

Policymakers' views regarding the introduction of new-generation vaccines against typhoid fever, shigellosis and cholera in Asia

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Abstract

Face-to-face interviews and meetings with more than 160 policymakers and other influential professionals in seven large Asian countries (Bangladesh, China, India, Indonesia, Pakistan, Thailand and Vietnam) were conducted to survey opinions regarding the need for, and potential uses of new-generation vaccines against cholera, typhoid fever and shigellosis. Despite several barriers to their uptake—notably uncertainty of the burden of enteric diseases; preference for water, sanitation and other environmental improvements over vaccination for disease control; and high prices of the current vaccines relative to basic EPI vaccines, and their moderate protection levels—considerable interest was found in the targeted use of Vi typhoid vaccine in most countries, followed by (future) *Shigella* and oral cholera vaccines. The introduction of these vaccines in Asia could be greatly facilitated by country-specific evidence of disease burden, local or regional vaccine production, field studies demonstrating their safety and efficacy in local populations, evidence of potential economic savings from vaccination, and effective dissemination of research results to all those who make or influence immunization policy.

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1. Introduction

1.1. Background to the study

The past 5 years have seen increasing efforts—funded largely by the Gates Foundation—to accelerate the development and use of vaccines needed mainly in developing countries, but not viewed by the major vaccine producers as sufficiently profitable to justify the considerable research and development investments that are required. These projects include: the Malaria Vaccine Initiative (MVI), the International AIDS Vaccine Initiative (IAVI), the Meningitis Vaccine Project (to develop an appropriate meningococcal conjugate vaccine for Africa), the Rotavirus Vaccine Program and the

Pneumococcal Vaccines Accelerated Development and Introduction Plan (Pneumo ADIP).

One of the earlier projects of this kind was the Diseases of the Most Impoverished (DOMI) Program, launched in 1999 to accelerate the development and use of current and future new-generation vaccines against three serious enteric diseases responsible for many deaths in developing countries: typhoid fever, cholera and shigellosis. DOMI aims to achieve this goal by providing country-specific, multi-faceted data—on disease burden, vaccine safety and field effectiveness, vaccine cost-effectiveness, and private demand and willingness-to-pay for these vaccines—through a comprehensive, field research programme. The intent, therefore, is to translate solid, country-specific data into rational decisions regarding the use of new- and future-generation typhoid, cholera and *Shigella* vaccines.

But will the DOMI Program's research results necessarily lead to decisions by country-level policymakers to introduce a vaccine and to allocate sufficient resources to do so—even

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if the data provide powerful epidemiological and economic arguments for vaccine introduction? How will these diseases and vaccines fit in with the disease control priorities of policymakers in the target countries? How are these priorities determined and who determines or influences them? What factors or criteria do policymakers weigh in making decisions about a new vaccine? Are there other unforeseen obstacles to introducing these vaccines? What introduction strategies—in terms of vaccine source, distribution channels, financing and delivery mechanisms—are most likely to succeed for each of these vaccines? And finally, what specific types of data will be most critical to policymakers in making decisions regarding vaccine introduction and how and to whom can these data be disseminated to most effectively translate into policy decisions?

DOMI believed that answering these questions would help ensure that its research and advocacy programme meets the needs of those who make or influence vaccine introduction decisions—thus enhancing the likelihood that it will actually lead to vaccine introduction in countries where the data present a compelling case. Exploring these questions becomes increasingly important as government juggle decisions regarding a growing list of available and upcoming vaccines and technologies, while faced with many pressing health priorities and often severe budgetary constraints.

The DOMI Program, therefore, decided to conduct, at an early stage, a survey of policymakers and other influential professionals in the seven participating countries (Bangladesh, China, India, Indonesia, Pakistan, Thailand and Vietnam). The survey, consisting of face-to-face interviews and meetings, represents the first systematic effort to explore the views of policymakers and opinion leaders in developing countries concerning the need for and possible uses of new-generation enteric vaccines. This study was conceived not as a comprehensive stakeholder analysis, but rather as a rapid means to initially identify prevailing views, issues and data needs of policymakers in order to inform the DOMI Program's research agenda, information dissemination and advocacy activities and to begin the policy dialogue regarding these diseases and vaccines.

1.2. Background on typhoid fever, cholera and shigellosis and new-generation vaccines

Each year, an estimated 1.1 million people world-wide die from shigellosis, more than 200,000 from typhoid fever, and 120,000 from cholera—the majority of them children in developing countries [1–3]. The overall toll of these diseases is considerable—with an estimated 5–7 million cases of cholera, 21 million cases of typhoid fever and up to 165 million cases of shigellosis occurring each year [1–3]. Outbreaks of all three diseases also cause severe disruptions in less developed countries. In addition, rapidly rising rates of antibiotic resistance are increasing the cost and difficulty of treating both typhoid fever and shigellosis in many countries.

New-generation vaccines have been developed in the past three decades to replace the old injectable killed whole-cell cholera and typhoid vaccines, which produced high rates of side effects and, in the case of cholera vaccine, were minimally effective. These newer vaccines include typhoid Vi polysaccharide—an injectable one-dose vaccine developed by the US National Institutes of Health with proven effectiveness of 64–72% in persons 2 years and older for at least 17 months following vaccination and 55% protection for at least 3 years [4–6]—and oral killed whole-cell based (WC) cholera vaccines, both with and without the cholera toxin B subunit. The B subunit killed WC cholera vaccine has been demonstrated to confer around 60% protection after two doses to populations naturally exposed to cholera [7–9] for 2 years and is effective in persons 2 years and older. Both typhoid Vi and oral cholera vaccines are considered appropriate for use in public sector programmes in developing countries because of their proven effectiveness in populations at risk, their low rates of side effects, their relative ease in use, and their potential for low-cost production by local manufacturers. In addition, Vi vaccine, since it was developed in the US public sector, does not have patent protection and its technology is readily transferable to high-quality vaccine producers throughout the world.

The only *Shigella* vaccine in use to date is an oral live-attenuated *Shigella flexneri* 2a-*Shigella sonnei* (“FS”) vaccine, developed and licensed in China since 1999. The vaccine has a demonstrated efficacy of 60–70% and requires a regimen of three doses taken within a 2-week period [10,11]. Its use in China has been limited thus far because it has not been licensed for children under 5 years of age—who accounts for an estimated 60% of *Shigella*-related deaths [1]—and because of its relatively high price (reportedly up to US\$ 9.60 per series). Other *Shigella* vaccine candidates currently under development include oral, live, genetically attenuated vaccine strains [12], injectable polysaccharide-protein conjugate vaccines [13] and proteosome oral or intranasal vaccines [14]. The concept of ribosomal *Shigella* vaccines [15] is also being revisited.

Vi polysaccharide vaccine has been licensed in more than 40 countries, including many Asian countries, where it is mainly available in the private sector and used for school-aged children. Thus far, the vaccine has been used by a national immunization programme, either for universal or targeted use, only in Vietnam, which has provided the vaccine to a limited number of 3–10 year olds in high-incidence districts each year since 1997. In addition, in China, where six local vaccine production institutes produce the vaccine, following technology transfer from US NIH, several provincial or district governments in high-incidence areas have encouraged its use through school-based campaigns financed by reasonable user fees (e.g. US\$ 0.36–0.60 per dose). Local Vi production also began in Vietnam in 2003 and development and production efforts are currently underway in Indonesia and India (the latter in the private sector).

Oral cholera vaccine has been licensed in few developing countries to date and only in Vietnam, where a state-run vaccine company produces a version of the vaccine without the B subunit, is it provided by the national immunization programme for targeted use. Although the government's long-term goal is to immunize all 2–5 year olds in high-risk areas of the country, immunization has thus far been limited to around 300,000 children each year—a fraction of its target population—and for emergencies, such as floods, because of financial constraints.

Thus, despite the existence of new-generation typhoid and cholera vaccines for several years and the presumed need in many developing countries, their use remains extremely limited. The DOMI Program was established to speed up the introduction and use of these new-generation vaccines, where most needed, as well as to stimulate the development and testing of newer, improved enteric vaccines, such as conjugate Vi and *Shigella* vaccines that could theoretically have increased efficacy and be effective in infants.

2. Materials and methods

2.1. Data collection

At the time the study was undertaken, only a few systematic policy assessments regarding new vaccine introduction could be found in the literature, including a study of factors facilitating the introduction of *Haemophilus influenzae* type b (Hib) vaccine in four “early adopting” countries, and lessons learned from hepatitis B vaccine introduction [16,17]. The survey methodology drew upon these and unpublished studies that had explored factors influencing the uptake of new vaccines in developing countries [18–21]. A detailed question guide, consisting entirely of open-ended questions, was prepared. The questions explored factors influencing decisions concerning new vaccine introduction and the policy process involved in prior vaccine introductions. For each disease, the guide examined views and perceptions about:

- the scope, seriousness and level of priority of the disease;
- the effectiveness of current control measures;
- the need for and interest in a vaccine versus other control measures;
- respondents' criteria for the level of safety, efficacy and price of a vaccine;
- feasible or preferable strategies for vaccine introduction; and
- data requirements to facilitate decision-making regarding the future introduction of these vaccines.

Appropriate informants were also questioned in depth about the country's immunization programme, vaccine licensing and quality control requirements, local vaccine production, immunization financing, and the public and private sector vaccine markets in their country.

The use of a question guide with open-ended questions allowed for a semi-structured interview format, which was felt to be most appropriate for high-level informants, as opposed to a highly-structured questionnaire. This format facilitated the free expression of opinions and ideas among informants, allowed for probing and clarification of responses, and for the identification of new issues and topics as they arose.

Informants were interviewed on an individual basis or through group meetings with two to eight participants during country visits of 4–8 days conducted by two of the authors (DD and AN) between November 2000 and June 2001. The interviews and meetings lasted on average 60–90 min. In some cases, the persons interviewed had received the question guide in advance, and several had gathered data ahead of time to prepare for the interviews. Some persons interviewed in China had the questions translated.

2.2. Selection of interviewees

A list of persons to be interviewed was drawn up with guidance from the researchers and input from local collaborators. An effort was made to meet, within the given timeframe, as many groups and individuals as possible—from both the public and private sectors—who potentially had a role in making or influencing decisions regarding the introduction of enteric vaccines in their country. Efforts were also made to meet with the highest level of official in each category as possible. Interviewees included:

- Ministry of Health officials, including heads of communicable disease control, preventive medicine, diarrhoeal disease control, epidemiology, and research and planning departments, and national immunization programme managers;
- senior policymakers in health, finance and/or planning ministries (in all countries but China and Thailand);
- research institute directors, research scientists and leading academics in the field of enteric diseases and/or vaccine development;
- top officials from professional associations (e.g. national paediatrics and national medical societies);
- officials from national regulatory agencies and (in some countries) national regulatory laboratories; and
- representatives from local vaccine manufacturers.

In several countries, interviews were also held with directors and practitioners from large, public hospitals; representatives of multi-national pharmaceutical companies; health authorities at the state, provincial or municipal level (in China, India, Pakistan and Vietnam) and officials from international agencies (e.g. World Health Organization). A breakdown of informants by category and country is shown in Table 1. Between 7 and 16 meetings or interviews were held in each country, involving a total of 20–31 participants per country. In all, 167 informants took part in 86 interviews/meetings in the seven countries.

Table 1
Number of informants taking part in interviews or meetings by country and type of position

Type of position	Bangladesh	China	India	Indonesia	Pakistan	Thailand	Vietnam	Total
Ministry of Health Department/division heads, EPI programme managers, others	7	2	1	6	3	2	7	28
Senior policymakers (in health, finance or planning ministries)	1	–	2	1	2	–	1	7
Professional society representatives	1	–	3	1	1 ^a	2	1 ^a	9 ^a
Research institute officials, scientists and academics	4	2	9	7	2	5	2	31
Local vaccine producer representatives	4	6	6	6	1	2	6	31
National regulatory agency/laboratory officials ^b	1	5	5	2	–	13	1	27
International pharmaceutical company representatives	1	–	–	2	5	2	–	10
State/provincial or municipal health officials	–	5	2	–	2	–	1	10
Public hospital directors and other representatives	–	–	1	1	4	–	–	6
International agency officials (e.g. WHO)	2	2	–	–	–	1	–	5
Other ^c	–	–	2	–	1	–	2	5
Total number of informants	21	22	31	26	20	27	20	167
Total number of interviews or meetings	13	7	14	16	13	11	12	86

^a The medical association officials interviewed in Pakistan and Vietnam were also counted in another category and thus not included in the totals.

^b NRA officials were met in all countries but India and Pakistan. National control laboratory representatives were interviewed in India and Thailand.

^c These include army medical officials in India and Pakistan and a Parliament member and local (commune) political leader in Vietnam.

2.3. Data analysis

A complete set of notes for each country was transcribed and organized by topic area and by person or group interviewed. Patterns of responses were analyzed by the type and level of respondent. Country-specific reports were then prepared and sent to local collaborators in each country for feedback and validation of the findings. Brief country-specific summaries of the findings and conclusions were also sent for feedback to all persons or groups interviewed. Several local collaborators provided comments to the detailed reports; however, little feedback on the summaries was received from informants.

3. Results

3.1. Uncertain disease burden and data gaps

Most persons interviewed across the seven countries believed that the true extent and seriousness of cholera, typhoid fever and shigellosis in their countries was largely unknown and that official incidence data were unreliable. Reasons for the uncertainty of the burden of these diseases include: the infrequency of laboratory testing; the common inability of physicians to correctly diagnose these diseases and their tendency to report them simply as enteric infections or diarrhoeal disease; the population's heavy use in several countries of the private health care sector, which rarely reports diseases to the government; and the common practice of self-treatment with readily available antibiotics. In the case of cholera, there was

also the belief that governments suppress reports of cases, due to their fear of negative economic consequences from reports of cholera outbreaks. Adding to the uncertainty was the fact that a number of informants in some countries were unaware of existing data from epidemiological studies of these diseases that had taken place in their country.

This uncertainty often led to a reluctance among informants—especially central government officials—to state opinions about the magnitude of these diseases, and to sometimes vast differences in opinion among informants within the same country. For instance, while several high-level government officials in Pakistan did not believe shigellosis to be a significant problem, one leading paediatrician estimated that dysentery—much of it presumably shigellosis—was responsible for at least 25% of all diarrhoeal disease deaths among children in the country. In China, some Ministry of Health officials did not consider shigellosis to be an important priority, while one provincial health official ranked it as the third most important infectious disease in his province, after HIV/AIDS and hepatitis B. A range of views within countries on cholera and typhoid fever incidence was also found.

3.2. Perceived importance of typhoid fever, shigellosis and cholera and need for new-generation vaccines

These enteric diseases were not generally among the top infectious disease priorities of national governments or of government officials interviewed. Top priorities in the seven countries tended to be tuberculosis, HIV/AIDS, malaria, dengue fever, acute respiratory infections, infant dehydrating

diarrhoea (e.g. rotavirus) and hepatitis B. Exceptions were in Vietnam, where both new-generation cholera and typhoid vaccines are being incorporated incrementally into the national immunization programme, and among practitioners and local-level health officials in specific disease-endemic areas within countries.

Many policymakers and influential professionals interviewed in the seven countries viewed improvements in water and sanitation systems, along with health education and general improvements in living standards, as the best and most sustainable means of controlling these infections. These informants viewed vaccination as a “short-term” solution requiring repeated action and funding. And nearly all those interested in the use of enteric vaccines believed that they should be only one tool in an “arsenal of weapons” that includes water and sanitation improvements, disease surveillance, health education and literacy programs. As one Indian expert declared, “What’s the point of providing Vi, if you don’t also clean up the water?”

But there was also recognition among many policymakers in these countries that these improvements would require huge government investment and take many years at current funding levels to reach the poorest and highest-risk populations. These informants therefore saw a potentially useful role for vaccines in controlling these diseases in the short to medium term.

Of the three diseases, typhoid fever generated the greatest concern and interest in vaccines overall, followed by shigellosis and cholera (Table 2).

3.2.1. Typhoid fever

The consensus that typhoid fever is a serious and widespread problem was greatest in Vietnam and Pakistan. Vietnamese policymakers pointed to local data showing a six-fold increase in reported incidence from 1990 to 1995, which they attributed in part to an increase in the number of chronic carriers resulting from patients taking sub-optimal doses of antibiotics. Rising rates of antibiotic resistance are also behind much of the concern about typhoid fever in Vietnam and in Pakistan, where the disease is perceived as a universal problem that strikes children from all areas and social classes.

While opinions were more mixed in Indonesia, India, Bangladesh and China, many informants in these countries considered typhoid fever a serious and common public health problem. Several Indian informants described typhoid as “rampant” and “prevalent in huge belts”, with one providing anecdotal evidence that the emergency room of any children’s hospital is filled mainly with cases of malaria and typhoid fever. However, other Indian interviewees, including a top government health official, considered the disease much less of a problem, claiming that antibiotics are still very effective or that typhoid fever is confined to certain, mainly urban areas. The universality of risk across social classes was also behind the concern among several informants in Bangladesh and in Indonesia, where, according to one hospital director, one sees as many cases of typhoid fever in hospitals serv-

ing middle and upper classes as in those primarily serving the poor. This is considered due to its transmission commonly through “street food”—which is eaten by children of all socio-economic classes—and by chronic carriers. In general, those at the “frontlines”, such as clinicians, hospital directors and local government officials, considered typhoid fever incidence higher and showed greater concern than did central government officials in these four countries.

Among the seven countries, only in Thailand did most persons interviewed feel that typhoid fever was no longer a serious problem, citing a sharp decrease in incidence in recent decades, due to economic development and improvements in water and sanitation systems. They also noted that the reported incidence of typhoid fever has not increased since the government stopped its school-based immunization programme using the old, injectable killed whole-cell vaccines in the 1980s, which is credited in successfully reducing disease incidence [22].

Despite the expressed preference among many policymakers for “long-term solutions” to control typhoid fever, such as water and sanitation improvements and increased health education, the study found considerable interest among many informants—especially in Pakistan, Vietnam, Indonesia and India—in the use of Vi or the still experimental Vi conjugate vaccine as a key strategy to reduce typhoid incidence in the near term. In Vietnam, the government began incremental immunization of 3–10 year olds in high-incidence districts in 1997 through vaccination posts (for pre-schoolers) and schools (for 6–10 year olds), using imported vaccine obtained at a special, low price. Its long-term goal is to vaccinate all kindergarten and primary school children nationwide. The programme will gradually replace the imported Vi with a locally-produced vaccine, which was licensed in 2003. Due to concerns about antibiotic resistance, the Indian Ministry of Health has shown renewed interest in using a typhoid vaccine and in conducting comparative research of the three commercially available vaccines (killed whole-cell vaccine, Vi and the live, oral Ty21a vaccine) as a first step. Most informants in Pakistan expressed interest in typhoid vaccines, believing they would generate considerable population demand due to the public’s fear of the disease and its perceived pervasiveness. However, interest in and commitment to Vi use among key central government officials in Pakistan, India and Indonesia was generally less than it was among clinicians, local-level health officials and researchers.

The survey found considerable interest in the production of Vi among local vaccine producers in most of the countries visited. Besides Vietnam, Indonesia and India, where Vi development and production efforts have gotten underway, public sector vaccine manufacturers in Pakistan and Bangladesh expressed interest in producing the vaccine, despite currently limited production capabilities. This interest is driven in part by the ready access to the technology for producing Vi, the relative low cost of production and the perceived potential population demand for the vaccine. These producers believe that even if national immunization programmes do not buy

Table 2
Level of interest among policymakers and other informants in new-generation vaccines against cholera, typhoid and shigellosis and reasons given

Interest level	Countries/informants	Major reasons given
Typhoid		
Higher	Vietnam	Disease is rampant and endemic
	Pakistan	All children are at risk (across social classes)
Lower	Clinicians, medical associations, local producer in Indonesia	Incidence may be increasing due to economic decline, refugees, etc. (Pakistan, Bangladesh)
	Local health officials in endemic areas of China	Antibiotic resistance is making disease more difficult and expensive to treat
	Researchers, medical associations, EPI, army, producers in India	Recovery period can be long and there is no quick fix like oral rehydration therapy
	Some MOH officials, army, local producer in Bangladesh	There is a potentially large private sector market (India, Pakistan, Indonesia)
Lower	Thailand	Incidence is unknown
	Central government officials in Indonesia	Incidence is low so need and demand will be low (Thailand)
	Central government officials in China	Low priority of enteric vaccines in general (Bangladesh, Indonesia)
	Some informants in Bangladesh and India	Disease is not killer it once was due to antibiotics and improvements in living standards and education (India)
Shigella		
Higher	Thailand	Disease is very pervasive and endemic and is responsible for large portion of diarrhoeal disease burden
	Bangladesh	High level of morbidity and mortality in very young children
	Local health officials in China	Disease is highly contagious and difficult to control
	Practitioners and medical societies in Pakistan	Disease is difficult to treat and not as manageable as cholera
Lower	Indonesia	Antibiotic resistance is making treatment more difficult and costly and could lead to epidemics
	India	Incidence is unknown or considered low
	Vietnam	Disease is often mild and can be treated mainly on an out-patient basis
	Central government officials in Pakistan	Relatively cheap antibiotics are still effective
	Central government officials in China	Need to determine main sources of transmission and high-risk groups and to educate physicians before considering vaccine use
Cholera		
Higher	Vietnam	Potentially large economic consequences of reported outbreaks
	Central government officials in China	Incidence is still high in certain areas
	Central government officials in Thailand	Disease is spreading to new areas (India)
	Local health officials in endemic areas of India	Water and sanitation improvements are costly and will take many years to reach neediest populations
	Practitioners, research scientists in Indonesia	
Lower	Bangladesh	Incidence is low or has decreased substantially
	Pakistan	ORT has reduced mortality to very low levels, reducing need for a vaccine
	Central government officials in India	Water and sanitation improvements are the best, most sustainable way to control disease
	Central government officials in Indonesia	The efficacy of current vaccines is too low to justify widespread government use

the vaccine, they can find viable markets for Vi in the armed forces, the private sector—given the perceived risk of getting typhoid to middle and upper classes—and other sectors.

Interest in government use or local production of Vi was low among most informants in Thailand due to the perceived low incidence of the disease and the assumed limited market potential for the vaccine.

3.2.2. Shigellosis

Despite the lack of reliable incidence data, many of those interviewed in most countries perceived shigellosis to be a serious problem. The highest level of concern across the board was expressed in Thailand, where the disease is considered

responsible for a significant portion of the country's overall diarrhoeal disease burden, and in Bangladesh, where informants at all levels and in both the public and private sectors viewed it as “dangerous” and prevalent “throughout the country”. Reasons given for their concern were: its perceived high incidence; its high level of contagiousness; the potential for complications and death; problems in delivering adequate clinical care, especially in peripheral areas; growing rates of antibiotic resistance and the resulting difficulty and growing cost of treatment. One leading paediatrician in Thailand considered shigellosis a top priority—not because of its current incidence in the country, which he believed to be quite low—but because of rising rates of multi-drug resistant

Shigella strains, which could lead to future epidemics. In both Thailand and Bangladesh, there was considerable expressed interest in future *Shigella* vaccines among Ministry of Health and other central government officials.

Views on the importance of shigellosis and the need for a vaccine varied more widely in the other countries. Although several central-government informants in Pakistan and China expressed little concern about the disease, due to the lack of epidemiological data or to its perceived low incidence, local health officials and practitioners interviewed viewed it as a more serious problem. Several leading paediatricians in Pakistan placed a higher priority on a *Shigella* vaccine than on vaccines against cholera or even typhoid, due to their perception of the greater morbidity and mortality caused by shigellosis and to growing rates of antibiotic resistance. Health officials from a municipality and a Southern province in China had explored starting a targeted vaccination programme using the Chinese FS vaccine (e.g. for food workers), but the relatively high cost of the vaccine has curtailed these efforts.

In India, because of their uncertainty of the disease burden and growing rates of antibiotic resistant *Shigella* strains, many informants expressed interest in having shigellosis disease burden studies conducted in the country. Yet concern about antibiotic resistance was not uniform across regions of India. While an estimated 55–60% of diarrhoeal disease patients coming to the main infectious disease hospital in Calcutta have dysentery—much of it presumed to be shigellosis—West Bengal state health officials consider the disease mainly ‘mild’ and highly manageable, since most patients are readily treated with antibiotics on an outpatient basis. They estimated that dysentery cases account for less than 2% of all diarrhoeal disease admissions to the hospital.

Most informants in Indonesia believed the incidence of shigellosis, though not necessarily dysentery, to be relatively low and thus showed limited interest in a *Shigella* vaccine. In Vietnam, while the shigellosis disease burden is recognized as being substantial, the disease is of less immediate concern to central government officials, since antibiotic resistance rates remain low and the disease is still highly treatable at relatively low cost.

3.2.3. Cholera

Although most persons interviewed believed that the true incidence of cholera was unknown, there was a general consensus in most countries that the disease is much “less frightening” than it was in past decades. Cholera incidence is believed to have decreased to low levels in Thailand and in China, due to economic development and improvements in water and sanitation systems. Even in countries viewed by the international health community as cholera-endemic, such as India, Pakistan and Indonesia, many informants—especially central government officials—described cholera incidence as “sporadic”, occurring only in “spurts” or limited to specific areas (e.g. North Jakarta in Indonesia and along the Bay of Bengal in India).

But more than the perceived decline in incidence, the reduced concern about cholera among many policymakers in such countries as India, Bangladesh, Indonesia and Pakistan is due to perceived dramatic reductions in cholera mortality resulting from the widespread use of oral rehydration therapy (ORT) and, to a lesser extent, antibiotics. While several senior health officials in Bangladesh believed cholera incidence still to be high, they described the disease as “well managed” and cholera mortality as “very low”. In both India and Bangladesh, several government officials and researchers quoted cholera case fatality rates of less than 1%—down in Bangladesh from an estimated 30% before widespread ORT use. Some informants conceded that some cases in more isolated areas probably never reach the hospital. Several informants in Indonesia and Pakistan ranked cholera number two in priority among the DOMI diseases, after typhoid fever or shigellosis, due to the perceived reductions in both incidence and mortality.

This relatively complacent view of cholera incidence and mortality was not shared by all informants in traditionally cholera-endemic countries. The disease was of great concern to state health officials and practicing physicians in West Bengal, India, where cholera cases account for more than 20% of diarrhoeal disease admissions in Calcutta’s main infectious disease hospital—the third highest cause after rotavirus and enterotoxigenic *Escherichia coli* (ETEC). Government researchers in India described how cholera outbreaks are spreading to new areas, such as Kerala state—beyond the traditional “cholera belt” of Northeast India. Another Indian informant claimed that contaminated water systems are spreading the disease to urban areas throughout the country. To several research scientists in Indonesia, cholera was their top concern among the three DOMI diseases due to its virulence and continued high incidence.

In contrast to these mixed views, there was a consensus among informants in Vietnam that cholera is endemic in large sections of the country. The disease was a top concern to almost all persons interviewed. This general agreement about the seriousness of the cholera problem may be due in part to the country’s extensive disease surveillance system. Instead of downplaying reported cases of cholera, the government’s fear of the economic impact of the disease, among other factors, has led Vietnam to be the first country in the world to add a new-generation cholera vaccine to its national immunization programme, through which it plans to eventually vaccinate all 2–5 year olds in high-risk areas.

Apart from Vietnam, the greatest interest among central government officials in the use of cholera vaccines was found in China and Thailand. Despite the belief that cholera incidence is low and sporadic in both countries, the fear of the disease crossing their national borders and causing outbreaks with potentially serious economic consequences (e.g. on tourism and food export industries) generates concern among these officials. Government scientists in Thailand were eager to develop a new-generation cholera vaccine and in China, efforts are underway to develop a vaccine, with

encouragement and financial support from the central government.

The interest in the use of cholera vaccines among informants in Indonesia and India was more mixed. While health officials in West Bengal (where Calcutta is located) viewed water, sanitation and housing improvements as the key to controlling cholera in the long term, they saw a more immediate role for the vaccine and believed there would be a public demand for it in their area. A key health ministry official also believed there was a need for an effective, safe cholera vaccine in India. Practitioners working at the local level in Jakarta, Indonesia saw a role for a “good” cholera vaccine, while central government officials showed less interest in a vaccine or were reluctant to voice an opinion, due to their uncertainty about the country’s cholera disease burden.

Interest in a cholera vaccine was lowest among policy-makers and other informants in Pakistan and Bangladesh. According to central government officials, because of the poverty level and health conditions in their countries, priority should be given to vaccines that would significantly reduce child mortality. Since ORT is believed to have driven cholera mortality to low levels, they believed that a cholera vaccine is no longer needed, except perhaps for limited uses, such as for outbreak control among refugees.

3.3. Key factors influencing decisions regarding vaccine introduction

Informants in the seven countries cited the following factors as key in influencing decisions regarding new vaccine introduction:

Disease burden: Policymakers across countries consistently mentioned disease burden as the number one factor in setting priorities for vaccines to introduce into immunization programmes. Disease burden data are also used by local producers to target vaccines for development, since they must be convinced of a vaccine’s potential demand, in either the public or private sector, before investing in development, testing and production. Survey data revealing high rates of shigellosis in China led Lanzhou Institute to focus on developing the *Shigella* FS vaccine. Professional associations use disease burden evidence to recommend use of a new vaccine in the private sector. To several key policymakers in Pakistan and Bangladesh, a vaccine’s potential impact on infant or child mortality were also critical considerations in setting vaccine priorities, due to the relatively high infant mortality rates and limited resources in these countries.

Economic considerations: The economic impact of a disease and potential cost savings from a vaccine figured prominently in discussions about the need for enteric vaccines. The fact that, of the vaccines targeting DOMI diseases, the Chinese government has financially supported research and development only for cholera vaccines stems from its concern about the potentially devastating economic impact of cholera outbreaks, and not from the cholera disease burden, which is likely to be the least of the three DOMI diseases in

China. The rising cost of treating typhoid fever, due to growing antibiotic resistance, and the economic costs to families from the loss of work to care for a child during increasingly long recovery periods appear to contribute significantly to growing interest in typhoid vaccines among many policymakers. The need for typhoid vaccines was generally perceived as most urgent in countries, such as Pakistan and Vietnam, where newer generation antibiotics (e.g. ciprofloxacin and third-generation cephalosporins) must be imported and are quite costly, than in countries, such as Bangladesh, where inexpensive locally-made ciprofloxacin is reportedly purchased even by the poor.

Evidence of cost-effectiveness or cost-benefit of vaccines—as opposed to treatment—was cited by informants in Thailand, India, Bangladesh, Pakistan and Vietnam, as increasingly critical to convince government decision-makers to finance public sector use of a new vaccine.

Vaccine price and affordability: Across countries, vaccine price was mentioned as one of the most important factors in influencing decisions to introduce a new vaccine, often second only to disease burden. Informants in several countries cited US\$ 1 per dose as the maximum acceptable price the government would pay for new-generation enteric vaccines. A key government official in Thailand—the wealthiest of the seven countries—felt that a price of US\$ 1 or less per dose would be critical for government approval to purchase a new cholera vaccine, especially given the presumed low cholera incidence in the country. Several informants in India and Bangladesh felt that even lower thresholds (e.g. US\$ 0.25–0.35 per dose) would be required for public sector use of a cholera vaccine. Vaccine price is also considered a key determinant of public demand for these vaccines in China, where patients are charged user fees for all but the basic Expanded Programme on Immunization (EPI) vaccines.

Vaccine safety and performance: Most informants mentioned safety, low rates of side effects and vaccine performance as key criteria in considering introduction of a new vaccine. The countries in the study increasingly require evidence of vaccine safety and effectiveness in the local population before considering their use in the public sector, even for vaccines already licensed locally and used in the private sector. While many policymakers were hesitant to define minimum acceptable performance levels for these vaccines, several gave a minimum length of protection of 5 years and efficacy rates ranging from 75 to 85%—while some government officials expected rates of at least 90% for government use. These informants thus considered the current Vi vaccine—with demonstrated efficacy of 64–72% at 17 months and 55% for at least 3 years—as just below or just meeting their minimum requirements. They viewed the oral cholera vaccines—which confer around 60% protection for 2 years—as mainly suitable for emergency situations and not for routine use in endemic areas. Several other informants, however, notably in Indonesia, Thailand and India, believed that enteric vaccines with efficacy rates of as low

as 60–70% and 3 years of protection would be acceptable if demonstrated to be cost-effective. Officials in China and Vietnam—both countries that place an extremely high value on immunization—generally gave lower minimum performance criteria and considered the currently available new-generation enteric vaccines as acceptable.

Feasibility of local production: According to policymakers in most of the seven countries, the possibility of government uptake of a vaccine will be greatly enhanced if it is produced locally. The feasibility of local production has become a critical factor in decisions regarding vaccine introduction in four countries with national policies of self-reliance in vaccine production—namely, China, Vietnam, India and Indonesia. Policymakers view local vaccine production as the most likely means of driving down vaccine prices to the point where new private sector markets are created and governments are willing to consider their use. Local vaccine production was also seen as saving foreign exchange, reducing the effects of currency devaluations, increasing self-reliance and therefore as more sustainable than relying on imported vaccine. In India, local production and promotion of vaccines, especially by private sector producers, was increasingly viewed as critical to raise the awareness of, and create demand for new vaccines among policymakers, opinion leaders and the public.

Local production was considered less of a factor in vaccine introduction decisions in Thailand, Pakistan and Bangladesh, due to more limited production capabilities at present.

Other factors: The burden that adding a new vaccine places on already strapped and often undermanned immunization programmes—in terms of delivery, training, cold chain and storage needs—was mentioned by policymakers, especially in Bangladesh, Pakistan and India, as an important factor in making decisions to introduce new vaccines. To minimize this burden and to reduce the total number of injections required for each child, informants generally preferred oral vaccines, those requiring two or less doses, and combination vaccines. There was also a preference to incorporate any new enteric vaccine into the infant immunization schedule. Government informants in some countries also believed that a recommendation from WHO would be critical to government decisions to introduce a new enteric vaccine into the national immunization programme.

3.4. Likely strategies for introduction and financing of new-generation enteric vaccines in Asia

With more and more new vaccines becoming available on the market, informants in most countries believed that strategies for targeting, distributing and financing many of the new vaccines will differ from those used for the traditional EPI vaccines, which are mainly provided through nation-wide immunization programmes managed and financed by the central government. New approaches will be needed because of financial and human resource constraints of many national immunization programmes, the often higher prices of newer

vaccines as compared to basic EPI vaccines, and, in the case of current new-generation enteric vaccines, the need to administer them outside of the infant EPI schedule, since they are not effective in infants. Among the likely introduction strategies for new-generation enteric vaccines raised by informants are:

Targeted vaccination: Most informants across countries envisioned government use of new-generation enteric vaccines as limited and targeted, at least initially. No policymaker in any of the countries advocated universal immunization against cholera, but instead would target high-incidence areas, such as coastal regions of Thailand and China and the Ganges River Basin in India; high-risk populations, such as refugees, fishermen, the poor and food workers; and high-risk situations, such as floods and other natural disasters. The broadest use of a cholera vaccine in relative terms is envisioned in Vietnam, where the government plans to eventually immunize 10 million people in endemic areas of the country.

Informants in various countries also envisioned targeted use of new-generation typhoid vaccines—e.g. for soldiers, slum dwellers, urban school-aged children, refugees and food workers. Vietnam, as mentioned, is already targeting children in high-incidence districts for Vi immunization in limited quantities. However, several persons in Pakistan, India and Indonesia, especially active physicians, advocated eventual universal childhood immunization through the EPI programme. They believed this was warranted because of the perceived pervasiveness of typhoid fever and, in the case of India [23] and Pakistan, the growing evidence of a high disease burden in very young children. An estimated one-third of typhoid cases in Pakistan occur in children under 2 years of age (Bhutta, personal communication, Feb 2001). Incorporation into the infant EPI schedule would require use of a future vaccine suitable for infants.

Strategic, targeted use of *Shigella* vaccines was suggested in several countries, such as Bangladesh, India and China, especially for high-incidence areas, outbreak control and for food workers. However, several policymakers in Thailand and Vietnam considered the vaccine suitable for mass immunization of children and for incorporation into the EPI schedule, because of its widespread incidence and its disproportionate toll on very young children.

Targeted vaccination, if done well, requires solid disease burden data from different parts of the country, disaggregated by geographic area, age group and other relevant demographic characteristics.

Increased role of decentralized governments in the provision and funding of new vaccines: In countries with decentralized health systems, such as China, India and Indonesia, public sector introduction of new vaccines may increasingly be initiated and financed by local governments. This is already the case in China, where provincial and municipal governments are now responsible for providing and financing the EPI programme, as well as for deciding whether or not to provide and sell non-EPI vaccines to patients. Several local governments in Southern China are already providing Vi vaccina-

tion and some have purchased the Chinese *Shigella* vaccine on an experimental basis. In India, the central government is shifting responsibility for adding and financing non-EPI vaccines to state governments, and a few states have begun purchasing and providing some newer vaccines (e.g. hepatitis B, Japanese encephalitis and measles–mumps–rubella) on their own. According to a top government official, because of the great diversity in health and economic conditions within India, the “regional” nature of diseases such as cholera, and the many pressing priorities of the national immunization programme, it is appropriate for decentralized governments to implement and finance non-EPI vaccines, based on each state’s needs and capacity. Indian informants felt that localized introduction of a vaccine such as Vi could put pressure on neighboring states and eventually on the federal government to add the vaccine to their immunization programme.

Increased role of the private sector in vaccine promotion and delivery: In countries with vibrant private health sector, such as India, Pakistan and Indonesia, many informants believed that expansion of Vi vaccine use through the private sector would be an appropriate and feasible means of increasing typhoid immunization initially, given the potentially sizeable demand for the vaccine among middle class and urban residents. Indian and Pakistani informants cited as a possible model for Vi the rise in hepatitis B vaccine use through the private sector, prior to its introduction into their national immunization programmes with support from the Global Alliance for Vaccines and Immunization (GAVI). The private sector growth in hepatitis B vaccine use in both countries was achieved through aggressive marketing by producers; active promotion by physician associations; adoption by employee health services of large, state-run enterprises; and innovative means of reaching beyond traditional private sector elites with the help of non-governmental organizations, such as large-scale immunization camps using discounted vaccine.

In fact, policymakers in India, Pakistan and Indonesia increasingly view the role of the private sector as a key component of a comprehensive and rational strategy to introduce new vaccines, as opposed to merely serving a tiny, wealthy elite. This would be especially true for vaccines against diseases that strike across socio-economic classes. Initial broader introduction through the private sector is viewed as a means of both assessing and creating population demand for a new vaccine, eventually putting pressure on the government sector to provide the vaccine. Several government officials in India and Indonesia also suggested, as a potential cost-containment strategy, a “duel channeling” approach that would limit public sector distribution of a vaccine, such as Vi, to the poor, while referring others to the private sector.

A strategy that focuses on public sector distribution of Vi and other enteric vaccines was viewed as more appropriate in Bangladesh, where only around 2% of immunizations are provided through the private sector [24] and in Vietnam and China, both countries where private sector provision of immunizations is either illegal or discouraged. In most coun-

tries, public sector introduction was also considered as the most appropriate strategy for cholera and *Shigella* vaccines, since these diseases disproportionately affect rural populations and the poor.

4. Discussion

4.1. Limitations of the study

Several potential limitations of the study warrant consideration. The findings are qualitative and were collected through interviews, thus leaving analysis potentially open to interpretation and to the bias of the researchers. There could also be misinterpretation of responses due to language barriers. To minimize misinterpretation, the interviews were structured to allow for probing and to clarify responses. Feedback from local collaborators in several countries also partially validated the findings and conclusions.

One could also argue that those interviewed did not represent decision makers in the country as a whole, or that not all key policymakers were interviewed. This is especially true in countries where decision making increasingly takes place at the decentralized level, such as China, India and Indonesia, since health authorities from only a few localities were interviewed. However, the team interviewed people in every country who are considered critical to programmatic and budgetary decisions regarding immunization, including directors general of health, heads of communicable disease control divisions, EPI managers, members of national immunization committees, and health division heads of finance or planning ministries. We therefore believe that the findings are indicative of the prevailing beliefs and opinions of many decision makers and influential leaders in these countries regarding enteric diseases and vaccines.

4.2. Summary of key findings

As Wenger et al. [16] found in their study of Hib vaccine introduction, local disease burden data was considered one of the most critical factors influencing government decisions to introduce a new vaccine. The study found considerable uncertainty among policymakers and other informants of the disease burden of cholera, typhoid fever and shigellosis in most countries, due to limited laboratory-confirmed surveillance data. The lack of credible epidemiological data could contribute significantly to the lower priority level of these vaccines among a number of informants, especially central government officials without direct experience dealing with these diseases. Views on cholera mortality in endemic countries, such as India and Bangladesh, illustrate the need for solid, well-disseminated disease burden data. The less than 1% case fatality rates quoted by several informants in these countries are those from hospitals providing intensive, high-quality treatment for severe cholera and are unlikely to be replicated in rural areas, where ORT use in clinical or home

settings has been shown to often be inadequate for the proper management of moderate to severe cholera [25] or where its use is still low, as has been found to be the case in many states in India [26].

These findings led to efforts within the DOMI Program to obtain additional disease burden information by conducting meta-analyses of existing data in each country and by expanding prospective disease surveillance studies.

Besides the dearth of credible disease burden data, there are several other factors impeding the introduction or expanded use of existing and future new-generation enteric vaccines in Asia in the near term. These obstacles include:

- the preference among policymakers for water and sanitation and other environmental improvements as the key means of preventing these diseases and the perceived competition for the same limited resources between these improvements and vaccination;
- the moderate levels and length of protection of these vaccines, which do not meet the expectations of many policymakers;
- the current or expected prices of these vaccines, which will have to be US\$ 1 or less per dose or series before many governments will consider their uptake;
- the need to administer cholera and typhoid vaccines outside of the infant EPI schedule, since these vaccines are not licensed for use in infants and since a broader age group may have to be vaccinated to have a major, immediate impact on disease incidence;
- severe financial constraints of national immunization programmes in many Asian countries, several of which (e.g. Pakistan, Bangladesh, Vietnam) still rely heavily on donor funding or World Bank loans; and
- competition with other infectious disease or immunization programme priorities, which, depending on the country, include polio eradication, hepatitis B introduction or expanded coverage, improving EPI coverage rates, and introducing Hib vaccine.

Despite these obstacles, the study found considerable interest among policymakers and other influential professionals in the use of typhoid Vi vaccine in most of the countries, as well as interest in *Shigella* and cholera vaccines among a number of informants in several countries. Major drivers of the interest in Vi vaccine appear to be growing rates of antibiotic resistance, the perceived pervasiveness of the disease and rising costs of illness. The perceived risk that typhoid fever poses to all socio-economic classes, including the class to which policymakers belong, may also contribute to their heightened awareness of the disease. The current availability of Vi on the market and the prospect for local or regional production because of the relatively simple technology involved and lack of patent protection are other possible factors contributing to interest in the vaccine. Expanded use of Vi in several countries, such as India and Pakistan, will likely begin in the private sector, due to the potentially sizeable demand for the vaccine among middle class and urban

dwellers—especially once lower-cost, locally or regionally-produced vaccine becomes available—and to the uncertainty of public sector introduction in the immediate future. Initial public sector use of Vi will likely be targeted to high-risk areas and populations and, in some countries, may be initiated and financed by state, provincial or other local governments.

Interest in future *Shigella* vaccines was also driven by rising rates of antibiotic resistance, the perceived endemicity of shigellosis and the difficulty in managing the disease, especially in more rural, isolated areas. In contrast, the main factors driving policymakers' interest in new-generation cholera vaccines in Thailand and China—where interest at the central government level was strongest among the seven countries—were not any likely impact on morbidity and mortality, given the low presumed cholera incidence in both countries, but rather the fear of the potential negative impact of outbreaks on their growing economies and the public concern that cholera reports provoke. On the other hand, the perceived success of ORT in driving cholera mortality down to negligible levels has reduced interest in a cholera vaccine among policymakers in several endemic countries. This results in a paradox in which policymakers' interest in new-generation cholera vaccines was highest in countries with the lowest presumed need and was lowest in some countries where the need is thought to be greatest. In all countries, only strategic, targeted use of cholera vaccines, primarily through the public sector, was foreseen.

The study findings suggest that specific types of data could be critical to overcome existing obstacles and convince policymakers of the need to introduce one or more new-generation enteric vaccines. These data include country-specific evidence of disease burden, preferably obtained from multiple sites throughout the country to obtain a national picture of the disease. Besides demonstrating the need for a vaccine to budgetary decision-makers and local vaccine producers, such information would be critical to identify high-risk areas and populations for targeting immunization, and—in the case of *Shigella*—to determine the distribution of species and serotypes for the most appropriate vaccine formulation. Data on cost of illness, vaccine cost-effectiveness and potential cost savings from vaccination could also become critical decision-making tools to help policymakers prioritize between the growing number of new vaccines. This is especially true given the generally higher prices of new vaccines as compared to basic EPI vaccines and—in the case of new-generation enteric vaccines—their moderate levels and length of protection. As Wenger et al. also found in other regions, due to the potential differences between populations in the endemicity of a disease, immune response and ecological factors, evidence of a vaccine's safety and effectiveness in the local population is increasingly required by policymakers in Asia before they would approve vaccine introduction [16]. Controlled vaccine demonstration or pilot projects to collect such evidence would also demonstrate to policymakers the ability of existing health systems to successfully deliver new-generation enteric vaccines outside of the infant EPI schedule.

In addition, such pilot projects provide the prior experience with a vaccine that Wenger et al. found to be a key factor in decisions to introduce a new vaccine in “early adopting” countries, and can also serve as a catalyst to stimulate political will to introduce a new vaccine in the public sector [16,20].

Besides collecting this information, it will also be critical to develop a well-conceived plan to disseminate the research findings to all those that make and influence policy decisions as well as to improve regular communication and dialogue between researchers and policymakers.

4.3. Broader implications of the study

In addition to reporting the findings concerning these specific diseases and vaccines in the above countries, this paper demonstrates the utility of surveying the views of policymakers to inform the design of vaccine research and advocacy projects [27,28]. As these projects are being developed, it is critical to understand what the disease control priorities are in targeted countries; how vaccine-related policy decisions are made; what factors influence these decisions, including vaccine attributes and characteristics; and what data are most critical to inform these decisions. Without a clear understanding of these issues, these projects may not provide the necessary data or otherwise meet the needs of policymakers to ensure timely introduction of the targeted vaccines into public sector programs.

This paper has reported findings from large Asian countries on factors affecting vaccine introduction decisions, data needs of policymakers and likely strategies for vaccine introduction and financing that may be relevant to other vaccines under development (e.g. malaria, rotavirus, pneumococcal) and to other regions. We eagerly await policy-related data from these vaccine programs to begin drawing general lessons concerning successful strategies for vaccine research and introduction in developing countries.

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