evaluated oral decontamination with 2% chlorhexidine to prevent pneumonia in patients who received mechanical ventilation.

METHODS

Randomized Controlled Trial

The study was approved by the Ethics Committee on Human Research, Faculty of Medicine Siriraj Hospital. The study was conducted from January 2006 through March 2007 at Siriraj Hospital, which is a 2,300-bed, tertiary care university hospital.

Eligible patients were adults aged 18 years or older who were hospitalized in intensive care units (a total of 36 beds) or general medical wards (a total of 240 beds) at Siriraj Hospital and who received mechanical ventilation. Patients who had pneumonia at enrollment or who had a chlorhexidine allergy were excluded. Each eligible patient was randomized to the chlorhexidine group or the normal saline group by

TABLE 1. Demographic and Clinical Characteristics of 207 Study Patients Who Received Mechanical Ventilation and Oral Decontamination

Characteristic	Chlorhexidine group (n = 102)	Normal saline group (n = 105)	P
Age, mean ± SD, years	56.5 ± 20.1	60.3 ± 19.1	.15
Sex			
Male	50 (49.1)	51 (48.6)	.78
Female	52 (50.9)	54 (51.4)	
Ward			
Surgical ICU	50 (49.0)	51 (48.6)	.99
General medical ward	40 (39.2)	42 (40.0)	
Medical ICU	12 (11.8)	12 (11.4)	
Underlying disease			
Yes	75 (73.5)	75 (71.4)	.75
No	27 (26.5)	30 (28.6)	
Reason for endotracheal intubation			
Upper airway obstruction	15 (14.7)	23 (21.9)	.21
Oxygenation failure	66 (64.7)	61 (58.0)	.39
Airway protection	31 (30.4)	40 (38.0)	.30
Secretion obstruction	32 (31.4)	33 (31.4)	.99
Ventilatory failure	45 (44.1)	42 (40.0)	.57
Duration of mechanical ventilation, mean, days	4.5	5.2	.38
Risk factor for VAP			
Prior infection	23 (22.5)	30 (28.6)	.33
Prior antibiotic use	48 (47.0)	60 (57.1)	.16
Bronchodilator use	11 (10.8)	10 (9.5)	.82
Corticosteroid use	9 (8.8)	16 (15.2)	.2
Acid reduction agent use	75 (73.5)	69 (65.7)	.28
Reintubation	5 (4.9)	5 (4.8)	.99
Invasive device(s) present	59 (57.8)	65 (61.9)	.56
Nasogastric tube present	85 (83.3)	86 (81.9)	.99
Thoracoabdominal surgery	29 (28.4)	28 (26.7)	.87
APACHE II score, mean ± SD	16.7 ± 7.9	18.2 ± 8.1	.16

NOTE. Data are no. (%) of patients, unless otherwise indicated. APACHE, Acute Physiology and Chronic Health Evaluation; ICU, intensive care unit; VAP, ventilator associated pneumonia.

TABLE 2. Outcomes for 207 Study Patients Who Received Mechanical Ventilation and Oral Decontamination

Variable	Chlorhexidine group (n = 102)	Normal saline group (n = 105)	P
No. (%) of patients who developed VAP	5 (4.9)	12 (11.4)	.08[a]
No. of cases of VAP per 1,000 ventilator-days, mean	7	21	.04
No. (%) of patients with irritation of oral mucosa	10 (9.8)	1 (0.9)	.001

NOTE. VAP, ventilator-associated pneumonia.
[a] Relative risk, 0.43 (95% confidence interval, 0.16-1.17).

stratified randomization according to the sex and hospital location of the eligible patient. Patients in the chlorhexidine group received oral care 4 times per day that involved brushing the teeth, suctioning any oral secretions, and rubbing the oropharyngeal mucosa with 15 mL of a 2% chlorhexidine solution formulated and produced by the hospital's pharmacy department. The patients in the normal saline group underwent the same oral care procedure, except that their procedures used normal saline solution instead of chlorhexidine solution. The oropharyngeal cleaning with 2% chlorhexidine solution or normal saline solution was continued until the endotracheal tube was removed. All participating wards employed their usual care protocols, according to which a semirecumbent body position was maintained, if possible. Neither selective decontamination of the digestive tract nor continuous aspiration of subglottic secretions were performed for any patient.

Each patient was examined daily for the presence of pneumonia. A diagnosis of VAP was made if the patient had a new, persistent, or progressive infiltrate visible on a chest radiograph in combination with at least 3 of the following 4 criteria: (1) body temperature greater than 38°C or less than 35.5°C, (2) leukocytosis (defined as more than 10×10^3 leukocytes/mm^3) or leukopenia (defined as less than 3×10^3 leukocytes/mm^3), (3) purulent tracheal aspirate, and/or (4) a semiquantitative culture of tracheal aspirate samples that was positive for pathogenic bacteria. An oropharyngeal swab sample was taken from each patient immediately after endotracheal intubation, on day 3 after intubation, on day 7 after intubation, and every 7 days thereafter until the endotracheal tube was removed or the patient developed pneumonia. The oropharyngeal swab sample was placed on blood agar and McConkey agar for semiquantitative culture. The bacterial colonies on agar plates were graded as 1+, 2+, 3+, or 4+ to indicate growth seen in quadrants 1, 2, 3, or 4 of the plates; the plates without growth were graded "no growth."

A sample size of 108 patients per group was estimated to be necessary in order to determine whether oral decontamination with 2% chlorhexidine solution could reduce the rate of VAP from 14 to 7 episodes per 1,000 ventilator-days with 5% type I error (1-sided) and 80% power. The data were analyzed by descriptive statistics, the unpaired Student t test, χ^2 square statistics, and the Mann-Whitney U test, as appropriate. A P value of .05 or less was considered statistically significant.

Meta-analysis

Randomized controlled trials that used a 2% chlorhexidine formulation for oral decontamination as the sole intervention for patients receiving mechanical ventilation and reported the incidence of pneumonia as a study outcome were selected from the studies included in 3 recent meta-analyses.[19-21] The details of the selected studies were reviewed, and the data were combined with the data from the present randomized controlled trial by use of RevMan software, version 4.2 (Cochrane Collaboration). The pooled effect sizes of relative risk were estimated with the Mantel-Haenszel fixed effect model.

RESULTS

Randomized Controlled Trial

Of 207 patients enrolled to the study, 102 were randomized to the chlorhexidine group and 105 to the normal saline group. Patients' demographic characteristics, location, disease severity, and duration of mechanical ventilation did not differ significantly (Table 1). The effectiveness and safety of using a 2% chlorhexidine solution for oral decontamination to prevent VAP are shown in Table 2. The incidence of VAP was 4.9% (5 of 102) in the chlorhexidine group and 11.4% (12 of 105) in the normal saline group (RR, 0.43 [95% CI 0.16-1.17]; P = .08). The mean number of cases of VAP was 7 episodes per 1,000 ventilator-days in the chlorhexidine group and 21 episodes per 1,000 ventilator-days in the normal saline group (P = .04). In all patients, VAP was caused by gram-negative bacilli. Mild and reversible irritation of the oral mucosa was observed in 10 (9.8%) of the chlorhexidine group, compared with 1 (0.9%) of the normal saline group (P = .001). The outcomes for 110 patients who received mechanical ventilation for longer than 2 days are shown in Table 3. The patients in the chlorhexidine group also had less risk of developing VAP, compared with the normal saline group.

TABLE 3. Outcomes for 110 Patients Who Received Mechanical Ventilation for More Than 2 Days

Variable	Chlorhexidine group (n = 58)	Normal saline group (n = 52)	P
No. (%) of patients who developed VAP	5 (8.6)	10 (19.2)	.11[a]
No. of cases of VAP per 1,000 ventilator-days, mean	13	23	.06

NOTE. VAP, ventilator-associated pneumonia.
[a] Relative risk, 0.45 (95% confidence interval, 0.16-1.23).

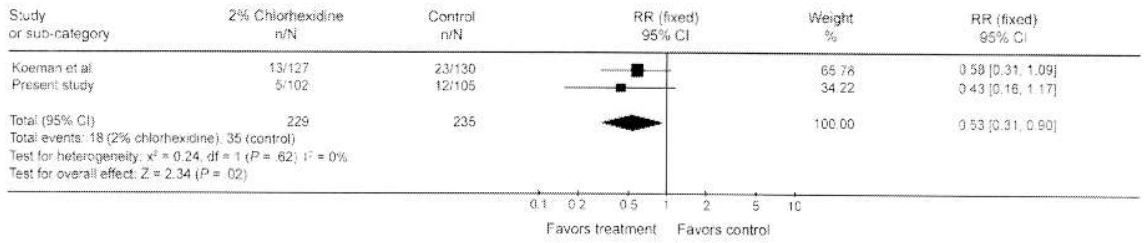

FIGURE. Forest plot of the meta-analysis (fixed effect model) of data from the Koeman et al.[22] study and data from the present study on all patients who received mechanical ventilation. CI, confidence interval.

Observations regarding oropharyngeal colonization with gram-negative bacilli revealed the following findings: (1) gram-negative bacilli were present on the day of enrollment in 63 (61.8%) of the chlorhexidine group and in 71 (67.6%) of the normal saline group, (2) a total of 15 (38.5%) of 39 patients in the chlorhexidine group and 28 (82.4%) of 34 in the normal saline group were newly colonized with gram-negative bacilli, (3) at total of 12 (19.1%) of 63 patients in the chlorhexidine group and 0% of the normal saline group converted from being colonized with gram-negative bacilli to not being colonized, (4) a total of 21 (53.8%) of 39 patients in the chlorhexidine group and 3 (8.8%) of 34 in the normal saline group had no gram-negative bacilli recovered from oropharyngeal swab samples over the whole study period, (5) the amount of gram-negative bacilli recovered on culture increased in 9 (14.3%) of 63 patients in the chlorhexidine group and 36 (50.7%) of 71 in the normal saline group; and (6) the amount of gram-negative bacilli recovered was reduced in 27 (42.8%) of 63 patients in the chlorhexidine group and in 10 (14.1%) of 71 in the normal saline group. The overall mortality rate for the patients in the chlorhexidine group was 32.3% (36 of 102), compared with 35.2% (37 of 105) in the normal saline group ($P = .7$).

Meta-analysis

We found that there was only 1 randomized controlled trial that evaluated oral decontamination with a 2% chlorhexidine formulation as the sole intervention for patients who received mechanical ventilation that also reported the incidence of pneumonia as a study outcome.[22] We performed a pooled analysis of data from that trial and data from all patients in the present trial, as well as a pooled analysis of data from that trial and data from the patients in the present trial who received mechanical ventilation for more than 48 hours. The results of the first pooled analysis are shown in the Figure. Heterogeneity was not detected in either analysis ($P > .5$). There was a significant reduction in the rate of VAP among patients in the chlorhexidine group, with a relative risk of 0.53 (95% CI, 0.31-0.90; $P = .02$) for all patients and a relative risk of 0.54 (95% CI, 0.31-0.92; $P = .02$) for patients who received mechanical ventilation for more than 48 hours. A total of 14 patients would need to receive oral decontamination with 2% chlorhexidine solution to prevent 1 additional case of VAP.

DISCUSSION

Chlorhexidine is a broad spectrum antiseptic agent. Its spectrum of antimicrobial activity includes gram-negative and gram-positive bacteria.[23] Among its most important attributes is its persistence: it remains chemically active on tissue for up to 6 hours. Chlorhexidine solution has been used as an anti-infective oral rinse in dental medicine. Although oral decontamination with low concentrations of chlorhexidine (0.12%-0.2%) has been found to be effective in preventing pneumonia in patients undergoing cardiothoracic surgery, its role in preventing pneumonia in critically ill patients who received mechanical ventilation had not been established prior to 2006.[19-21] Therefore, we hypothesized that oral decontamination with a higher concentration of chlorhexidine might be more effective at preventing pneumonia in critically ill patients than is decontamination with a low-concentration solution. We asked the hospital's pharmacy department to formulate and produce a 2% chlorhexidine oral solution. An in vitro study of locally produced 2% chlorhexidine solution in our laboratory revealed that it was active against multidrug-resistant bacteria, including *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and methicillin-resistant *Staphylococcus aureus*.

We were unable to do a blind study because the odor and taste of the chlorhexidine solution were quite different from those of the normal saline solution. However, the assessors who determined whether a patient developed pneumonia were unaware of the patient's study group assignment. The results of our randomized controlled trial demonstrated that oral decontamination with 2% chlorhexidine solution was effective at preventing pneumonia in patients who received mechanical ventilation, similar to the results of a recent study published in 2006.[22] Our study paid more attention to oropharyngeal colonization with gram-negative bacilli, because more than 90% of cases of VAP in our hospital were caused by gram-negative bacilli.[5] More than 60% of the patients in our study had oropharyngeal colonization with gram-negative bacilli, because a large proportion of them had chronic un-

derlying diseases or had been hospitalized prior to endotracheal intubation. Among the patients who received 2% chlorhexidine oral rinse, the rate of oropharyngeal colonization with gram-negative bacilli was reduced or the onset of colonization was delayed.

Although a combination of chlorhexidine and colistin resulted in better oropharyngeal decontamination for gram-negative bacteria than did chlorhexidine alone, both regimens appeared equally effective at preventing VAP.[22] Therefore, use of 2% chlorhexidine solution alone should be sufficient for prevention of VAP in patients who receive mechanical ventilation. It should be noted that 9.8% of the patients who received 2% chlorhexidine oral solution developed irritation of the oral mucosa. We observed that many patients who developed irritation were hospitalized in wards in which the personnel responsible for oral care usually vigorously rubbed the oropharyngeal mucosa with gauze soaked with 2% chlorhexidine solution. The incidence of irritation was reduced after personnel were instructed to clean the oropharyngeal mucosa gently. Healthcare workers should be aware of this side effect and should discontinue the use of 2% chlorhexidine oral solution if a patient experiences severe irritation of the oral mucosa.

We analyzed combined data from our study and another study because both studies were randomized controlled trials and both used the same concentration of chlorhexidine. Although there were several differences between the studies with respect to the formulation of 2% chlorhexidine solution and the eligibility criteria of the patients enrolled, the test of heterogeneity revealed a P value of greater than 0.1, indicating that there was no significant heterogeneity between the studies and that the results from both studies could be combined. Similar to the results from other meta-analyses, the pooled analysis of data from the other trial and data from all patients from our study revealed a significant reduction in the rate of VAP in the chlorhexidine group, as did a pooled analysis of data from the other study and data for patients in this study who received more than 48 hours of mechanical ventilation.[20]

Although oral decontamination with chlorhexidine reduced the risk of VAP in patients who received mechanical ventilation, no differences in duration of mechanical ventilation, length of intensive care unit stay, or mortality could be demonstrated.[20,22] Our study also failed to demonstrate a reduction in the mortality rate among patients who received oral decontamination with chlorhexidine. Nevertheless, oral decontamination with 2% chlorhexidine solution for the prevention of VAP is still considered a cost-effective strategy, because the cost of the solution in Siriraj Hospital was only 40 cents per day and the number needed to treat is 14. At our institution, the mean total cost of 2% chlorhexidine solution for 14 patients was $34, which is much less than the mean cost of antibiotic therapy to treat an episode of VAP ($400). Therefore, beginning in August 2007, Siriraj Hospital adopted a policy that recommended oral decontamination with 2% chlorhexidine solution for prevention of VAP for adult patients who receive mechanical ventilation.

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Funding agencies in low- and middle-income countries: support for knowledge translation

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Objective The aim was to describe how selected health research funding agencies active in low- and middle-income countries promote the translation of their funded research into policy and practice.

Methods We conducted inductive analysis of semi-structured interviews with key informants from a purposive sample of 23 national and international funding agencies that fund health research in Brazil, Colombia, India, the Philippines, South Africa and Thailand. We also surveyed web sites.

Findings We found a commitment to knowledge translation in the mandate of 18 of 23 agencies. However, there was a lack of common terminology. Most of the activities were traditional efforts to disseminate to a broad audience, for example using web sites and publications. In addition, more than half (13 of 23) of the agencies encouraged linkage/exchange between researchers and potential users, and 6 of 23 agencies described "pull" activities to generate interest in research from decision-makers. One-third (9 of 23) of funding agencies described a mandate to enhance health equity through improving knowledge translation. Only 3 of 23 agencies were able to describe evaluation of knowledge translation activities. Furthermore, we found national funding agencies made greater knowledge translation efforts when compared to international agencies.

Conclusion Funding agencies are engaged in a wide range of creative knowledge translation activities. They might consider their role as knowledge brokers, with an ability to promote research syntheses and a focus on health equity. There is an urgent need to evaluate the knowledge translation activities of funding agencies.

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Une traduction en français de ce résumé figure à la fin de l'article. Al final del artículo se facilita una traducción al español. الترجمة العربية لهذه الخلاصة في نهاية النص الكامل لهذه المقالة.

Introduction

For knowledge to benefit society, it needs to be shared, communicated and translated into policy, practice or community action.[1] Increased commitment to knowledge translation is reflected by the 58th World Health Assembly's declaration in 2005, which encouraged enhanced knowledge transfer.[2] Several international initiatives focus on knowledge translation in low- and middle-income countries (LMICs) such as the Overseas Development Institute's RAPID programme (Research and Policy in Development), the WHO/PAHO EVIPNet initiative (Evidence-Informed Policy Networks) and the WHO Knowledge Management and Sharing initiative.

The WHO Department of Knowledge Management and Sharing defines knowledge translation as: "The synthesis, exchange and application of knowledge by relevant stakeholders to accelerate the benefits of global and local innovation in strengthening health systems and improving people's health."[3] Because of the dearth of primary research performed in their own countries and the disproportionately low research resources available, LMICs need to engage in the translation of knowledge that is cost-effective and applicable to their local settings.[4]

Knowledge translation is a complex and nonlinear process, and is generally slow, particularly in LMICs.[5,6] Slow knowledge transfer can result in inappropriate care. Many examples in LMICs have shown variations in practice despite established guidelines; for

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example, antibiotic prophylaxis with caesarean section,[7] management of acute myocardial infarction[8] and management of pneumonia.[9] In one example, a study of Shanghai hospitals found that more than 70% of births involved clinical practices that are ineffective and should be avoided based on the best available evidence from the Cochrane Library.[10]

Knowledge translation may help bridge the know–do gap, particularly in disadvantaged populations.[3] Utilization of treatments with demonstrated effectiveness, such as immunization, oral rehydration for diarrhoea and treatment for acute respiratory infection, is up to 50% lower for the poorest.[11–13] Knowledge translation interventions that enhance access, diagnostic accuracy, provider compliance or consumer adherence could enhance community effectiveness of interventions in disadvantaged populations.[14]

Because research funding agencies are the gatekeepers to funds for conducting research, they may be able to encourage knowledge translation and exchange by their funding recipients. They can also actively disseminate information, involve end users in prioritizing research topics and fund implementation research. However, little is known about funding agency policies to promote knowledge translation.

This project was designed as an exploratory, descriptive study to increase understanding of the knowledge translation policies and activities of applied health research funders within LMICs and international funding agencies.

Methods

We conducted inductive analysis of semi-structured interviews with key informants from a judgement sample of funding agencies supplemented by document analysis from the agency web sites, including strategic plans, mandate and application procedures. This method provides a richness of data that cannot be assessed using questionnaire surveys since participants could respond freely as well as illustrate concepts with examples and the interviewer could probe for more details.[15] Document analysis and findings from interviews were triangulated to present a complete picture of knowledge translation activities. We used the Lavis framework of push, pull, linkage/exchange and integrated efforts to classify knowledge translation activities.[16]

Sampling

We selected six LMICs, based on the presence of substantial within-country health research funding: Brazil, Colombia, India, the Philippines, South Africa and Thailand. None of these countries were among the least developed countries, where external funding agencies would be responsible for a larger proportion of health research funding (e.g. Bangladesh or Mozambique).[17] Because this is an exploratory study of knowledge translation, we chose to use criterion-based purposive sampling, a non-probability sampling method that selects informants based on predefined criteria.[18] As with other non-probability sampling methods, purposive sampling does not produce a sample that is representative of a larger population, but it is useful to study a clearly defined group. Our criterion for selecting funding agencies was the extent to which they funded applied health research. We selected a total of 14 national funding agencies from these six LMICs and nine international funding agencies, based on these criteria. Some country investigators applied additional criteria that are listed in Table 1. For each agency, we aimed to interview three key informants: someone from senior management with strategic responsibility, a research manager with responsibility for applied research programmes and a knowledge transfer officer. We interviewed key informants from 23 agencies between September 2003 and September 2004 (Table 1).

Interviews

The interviews were conducted face-to-face or via telephone by one of the authors, using a semi-structured interview framework (Table 2). Participants were asked to provide relevant documents or web sites that contained policy statements on knowledge translation as well as copies of grant application forms. Data was extracted using the same framework as the interview guide.

The interview guide was translated into Portuguese, Spanish and Thai. Each translation was back-translated into English by a second translator who had not seen the original English version. The English back-translation and the original were then compared. If the back-translated items and the original did not agree, the first translator conducted a second translation. A second back-translation was repeated. This process continued until the translation was judged satisfactory.

The audio-tapes were transcribed verbatim and verified by the interviewer before analysis. Transcripts were coded in their original language, and then translated to English to permit comparison of the findings from all the countries using the same approach used to translate the interview guide.

Two types of bias threaten this type of semi-structured interview and inductive analysis: description bias and interpretation bias. To minimize description bias, we transcribed interviews verbatim and used back-translation methods to ensure accurate translations. To minimize interpretation bias, we asked agency interviewees to verify data and we verified the coding with all co-investigators.

Analysis

We used inductive analysis to code and categorize data.[19,20] We identified eight main themes: role of agency, background, researcher requirements, application process, dissemination activities, agency initiatives, evaluation and target audience. We further identified subcategories within each of these codes. Each of the LMIC investigators used these codes and subcategories to classify their data. The initial coding of all the data was performed by the interviewers in the LMIC and the co-investigator in that country.

To ensure that analysis was consistent between countries, we checked the classification of the verbatim transcripts at the central coordinating office in Ottawa, Canada, and finalized the coding by consensus through conference calls and e-mails with the investigators to ensure common understanding. We verified the final coding with the interviewees, allowing them to add or update information.

The analysis of this hypothesis-generating study focused on the nature of the knowledge translation activities of funding agencies and their perception about needs for improvement. We did not aim to compare funding

Table 1. **Funding agencies interviewed**

Country	Abbreviation	Organization	Additional selection criteria
International	CIDA	Canadian International Development Agency	–
	DFID	Department for International Development (United Kingdom)	–
	IDRC	International Development Research Centre	–
	USAID	United States Agency for International Development	–
	WHO/TDR	WHO – Special Programme for Research and Training in Tropical Diseases	–
International agencies interviewed at country offices	CIDAb	CIDA – Brazil office	Continued support of regional development
	PAHO	Pan American Health Organization – Brazil office	–
	WBp	World Bank – Philippines office	Chosen because of its extensive and innovative knowledge translation activities
Brazil	FAPESP	State of São Paulo Research Foundation	Most stable research granting institution
	CNPq	National Council for Scientific and Technological Development	Responsible for establishing national policies for research
Colombia	Colciencias	Instituto Colombiano para el Desarrollo de la Ciencia y la Tecnología	External recognition as research funders; number of projects supported; availability of key informants
	MSP	Ministry for Social Protection (equivalent to Ministry of Health)	
India	ICSSR	Indian Council for Social Science Research	–
	DFIDi	Department for International Development – India office	–
	ICMR	Indian Council of Medical Research	Largest national funding agency for medical research
Philippines	PCHRD	Philippine Council for Health Research and Development	Mandated by law to perform and promote basic and applied research
	DOH	Department of Health	Focused on systems and health-care delivery research
South Africa	MRC	Medical Research Council of South Africa	–
	HST	Health Systems Trust	–
Thailand	TRF	Thailand Research Fund	Major national funding agencies and the extent to which they were likely to perform knowledge translation
	HSRI	Health Systems Research Institute	
	NRCT	National Research Council of Thailand	
	NSTDA	National Science and Technology Development Agency	

agencies, hence individual results for each funding agency are not presented. Furthermore, because we did not interview all departments within each agency, we could not be certain that we had captured all knowledge translation activities.

Results

Coding

We developed the final coding of each interview by consensus discussion with the country teams and the Ottawa team. We kept records of the changes to the coding based on consensus discussion. We found that 89% of the coded text was identical between the original country team coding and the final coding. Most of the differences in coding were due to country teams placing descriptions of specific activities into the five general activities of the funding agency, which were intended to contain broad approaches rather than specific activities.

Analytical framework

Based on analysis of the interviews, we defined five broad categories of funding agency activities related to knowledge translation as follows: (1) "pull" was defined as: activities where the research agenda was set by policy-makers, activities that aimed to increase skills and capacity of policy-makers to use research evidence; (2) "push" was defined as: activities that encouraged researchers to communicate effectively with decision-makers; (3) "linkage/exchange" was defined as: creating linkages between researchers and policy-makers (e.g. workshops, conferences or knowledge brokers); (4) "communication" was defined as: the funding agency itself translating or communicating research results to research users and policy-makers; and (5) "funding opportunities" were defined as: specific funding opportunities that encouraged researchers to engage in knowledge translation strategies themselves.

We added the last two categories based on inductive analysis since

Table 2. **Semi-structured interview framework on knowledge translation activities**

General	Specific
Research governance	• Overarching impact of legislative climate • Mandate for knowledge translation • Focus on disadvantaged
Mission statement mentions knowledge translation	• Overall strategy for knowledge translation • Future plans for knowledge translation • Definition of knowledge translation • Focus on disadvantaged
Resources allocated to knowledge translation activities	• Funding and research training grants in knowledge translation, including special calls • Policy on knowledge translation activities funded at the organization level • Budget for knowledge translation activities • Monitoring of knowledge translation activities • Impact of budget cuts on knowledge translation, if a priority
Documents dealing with knowledge translation	• Types and volume of materials produced • Means of dissemination of documents • Funder publishes monographs, executive summaries/fact sheets regarding research • Web pages devoted to research results • Focus on disadvantaged
Target audiences for knowledge translation activities	• Means of communication in knowledge translation activities
Evaluation	• Evaluation of impact of activities – efforts to monitor dissemination/impact • Examples of impact of activities • Examples affecting disadvantaged populations
Application form/procedure	• Statements about knowledge translation in application form – requirement for activities as a condition of funding • Partnership requirement between researcher and stakeholders • Requirement to address relevance of study at application stage • Lay summary requirements • Dedicated budget items • Policy for eligible expenditures • Contractual requirements for knowledge translation
Funders' expectations of researcher's responsibility for dissemination and implementation	Requirements for the researchers to engage in the following knowledge translation activities: • final reports to funding agency – format and level of detail • participation in workshops • intellectual property rights, acknowledgement and attribution of funding sources, etc.
Knowledge translation facilitation by funders working with researchers	• Funder has communication department to assist researchers (example of activities) • Funder issues press releases regarding funded researchers • Requirement to report back study outcomes • Target audience for activities – who are they and how do they identify them

communication efforts and funding opportunities were described as two important ways that funding agencies support knowledge translation. These categories did not fit into the Lavis framework of push, pull and linkage/exchange.

We found that these five codes for general knowledge translation activities were mutually exclusive, i.e. despite allowing double-coding of text where relevant, no text was placed in more than one of the five general activities. We found two cases from the 23 agencies where negotiation of meaning with the Ottawa team resulted in reclassifying push activities as pull activities.

Mandate

Thirteen of 23 agencies described a favourable political climate to knowledge translation, mainly due to increasing realization that research needs to infiltrate policy and action to benefit health. Respondents described the following barriers to knowledge translation: lack of tools, lack of funding for knowledge translation, little involvement of key stakeholders in the research process and competition between stakeholders.

"Do we have all the skills necessary, or the time even, ... to perhaps advise our partners how that's to have a policy impact ..."

"... needs to do a lot more consultation with stakeholders from the start,

so that consensus and coalitions supporting reform are established and gain momentum"

None of the respondents mentioned criteria regarding the type of knowledge or evidence needs to be translated into policy and practice, or when knowledge translation needs to be done.

Eighteen of 23 funding agencies describe some aspect of knowledge translation in their mandate (Table 3). However, the activities and definition of knowledge translation varied dramatically across different funding agencies, ranging from dissemination to brokering between researchers and decision-makers (Table 3).

"We're not an activist funding organization, per se. That's where the broker versus advocate role comes in."

Nine of 23 agencies described the focus of the knowledge translation activities as ensuring that funded research contributed to improving the health of their communities.

Budget and priority

Eight of 23 agencies ranked knowledge translation as a high priority. Seven of 23 agencies were able to report the percentage of their total budget spent on knowledge translation; all reported less than 20%. Three agencies reported that the knowledge translation budget would withstand cutbacks to the total budget.

Dissemination

One-third of agencies viewed dissemination as a shared responsibility between researcher and the funding agency. Others defined the main responsibility for dissemination as the role of researchers, funding agencies or partners. Dissemination activities were described as highly variable.

Most of the activities that agencies required, expected or encouraged by researchers were traditional within science communication such as producing a final report or journal publication. Thirteen of 23 agencies also required or encouraged researchers to partner with decision-makers and research users. Six agencies stated that researchers were encouraged to engage in pull activities that aim to increase the appetite for research by decision-makers. For example, Pan American Health Organization (PAHO)

Table 3. **Funding agencies and knowledge translation definition**

Country	Abbreviation	Mandate	Selected quotes defining knowledge translation
International	IDRC	yes	"Do you want to be a broker, or do you want to be an advocate?"
	CIDA	no	"Knowledge is demand driven, based on political will"
	USAID	yes	"Whole series of advocacy, engagement"
	DFID	yes	"Research communication"
	WHO/TDR	yes	"Making that leap between the science and its application"
Brazil	FAPESP	no	"Research to be placed on a production scale"
	CNPq	no	"Transformation of more basic knowledge to an application in society"
	CIDAb	no	"Translation of knowledge into action"
Colombia	Colciencias	yes	"Social appropriation of knowledge"
	PAHO	yes	"If there is access to information about health, the gap between haves and have-nots will be closed"
	MSP	no	"Intent to make the findings public"
India	ICSSR	yes	"Building greater awareness about research and other activities with a view to promoting the social sciences"
	DFIDi	yes	"Knowledge exchange wherein the research findings are discussed and shared among partners"
	ICMR	yes	"Applied and operational research ... translation of research findings into policy and action"
Philippines	WBp	yes	"Creating, sharing, and applying knowledge and managing that knowledge"
	PCHRD	yes	"[It] is really evidence-based policy making ... It suggests that whenever you do research, you'll have to involve the stakeholders, the users (potential users) even in the conception and in every step of the research process"
	DOH	yes	"Ensure access to knowledge for evidence-based decision making"
South Africa	MRC	yes	"Knowledge translation is also taking possession of (transferred) knowledge"
	HST	yes	"Implementation on the ground, as well as the communication on advocacy component"
Thailand	TRF	yes	"Use of research findings for national development"
	HSRI	yes	"Implement the essential knowledge and information obtained from research for the formulation of a national health policy"
	NRCT	yes	"Dissemination of research findings"
	NSTDA	yes	"Transfer the research findings to the public and commercial sectors"

CIDA, Canadian International Development Agency; CIDAb, CIDA – Brazil Office; Colciencias, Instituto Colombiano para el Desarrollo de la Ciencia y la Tecnología; CNPq, National Council for Scientific and Technological Development; DFID, Department for International Development (the United Kingdom); DFIDi, DFID – India office; DOH, Department of Health; FAPESP, State of São Paulo Research Foundation; HSRI, Health Systems Research Institute; HST, Health Systems Trust; ICMR, Indian Council of Medical Research; ICSSR, Indian Council for Social Science Research; IDRC, International Development Research Centre; MRC, Medical Research Council of South Africa; MSP, Ministry for Social Protection (equivalent to Ministry of Health); NRCT, National Research Council of Thailand; NSTDA, National Science and Technology Development Agency; PCHRD, Philippine Council for Health Research and Development; PAHO, Pan American Health Organization; TRF, Thailand Research Fund; USAID, United States Agency for International Development; WBp, World Bank – Philippines office; WHO/TDR, WHO – Special Programme for Research and Training in Tropical Diseases.

supported national research councils, including ministries of health.

Application process

At the time of application, 15 of 23 agencies described a requirement to partner with decision-makers, 12 of 23 agencies required researchers to state the policy relevance and significance of their research, and 11 of 23 agencies required researchers to define a knowledge translation audience (Table 4). Other activities described at the application stage were provision of a lay summary proposal, and a knowledge translation plan including dissemination, web development, publication and conferences (Table 5).

Table 4. **Requirements from the researcher at the time of application**

Requirements	No. of international agencies	No. of national agencies
Partner with decision-makers	7/9	8/14
Provide knowledge translation plan	3/9	10/14
State policy relevance	4/9	8/14
Define knowledge translation target audience	3/9	8/14
Provide lay summary proposal	3/9	3/14

Agency initiatives

The agencies used five general strategies to support knowledge translation. These were classified as push, pull, linkage/exchange, communication and funding opportunities.

Funding mechanisms to promote knowledge translation included funding teams (including research users); funding conferences of researchers and research users; knowledge translation requests for applications; funding special centres and chairs for knowledge translation; and seeking commercialization opportunities (Table 6).

Twenty-two of 23 agencies described active involvement in communication activities such as communication to different audiences through web sites and paper journals (Table 6). These included development of audience-tailored web pages such as the South Africa Medical Research Council's AfroAIDS web site (available at: http://www.AfroAIDSinfo.org), lay summaries and use of media.

Linkage/exchange activities were described by 22 of 23 agencies, and included activities such as consulting stakeholders to set the research agenda, creating networks and programmes for decision-makers (Table 6). For example, the Indian Council of Medical Research funded partnerships with the private sector to improve access and availability of drugs for diseases of poverty, such as typhoid and measles vaccines.[21]

Half the agencies described some type of pull activity to increase skills of policy-makers to use research or increase their involvement in setting the research agenda, and fewer of these activities were described by each agency than the push and linkage/exchange types. These activities included tools development, programmes for decision-makers and workshops for decision-makers. For example, the Philippines Council for Health Research and Development described hosting research forums to expose decision-makers to research evaluation and critical appraisal.

The research team selected seven examples of innovative techniques ("gems") based on how they illustrate the diversity of ways in which funding agencies are engaging in knowledge translation (Table 7).

Equity

Nine agencies described poverty reduction or improved health equity as part of their main focus. Examples of equity-focused knowledge translation activities by funding agencies included: the WHO/TDR (Department of Research and Training in Tropical Diseases) programme to eliminate leprosy, the investment in schistosomiasis research in Brazil by FAPESP (Foundation for Research Support of the State of São Paulo), support of higher education for women and girls by USAID (United States Agency for International Development), and the destigmatization of groups at high-risk for HIV/AIDS sponsored by CIDA (Canadian International Development Agency).

Evaluation of agency activities

Thirteen agencies described evaluation tools to assess whether projects met their expectations. Eight agencies reported that they had an evaluation framework for knowledge translation activities. Tools used to evaluate the impact of knowledge translation activities were: (1) client/user surveys to assess how knowledge was used in practice and policy, and which products were most effective and useful; (2) visits to web sites; (3) number of telephone or e-mail queries on an information system; (4) requests for information from research users; and (5) outcome mapping.[22]

"There was a study..., [which showed that] only about 15% [of research funded by our agency] has been translated, meaning actually utilized into something – commercialized, adopted ... really utilized."

Target audience

All funding agencies described several target audiences. The most commonly described target audience was decision-makers (16 agencies) and academics (12 agencies), followed by hospital managers (10 agencies), practitioners (10 agencies), other researchers (9 agencies), industry (9 agencies), researcher funders (8 agencies), general public (7 agencies), health-care professional organizations (7 agencies), media (6 agencies) and consumer organizations (3 agencies).

Table 5. **Budget allowances related to knowledge translation**

Budget allowances	No. of international agencies	No. of national agencies
Dissemination	3/9	7/14
Workshops	1/9	8/14
Publication	1/9	7/14
Translation	2/9	4/14
Web development	1/9	1/14

National versus international funding agencies

In this sample, the national agencies engaged in more knowledge translation activities than their international counterparts across all categories. For example, more national agencies required researchers to provide a knowledge translation plan (10/14 versus 3/9), identify a target audience (8/14 versus 3/9) and provided a budget for workshops (8/14 versus 1/9). More national agencies reported issuing requests for applications on knowledge translation using the media (13/14 versus 4/9) and stakeholder consultation (13/14 versus 6/9). The World Bank in the Philippines was a notable exception to other international funding agencies, as it had strong knowledge translation activities globally.

Table 6. **Agency initiatives**

Initiatives	No. of international agencies	No. of national agencies
Push		
Use of media	4/9	13/14
Lay summaries on web site	6/9	5/14
Use of drama	0/9	3/14
Pull		
Development of tools	3/9	5/14
Programmes for decision-makers	3/9	5/14
Linkage/exchange		
Linkage/exchange	9/9	13/14
Consult stakeholders to set research agenda	6/9	13/14
Create/fund networks	7/9	8/14
Meta-linkage	3/9	5/14
Organize video conferences	1/9	2/14
Communication		
Audience-tailored publications	9/9	13/14
Audience-tailored web pages	8/9	7/14
Produce/fund journals	3/9	9/14
Funding opportunities		
Fund targeted workshops	7/9	11/14
Fund conference grants	4/9	10/14
Fund teams of investigators	6/9	7/14
Fund knowledge translation requests for applications	2/9	7/14
Fund knowledge translation centres	3/9	6/14
Fund chairs	2/9	1/14
Other funding opportunities	2/9	1/14

Discussion

This was a descriptive, exploratory study which identified substantial interest in knowledge translation of research results by both national and international funding agencies that support research in LMICs. We generated four hypotheses useful to studying the role of funding agencies in knowledge translation. First, national funding agencies in this sample demonstrated a greater commitment to knowledge translation activities than international funding agencies. Second, adoption of a systematic framework to knowledge translation might contribute to conceptual clarity in this field. Third, knowledge translation frameworks need to be modified to capture activities by funding agencies. Fourth, funding agencies are moving away from traditional methods of disseminating results and are being creative about reaching relevant audiences.

These findings suggest that national agencies may be more motivated to engage in knowledge translation activities than international funding agencies (with the exception of the World Bank in the Philippines). These findings lend credence to the perception that international funding agencies may not be well connected to realities on the ground at country-level. Furthermore, these findings support the focus on increasing funding for national health research within countries, as recommended by the Commission on Health Research for Development in 1990 (Karolinska Institute, Sweden). However, since international funding agencies still support over 90% of research in some low-income countries,[16] their lack of focus on knowledge translation is worrisome. Encouragingly, there was interest in all international funding agencies to increase their knowledge translation activities in the next five years.

A common terminology for knowledge translation could be useful in better defining both existing and planned funding agency activities. We found different definitions and understanding of knowledge translation both within and between agencies (Table 3). The different terminologies reflect differences in the mandates of these organizations but also suggest a lack of conceptual clarity around knowledge translation.

We found a lack of consideration in determining which evidence required translation and the need for tailored approaches for different audiences. Despite the relatively incomplete evidence-base on the effectiveness of different knowledge translation strategies, there is evidence to support the use of audience-specific strategies (e.g. consumers, practitioners, policy-makers) to address audience-specific barriers and facilitators.[23–25] Furthermore, there are convincing arguments that knowledge transfer should be based on rigorous meta-analysis of systematic reviews based on all available studies rather than single studies, because systematic reviews increase confidence in results, reduce the chances of being misled and efficiently summarize all published literature.[26] Adoption of a systematic framework to knowledge translation would contribute to conceptual clarity in this field. For example, the five step approach to knowledge transfer, described by Lavis, provides a framework to assess what should be transferred, to whom, by whom, how and with what effect.[24]

Table 7. **Examples of innovative and promising knowledge translation activities ("gems")**

Agency	"Gem" activity	Category	Description
DFID	Increase incentives for researchers to engage in knowledge translation by addressing rules for university rankings that are based on publications	Push	Working with the Offices of Science and Technology in the United Kingdom to change the higher education funding system to increase recognition for knowledge translation by modifying the research assessment exercise (which rates universities according to what they publish in high-tech and high level journals)
Colciencias	Cartoons for children on television with important research findings	Communication	Five-minute cartoons describing research results to children are produced by the agency along with the researchers involved; these cartoons are broadcast through a large private national television network twice a week (Saturday and Sunday) in schedules appropriate for children; 25 programmes were produced during the first season
IDRC	Small grants available to move research into practice	Funding opportunities	"Windows of Opportunity" small grants available for teams to move research further into practice in specific environment
FAPESP	Private sector and public partnerships for technology transfer	Linkage/exchange	In Brazil, partnerships between private enterprises and public agencies for funding basic research and developing technology based on that locally-conducted basic science
Department of Health, Philippines	Creation of a knowledge translation bureau	Linkage/exchange	The Health Policy Development and Planning Bureau was created with a mandate to link research and policy
World Bank-Philippines	Call for proposals addressed to the general public in the Filipino language	Funding opportunities	In the Philippines, requests for proposals are usually written in English and addressed to researchers
ICMR-India	Establishing partnerships for improving the availability and access and decreasing cost of drugs needed for diseases of poverty	Linkage/exchange	E.g. TDR and Asta Medical (Germany) for a microbicide; WHO and Smith Kline Beecham for filariasis elimination strategy

Colciencias, Instituto Colombiano para el Desarrollo de la Ciencia y la Tecnología; DFID, Department for International Development (the United Kingdom); FAPESP, State of São Paulo Research Foundation; ICMR, Indian Council of Medical Research; IDRC, International Development Research Centre.

We found that the Lavis framework of push, pull and linkage/exchange was a useful tool to categorize knowledge translation activities. However, we found that these three categories alone did not capture all of the activities of funding agencies, therefore we added two codes for general activities by funding agencies: communication and funding opportunities. These five categories represented mutually exclusive codes that provided a useful basis for classifying activities. In our analysis of the discrepancies in coding between country teams and the Ottawa team, we found the greatest differences in interpretation between the push and communication categories. Our category of push was intended to capture activities that focused on researchers summarizing the actionable messages based on their research, going beyond traditional publications or reports to stating the policy relevance of their research findings.

We found several creative and innovative strategies such as the "gems" in Table 7. These creative strategies show that funding agencies are moving away from traditional methods of disseminating results.

Ability to evaluate the impact of knowledge translation strategies was lacking in all agencies. Lack of evaluation frameworks limit the ability to show whether knowledge translation efforts indeed enhance research-related policy, services (health and intersectoral) and societal impacts.[27]

Knowledge translation is a complex process which can enhance the health of disadvantaged populations, by improving access, diagnostic accuracy, compliance and adherence of effective services.[3,13] We found a commitment to enhancing health of disadvantaged populations by one-third of funding agencies. We also found examples of knowledge translation activities that were focused on enhancing the health of the disadvantaged, such as the WHO/TDR programme to eliminate leprosy. Increased focus is needed to ensure that knowledge translation activities benefit the most disadvantaged populations.

An increasing number of organizations internationally are dedicated to knowledge translation. The activities of these organizations were not captured by our study, such as the WHO/PAHO EVIPNet), the Overseas Development Institute's RAPID programme and the Getting Research into Policy and Practice (GRIPP) initiative. These international initiatives represent an exciting opportunity to explore the effectiveness of different knowledge translation strategies.

Our results may overestimate the amount of knowledge translation activities since any activity (no matter how small) was scored as a "yes". We only interviewed three people from each agency so we may not have cap-

tured all knowledge translation activities. However, we tried to ensure interviewees represented a senior policymaker, someone responsible for knowledge translation and a project officer. Three funding agencies interviewed for this study did not consider knowledge translation a main part of their mandate. This data was collected between September 2003 and September 2004, before the Ministerial Summit on Health Research convened by WHO in Mexico. Advocacy for knowledge translation has increased since the Summit, but it remains to be seen if funding agencies have actually shifted significant resources to this important area. This study provides a useful scan of the activities of these 23 agencies and the types of activities in which they are engaging.

Because this is a qualitative research study that used a judgement sample, we focused less on external validity and more on maximizing internal validity. Therefore, these results apply to the sample of funding agencies selected and included in this study and are not intended to be generalized to other funding agencies.

Conclusion

Previous research on knowledge translation has mostly ignored the role of funding agencies. This descriptive study shows an encouraging support for knowledge translation by national funding agencies, with a lag in support from international funding agencies. Funding agencies need to agree on a common terminology, consider the need for approaches tailored to specific audiences and identify their niche roles in knowledge translation, which may differ according to their defined mandates. Funding agencies might consider their role as knowledge brokers, by fostering and encouraging interactions between researchers and relevant stakeholders. As knowledge brokers, funding agencies could promote research syntheses and a focus on health equity. There is an urgent need to evaluate these funding agency knowledge translation activities to learn what works, why and in what context, in order to better justify spending on knowledge translation and to improve performance. ■

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Résumé

Aide à la transposition dans la pratique des connaissances par les agences de financement des pays à revenu faible ou moyen

Objectif Décrire comment certaines agences, qui financent la recherche en santé dans des pays à revenu faible ou moyen, favorisent la transposition sous forme politique et pratique des recherches financées.

Méthodes Nous avons réalisé une analyse inductive d'entretiens semi-structurés menés avec des informateurs clés d'un échantillon choisi à dessein de 23 agences nationales et internationales, qui financent des recherches en Afrique du Sud, au Brésil, en Colombie, en Inde, aux Philippines, et en Thaïlande. Nous avons également effectué une enquête sur des sites Internet.

Résultats Nous avons relevé un engament à transposer les connaissances en pratique dans le mandat de 18 des 23 agences de l'échantillon. Cependant, la terminologie utilisée était peu homogène. La plupart des activités mentionnées sont des efforts classiques de diffusion auprès d'une large audience, par le biais par exemple de sites Internet ou de publications. En outre, plus de la moitié des agences (13 sur 23) encouragent les liens et les échanges entre chercheurs et utilisateurs potentiels et 6 agences sur 23 décrivent des activités de type « pull » pour intéresser les décideurs aux travaux de recherche. Un tiers des agences (9 sur 23) indiquent dans leur mandat vouloir améliorer l'équité en matière de santé par une meilleure transposition dans la pratique des connaissances. Seules 3 des 23 agences sont en mesure de mentionner une évaluation des activités de transposition en pratique des connaissances. Nous avons en outre constaté que les agences de financement nationales faisaient de plus grands efforts pour assurer cette transposition que les agences internationales.

Conclusion Les agences de financement ont entrepris des activités très diverses de transposition en pratique des connaissances. Elles peuvent se considérer comme ayant un rôle de courtier en connaissances et comme ayant la capacité de promouvoir une synthèse des recherches et une convergence de l'attention sur l'équité en termes de santé. Il est urgent d'évaluer les activités de transposition en pratique des connaissances menées par les agences de financement.

Resumen

Organismos de financiación en países de ingresos bajos y medios: apoyo a la traslación de conocimientos

Objetivo Describir cómo algunos organismos de financiación de investigaciones sanitarias que operan en países de ingresos bajos y medios promueven la traslación de las investigaciones que financian en políticas y prácticas.

Métodos Realizamos análisis inductivos de entrevistas semiestructuradas con informantes clave a partir de una muestra intencionada de 23 organismos nacionales e internacionales que financian investigaciones sanitarias en el Brasil, Colombia, la India, Filipinas, Sudáfrica y Tailandia. También sondeamos diversos sitios web.

Resultados Detectamos muestras de compromiso en favor de la traslación de conocimientos en el mandato de 18 de 23

organismos. Sin embargo, no había una terminología común. La mayoría de las actividades consistían en las iniciativas tradicionales de difusión de información entre un público amplio, por ejemplo a través de sitios web y publicaciones. Además, más de la mitad (13 de 23) de los organismos fomentaban el establecimiento de vínculos y el intercambio entre los investigadores y los usuarios potenciales, y 6 de los 23 organismos describieron actividades de «atracción» para generar interés por las investigaciones entre los decisores. La tercera parte (9 de 23) de los organismos de financiación tenían encomendado el fomento de la equidad sanitaria mediante la mejora de la traslación de conocimientos. Sólo 3 de los 23 organismos podían hacer una evaluación posterior de sus actividades de traslación de conocimientos. Además, observamos que los organismos de financiación nacionales hacían un mayor esfuerzo de traslación de conocimientos que los organismos internacionales.

Conclusión Los organismos de financiación participan en una amplia gama de actividades creativas de traslación de conocimientos y podrían tal vez estudiar su papel como intermediarios en ese ámbito, facultados para promover síntesis de investigaciones y un mayor énfasis en la equidad sanitaria. Es necesario evaluar urgentemente las actividades de traslación de conocimientos de los organismos de financiación.

ملخص

وكالات تمويل البحوث الصحية في البلدان المنخفضة والمتوسطة الدخل، ودورها في دعم ترجمة المعارف إلى سياسات وممارسات

الغرض: استهدفت هذه الدراسة بيان إلى أي مدى تقوم بعض الوكالات الممولة للبحوث الصحية، العاملة في البلدان ذات الدخل المنخفض والدخل المتوسط، بتعزيز ترجمة نتائج البحوث التي تمولها إلى سياسات وممارسات.

الطريقة: أجرى الباحثون تحليلاً استقرائياً لنتائج مقابلات شبه منظمة مع مقدمي المعلومات الرئيسيين في عينة قوامها 23 وكالة اختيرت عن قصد من بين الوكالات الوطنية والدولية الممولة للبحوث الصحية في البرازيل، وكولومبيا، والهند، والفلبين، وجنوب أفريقيا، وتايلاند. كما أجرى الباحثون مسحاً لمواقع الإنترنت.

الموجودات: لاحظ الباحثون التزاماً بترجمة المعارف إلى سياسات وممارسات في اختصاصات 18 وكالة من الـ 23 وكالة. ولكن لوحظت قلة في المصطلحات المشتركة في اختصاصات هذه الوكالات. وكانت معظم الأنشطة مجرد جهود تقليدية لبث المعارف إلى الجمهور العام، باستخدام المنشورات ومواقع الإنترنت، على سبيل المثال. كما لوحظ أن أكثر من نصف الوكالات (13 من 23 وكالة) تشجع التواصل أو تبادل المعلومات بين الباحثين والمستخدمين المحتملين للمعارف، وأن 6 من 23 وكالة قدّمت تصوراً لبعض الأنشطة التي تولد الاهتمام بالبحوث لدى متخذي القرار. ولوحظ أن ثلث العينة (9 من 23 وكالة) قدمت تصوراً للاختصاصات التي تكفل تحسين مظاهر المساواة في الصحة، من خلال تحسين ترجمة المعارف إلى سياسات وممارسات. وقد نجحت 3 وكالات فقط من 23 وكالة في وضع تصور لعملية تقييم أنشطة ترجمة المعارف. كما لاحظ الباحثون أن وكالات التمويل الوطنية تبذل جهوداً أكبر في ترجمة المعارف، بالمقارنة مع الوكالات الدولية.

الاستنتاج: تشارك وكالات التمويل في طيف عريض من الأنشطة المبتكرة لترجمة المعارف. وترى هذه الوكالات أن دورها هو دور وسيط للمعارف، لديه القدرة على تعزيز عملية تجميع البحوث، ويركز على تحقيق المساواة في الصحة. وخلُصَت الدراسة إلى وجود حاجة عاجلة إلى تقييم أنشطة وكالات التمويل في ترجمة المعارف إلى سياسات وممارسات.

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In vitro activity of ceftobiprole against *Burkholderia pseudomallei*

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Keywords: *B. pseudomallei*, melioidosis, cephalosporins

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Sir,

Burkholderia pseudomallei, a Gram-negative bacterium, causes a disease called melioidosis in humans and animals.[1] The bacterium is a soil organism found mainly in Southeast Asia and Northern Australia. Antibiotics currently recommended for therapy of melioidosis are ceftazidime, imipenem, meropenem, amoxicillin/clavulanate, trimethoprim/sulfamethoxazole, doxycycline and chloramphenicol.[1] A development of resistance of *B. pseudomallei* to the aforementioned antibiotics has been recognized;[2,3] hence, a search for new agents effective against *B. pseudomallei* is needed.

Ceftobiprole is a novel parenteral cephalosporin whose broad spectrum of activity includes most clinically important Gram-positive and Gram-negative bacteria.[4]

One hundred and fifteen strains of ceftazidime-susceptible *B. pseudomallei* from different infected patients were selected from our collection. All strains were identified as *B. pseudomallei* by API 20NE (bioMérieux, France). *In vitro* susceptibility was determined by Kirby-Bauer disc diffusion for all 115 strains and Etest for 5 randomly chosen strains. Paper discs containing 30 μg ceftobiprole per disc (MASTDISC) and Etest strips of ceftobiprole at concentrations of 0.016–256 mg/L were provided by Janssen-Cilag (Thailand). The disc diffusion test was repeated for six strains of *B. pseudomallei* in order to determine the reproducibility of the test. The methodology for susceptibility testing was performed by direct colony suspension according to guidelines suggested by the CLSI.[5] Quality control was performed by testing susceptibility of *Pseudomonas aeruginosa* ATCC 27853. The proposed breakpoints for inhibition zone diameters of ceftobiprole are $\geq$20 mm for susceptible, 17–19 mm for intermediate and $\leq$16 mm for resistant. The proposed breakpoints for MICs of ceftobiprole are $\leq$4 mg/L for susceptible, 8 mg/L for intermediate and $\geq$16 mg/L for resistant.

The inhibition zone diameter of ceftobiprole against *P. aeruginosa* ATCC 27853 was within the reference limits. The distribution of inhibition zone diameters of ceftobiprole against *B. pseudomallei* is shown in Table 1. Inhibition zone diameters of $\geq$20, 17–19 and $\leq$16 mm were observed in 46 (40%), 55 (47.8%) and 14 (12.2%) strains, respectively. Four strains of *B. pseudomallei* with inhibition zone diameters of 15–19 mm on the initial disc diffusion test had identical inhibition zone diameters on the second test. Another two strains with an inhibition zone diameter of >20 mm had 1 mm difference in inhibition zone diameter on the second test, but the inhibition zone diameters from both tests were still within susceptible values. Four *B. pseudomallei* strains with an inhibition zone diameter of 17–19 mm had MICs of ceftobiprole of 6–8 mg/L, whereas a strain with an inhibition zone diameter of 16 mm had an MIC of 16 mg/L.

Our findings indicate that the *in vitro* activity of ceftobiprole against *B. pseudomallei* determined by Kirby-Bauer disc diffusion is reproducible and correlates with that determined by Etest. Ceftobiprole has less *in vitro* activity than ceftazidime against *B. pseudomallei*, and only 40% of *B. pseudomallei* strains are susceptible to ceftobiprole.

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Transparency declarations

None to declare.

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Table 1. Distribution of ceftobiprole inhibition zone diameter for 115 strains of *B. pseudomallei*

No. of strains (%) for which the inhibition zone diameter was										
13 mm	15 mm	16 mm	17 mm	18 mm	19 mm	20 mm	21 mm	22 mm	23 mm	25 mm
1 (0.9)	5 (4.3)	8 (7.0)	25 (21.7)	19 (16.5)	11 (9.6)	30 (26.1)	7 (6.1)	3 (2.6)	4 (3.5)	2 (1.7)

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Treatment of external ventricular drain-associated ventriculitis caused by *Enterococcus faecalis* with intraventricular daptomycin

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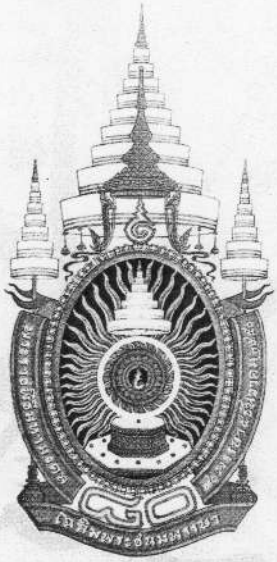
Sir,

External ventricular drains (EVDs) are essential monitoring devices in neurosurgery, and direct portals for the removal of cerebrospinal fluid (CSF), including the temporary control of raised intracranial pressure, and for the instillation of therapeutic agents. Their benefits must be balanced against the complications associated with their use, the most important of which is infection (ventriculitis). Most patients with EVD-associated ventriculitis can be cured by instilling antibiotics directly into the ventricles.[1] We describe here a patient with such an infection treated by administering daptomycin using this route.

A 62-year-old man was admitted to this hospital with a subarachnoid haemorrhage and underwent coil occlusion of an anterior communicating artery aneurysm. Four days later, he became confused and was noted to have raised intracranial pressure; a lumbar drain was inserted. He subsequently became pyrexial and culture of CSF obtained via the lumbar drain yielded *Klebsiella pneumoniae*. An EVD was inserted and the ventriculitis was successfully treated with a 14 day course of intravenous ceftazidime and intraventricular gentamicin. The intention was to remove the EVD on day 30. However, Gram's stain examination of a sample of CSF showed Gram-positive cocci, and *Enterococcus faecalis*, which was susceptible to ampicillin and vancomycin, but exhibited high-level resistance to gentamicin (MIC > 200 mg/L), was isolated. Vancomycin (10 mg) was instilled into the ventricles, but, after 8 days of therapy, *E. faecalis* was still recovered from the CSF. The MIC of daptomycin for this strain was 2.0 mg/L, as determined by an Etest on Mueller–Hinton agar, and this drug was administered intravenously at a dosage of 1 g (12 mg/kg) once daily. In addition, the EVD was removed and an Ommaya reservoir was implanted. Following a further 4 days of therapy with intraventricular vancomycin, *E. faecalis* was again recovered from the CSF. It was therefore decided to instil daptomycin into the ventricles at a dosage of 10 mg every third day; consent was obtained from the patient. Trough and peak daptomycin CSF concentrations (determined just before and 30 min after a dose, respectively, by high-performance liquid chromatography at the Department of Medical Microbiology, Southmead Hospital, Bristol, UK) were 23 and 483 mg/L, respectively. The dosage of daptomycin was reduced to 5 mg every third day, and trough and peak daptomycin CSF concentrations at the lower dosage were 9.9 and 139 mg/L, respectively. The CSF became sterile within 3 days of commencing intraventricular daptomycin and remained so throughout the 2 week treatment period. The patient remained well and he was eventually discharged from hospital. However, he was re-admitted 28 days later with symptoms and signs of meningitis. Culture of a sample of CSF yielded *E. faecalis* with the same antibiogram as the original isolate and treatment with intraventricular daptomycin at a dosage of 5 mg every third day was restarted. In addition, the Ommaya reservoir was replaced with an EVD. Daptomycin was administered for 4 weeks during which time he experienced transient pyrexias after each instillation of daptomycin; this side effect was resolved when the treatment was discontinued. The CSF became sterile, the EVD was removed and he was discharged from hospital 39 days after he had been re-admitted. Clinical and bacteriological cures were sustained after follow-up for more than 1 year.

EVD-associated ventriculitis is one of the most common infections in neurosurgical practice. Until recently, only three antibiotics have been available in formulations suitable for intraventricular use: vancomycin, gentamicin and colomycin. Enterococci are increasingly being recognized as causes of ventriculitis in neurosurgical patients, and some strains exhibit resistance to vancomycin or high-level resistance to the aminoglycosides, thereby limiting treatment options. Linezolid has been used successfully as systemic therapy in such cases.[2,3] However, this antibiotic is not bactericidal and prolonged courses increase the risks of adverse effects. Daptomycin is the first of a new class of antibiotics, the cyclic lipopeptides. It has been shown to be rapidly bactericidal against enterococci, including vancomycin-resistant strains.[4] Daptomycin penetrates poorly into the CSF compartment when given by the systemic route. In a rabbit model of meningitis caused by *Streptococcus pneumoniae*, only 5% of the corresponding serum concentration was achieved in the CSF, and the drug failed to sterilize the CSF after 4 days, despite the administration of a high dosage.[5] On the other hand, a study involving a rabbit model of *Staphylococcus aureus* ventriculitis demonstrated that intraventricular daptomycin achieved greater bactericidal activity, more rapid killing kinetics and a longer half-life in the ventricles than intraventricular vancomycin.[6] Many years' experience of managing patients with EVD-associated ventriculitis by instilling antibiotics into the ventricles encouraged us to treat the patient described in this report with intraventricular daptomycin. This present experience suggests that intraventricular daptomycin is an effective therapy of patients with EVD-associated ventriculitis caused by enterococci; it may be equally appropriate as treatment



งานวิจัยพื้นฐาน
ฐานรากของการพัฒนาประเทศ ตามปรัชญาเศรษฐกิจพอเพียง

การวิจัยพื้นฐานเพื่อพัฒนาสุขภาพ

หนังสือเฉลิมพระเกียรติ
เนื่องในโอกาสมหามงคลเฉลิมพระชนมพรรษา ๘๐ พรรษา
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สำนักงานกองทุนสนับสนุนการวิจัย (สกว.)

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การจัดการความรู้เพื่อพัฒนาบริการสุขภาพ

ศ.นพ. วิษณุ ธรรมลิขิตกุล