

WORLD HEALTH ORGANIZATION
REGIONAL OFFICE FOR THE WESTERN PACIFIC



REPORT

**BI-REGIONAL MEETING ON PREVENTION OF CHILDHOOD PNEUMONIA
AND MENINGITIS BY VACCINATION**

**Kuala Lumpur, Malaysia
30-31 March 2006**

Manila, Philippines
May 2006

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Convened by:

**WORLD HEALTH ORGANIZATION
REGIONAL OFFICE FOR THE WESTERN PACIFIC**

**WORLD HEALTH ORGANIZATION
REGIONAL OFFICE FOR SOUTH-EAST ASIA**

GLOBAL Hib INITIATIVE

PneumoADIP

Not for sale

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NOTE

The views expressed in this report are those of the participants in the Bi-regional Meeting on Prevention of Childhood Pneumonia and Meningitis by Vaccination and do not necessarily reflect the policies of the World Health Organization.

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SUMMARY

Infections due to Hib and *S. pneumoniae* account for up to 14% of all deaths among children <5 years old in developing countries. Together, they account for an estimated two-thirds of bacterial meningitis cases and pneumonia deaths among children less than five years of age. Given the enormous potential to prevent childhood mortality with vaccine interventions, country policy-makers, researchers and public health stakeholders, including WHO, the United Nations Children's Fund (UNICEF) and the Global Alliance for Vaccines and Immunization's (GAVI) *Haemophilus influenzae* type b (Hib) Initiative and Pneumococcal Accelerated Development and Introduction Plan (PneumoADIP) came together to examine the evidence available to support the decision-making process regarding the introduction of new vaccines.

New vaccines have the potential to provide great value in developing countries by significantly reducing morbidity and mortality, helping countries come closer to reaching Millennium Development Goals, addressing inequities related to access to care, and contributing to the strength of the overall health system. Two vaccines, Hib conjugate and pneumococcal conjugate, potentially address a serious problem in countries in the South-East Asia and Western Pacific Regions.

Data were presented on the various studies supporting the burden of Hib and pneumococcal disease in the Region. Although many studies have been carried out, few have measured the largest impact of pneumonia. Two probe studies, one in Lombok and one in Bangladesh, suggest that Hib vaccine has the potential to prevent pneumonia. Furthermore, both studies demonstrate that routine surveillance underestimates the burden of disease significantly.

Country representatives reported on their specific experiences and how to overcome the challenges of initial underestimations of disease burden and/or difficulties in measuring disease through conventional surveillance and handle programmatic aspects of introduction. Each country evaluated its decision-making processes and recommended actions to expedite the evaluation of new vaccines and advocate for increased investment in life-saving interventions such as Hib and pneumococcal vaccines.

To achieve the important goals of saving children's lives and removing barriers for uptake of new vaccines, the Hib Initiative and PneumoADIP provide a much needed focus. They, along with partners, donors, suppliers and countries, all play a role in finding novel ways to measure disease burden and/or vaccine impact, making informed decisions on a more timely basis and showing interest and willingness to adopt new interventions so suppliers will produce larger, more affordable quantities of products that meet the needs of developing countries.

1. INTRODUCTION

Introducing "new and underutilized vaccines" is one of the four strategic areas in the Global Immunization Vision and Strategies (GIVS), developed jointly by WHO and the United Nations Children's Fund (UNICEF) to further reduce childhood mortality and morbidity. Bacterial pneumonia and meningitis are common and serious diseases of childhood, accounting for substantial morbidity and mortality among children under five years of age. *Haemophilus influenzae* type B (Hib) and *Streptococcus pneumoniae* together are estimated to account for two-thirds of pneumonia and meningitis deaths among children under five. WHO estimates that Hib causes three million cases of serious disease and about 400 000 deaths annually (or more than 1000 deaths a day), mostly in children under five years of age. Similarly, pneumococcal disease is estimated to cause approximately 800 000 to one million child deaths annually – in other words, a child dies of pneumococcal disease every 30 seconds somewhere in the world. Unlike Hib, the pneumococcal disease burden among adults is also high, with an estimated 600 000-800 000 adult deaths each year from pneumococcal pneumonia, meningitis and sepsis. In sum, 12% to 14% of all child deaths are probably due to these two vaccine-preventable diseases. Thus, accelerated introduction of these vaccines can contribute to achievement of the Millennium Development Goal (MDG4) of reduced childhood mortality.

A safe and effective vaccine for Hib, available since 1987, can be integrated into existing childhood immunization schedules. Several vaccines against pneumococcus are in advanced stages of development. Although 17 countries and areas in the Western Pacific Region have already introduced the Hib vaccine, they account for less than 4% of the regional population; those countries accounting for the majority of the population in the Region have not yet introduced the vaccine. The main perceived constraints are: an unclear disease burden, the expensive vaccine, the short supply of vaccine and a lack of awareness and appreciation of Hib among policy-makers. The Global Alliance for Vaccines and Immunization (GAVI) has sponsored the Hib Initiative with the mission to "expedite and sustain evidence-informed decisions at the global, regional and country levels regarding the use of Hib vaccination to prevent childhood meningitis and pneumonia" through a country-driven and health systems approach.

A 7-valent pneumococcal conjugate vaccine that is safe and effective for use in infants has been available since 2000. Vaccines that extend the protection against pneumococcal disease by including 10 or 13 serotypes are expected to be available as early as 2008. Given the potential health impact of these vaccines, GAVI created the Pneumococcal Vaccines Accelerated Development and Introduction Plan (PneumoADIP), with funding of US\$30 000 000, in 2003. The PneumoADIP aims to improve child health and survival by accelerating the evaluation of and access to new, life-saving pneumococcal vaccines. Current PneumoADIP projections show that accelerated introduction of pneumococcal vaccines can prevent up to 3.6 million child deaths between now and 2025.

The biregional meeting co-organized by the WHO Western Pacific and South-East Asia Regions, GAVI's Hib Initiative and PneumoADIP, and UNICEF, provided a forum to exchange information and experiences between countries and areas that have introduced the vaccine and those that have not, as well as between the researchers working in this arena and policy-makers. The meeting was expected to identify key priority actions to be implemented over the next two to three years at the regional as well as the country level.

1.1 Objectives

- (1) to review the existing Hib and pneumococcal disease-burden data in the WHO Western Pacific and South-East Asia Regions;
- (2) to learn from the experiences of the countries that have introduced the vaccine into their national programmes and gained knowledge of the latest available global information on vaccine issues, specifically the likely supply and price situation in the next few years; and
- (3) to identify key priority action areas for each participating country and for both regions for the next two to three years, based on current data.

1.2 Organization

A total of 49 participants and observers attended the meetings: 11 participants from seven Member States of the WHO Western Pacific Region, 20 participants from 13 Member States of the WHO South-East Asia Region, and seven observers from the Hib Initiative and PneumoADIP. The timetable of the meeting and list of participants are provided in Annexes 1 and 2, respectively.

1.3 Opening ceremony

Dr Han Tieru, WHO Representative in Malaysia, opened the meeting on behalf of the Regional Director for the Western Pacific and the Regional Director for South-East Asia. In his opening address, he emphasized the importance of introducing the new vaccines into national immunization programmes, which was justified on the basis of disease burden and cost-effectiveness, as outlined in the GIVS developed jointly by UNICEF and WHO.

He stressed that the global community had taken more than 20 years to utilize the benefits of hepatitis B vaccine despite a clear demonstration of disease burden in most developing countries, including those in the Western Pacific and South East Asia Regions. Early introduction of hepatitis B vaccine could have saved thousands of lives. Steps need to be taken to ensure that, in the future, the benefits of newly available vaccines are brought to those who need them at the earliest possible time. He highlighted the perceived 'high cost' of new vaccines as an obstacle to their introduction and the need for development of better demand forecasting based on established disease burden and use of new mechanisms such as advanced market commitments.

1.4 Administration of baseline questionnaire

A baseline questionnaire was administered to participants to assess their initial understanding of the disease burden due to Hib and pneumococcus, the vaccines available and decision-making process regarding new vaccine introduction in their countries. A total of 22 responses were received from 13 Member States. Results indicated that participants may not have been aware of the available data regarding Hib and pneumococcal diseases in their region and there was an opportunity to inform participants, not only about the data, but also possible interpretations.

All the respondents had heard of *H. influenzae* and ranked pneumonia (12), meningitis (9) and epiglottitis (1) as being the most important diseases caused by it. Only two respondents did not know the main age group affected, while 20 said the main age group affected is the under-fives (few differentiated the neonatal period). Most respondents said they were familiar with Hib vaccines, with only three reporting that they were not familiar at all. Twelve out of

22 respondents reported being 'very familiar' with Hib vaccines, and seven reported being 'somewhat familiar'. Regarding the cost of Hib vaccine, the majority (16) reported it being considerably high in cost compared with other EPI vaccines, but still a cost-effective option; three respondents reported it being much higher in cost and not cost-effective. Regarding the perception of the Hib situation in their country, only one respondent mentioned that it is not a serious concern, 10 opted for response category D (data indicates that Hib may be a serious concern but more data are needed to confirm this) and the other 10 opted for category E (data indicates that Hib is a cause of concern in the country).

All respondents reported having heard about *S. Pneumoniae*, with 17 listing pneumonia as the most common disease caused by it and the remaining five listing meningitis. Seventeen respondents reported 'under five years of age' as the main age group affected, followed by under two years of age (4) and under one year old (1). A smaller number of respondents reported familiarity with pneumococcal vaccines than with Hib vaccines (very familiar [9]; somewhat familiar [7] and not very familiar [6]). Perceptions about the pneumococcal disease burden in their countries resulted in similar responses to Hib: this is the first time you have heard about pneumococcal infections and there are no sufficient data about it to answer the question (3); pneumococcal infections are not a serious concern in the country (1); pneumococcal infections may be a serious concern in the country but more data are needed (7); and data indicate that pneumococcal infections are a cause of concern in the country (11). However, responses on the top causes of meningitis and pneumonia indicated that many of the respondents were not fully aware of the etiology of these two diseases while being aware of major causes of childhood morbidity and mortality.

2. PROCEEDINGS

2.1 Overview of Global Hib Initiative and PnemoADIP

Chairperson: Dr Patrick Zuber

Rapporteur: Dr Oya Afsar

2.1.1 The Hib Initiative: a new opportunity for prevention of meningitis and pneumonia (Dr Rana Hajjeh)

Pneumonia is the leading cause of death among children under five years of age in Asia, accounting for almost 560 000 deaths in the South-East Asia Region and 137 000 deaths in the Western Pacific Region annually, and Hib is already known to be a common cause of pneumonia. Hib has also been shown consistently to be the leading cause of bacterial meningitis in the two regions. However, the few studies conducted in Asia show wide disparities in Hib meningitis incidence rates, ranging from $\leq 10/100\ 000$ under-five population in Hong Kong, Thailand and Viet Nam to relatively higher rates in Sri Lanka (20) and Mongolia (36), to almost 60 in Indonesia, based on the results of a vaccine probe study.

Hib disease may be more prevalent than previously thought. The different incidence rates for Hib meningitis found in various studies may be due to true differences, but are most likely due to differences in the surveillance and laboratory methods used in the studies. Surveillance quality in detecting the Hib disease burden can be affected by many factors, such as health-seeking behaviour, access to health care, prior antibiotic use, lumbar puncture rate, transfer of specimens and laboratory materials and methods. As Hib is a difficult organism to identify, it is

usually accepted that culture (+) Hib meningitis cases represent only a small proportion of the actual disease burden and that Hib disease may be more prevalent than previously thought..

Hib vaccine introduction still remains very slow. Despite the excellent safety, efficacy and impact of Hib conjugate vaccines demonstrated in the last two decades in virtually eliminating the disease in industrialized countries for the last 15 years, 75% of the world's children still do not have access to Hib vaccine. Several studies looking at cost-effectiveness in developing countries have shown that the vaccine would be cost-saving in developing countries as well, although the benefit would depend on the burden of disease and the costs of health care.

Justification, mandate and scope of a global Hib initiative

Experience with hepatitis B vaccine has shown that, historically, 15 to 20 years pass before new vaccines reach the poorest children. Special focused efforts may be needed at both international and national levels to expedite the utilization of new vaccines. Considering that 75% of the world's children still do not have access to Hib vaccine, a four-year global project, the Hib Initiative, supported by a US\$ 37 million grant from GAVI, has been established with the mission to "expedite and sustain evidence-informed decisions at the global, regional and country levels regarding the use of Hib vaccination to prevent childhood meningitis and pneumonia". The Hib Initiative will invest in strategic coordination, communication, surveillance and research in selected countries and among partner agencies to achieve its mission. It acknowledges the different levels of evidence in different parts of the world and will customize its strategies according to varying needs.

Changing policy and programme environment for Hib vaccine at the international level

In 2005, the WHO Strategic Advisory Group of Experts (SAGE) recommended global implementation of Hib vaccination unless robust evidence exists on the lack of disease burden, lack of benefit or overwhelming impediments. On the financing front, GAVI will commit considerable financial support to the poorest 72 countries until 2015 to enable them to adopt the vaccine. Lastly, new manufacturers and vaccine products are expected to change the market by providing significantly higher capacity in the next year or so, which in turn will reduce prices as demand increases.

Discussion

A participant from India brought up the existence of many disease burden studies conducted in his country since the 1960s, and questioned the necessity of conducting additional studies that will take several more years. However, he pointed out that available studies are mainly rapid assessments or hospital-based studies, with very few providing an incidence rate. Thus his Government had asked for more data to show the feasibility of nationwide introduction. While the Hib Initiative plans to support selected studies, academicians in the countries could be instrumental in advising their governments about existing evidence.

2.1.2 Overview of GAVI's PneumoADIP (Dr Maria Knoll)

Why do we need a PneumoADIP?

Despite the fact that pneumococcal disease accounts for up to 10% of child mortality worldwide (800 000 to 1 million under-five deaths annually) and is the number one vaccine-preventable cause of death, few policy-makers are aware of the burden of the disease. A safe and effective pneumococcal conjugate vaccine (Prevenar) has been available since 2000 for routine infant immunization, but the vaccine uptake in developing countries has been almost negligible.

The 9-valent pneumococcal conjugate vaccine studied in two African countries has also been shown to be safe and effective. A three-dose regimen has been shown to reduce the incidence of X-ray pneumonia by 37%, and the overall under-five mortality rate by 16%. This was the first vaccine trial to show a significant reduction in all causes of under-five mortality in more than 20 years.

In 2003, the major issues limiting the wider use of pneumococcal vaccine included: uncertain country demand, driven in part by a lack of country-level disease burden data and vaccine impact information; a limited vaccine supply that kept prices relatively high; and the absence of long-term, predictable financing to procure vaccine in a sustainable manner. Considering the previous experience of slow uptake with HepB and Hib vaccines, a special time-bound project, PneumoADIP was set up in January 2003, with funding support of US\$ 30 million from GAVI, with its mission to “improve child health and survival by accelerating the evaluation of and access to new, life-saving pneumococcal vaccines for the world’s children”.

Mandate and scope of PneumoADIP

PneumoADIP has two strategic goals. The first strategic goal aims to provide information that enables national decision-makers, the GAVI board and its partners to make evidence-based decisions regarding the use of vaccine. The second strategic goal aims to accelerate the availability of affordable, new pneumococcal vaccines appropriate for use in developing countries. The strategies encompass defining the disease burden and vaccine impact at country level, generating political will to prioritize disease prevention, and achieving a reliable supply of affordable vaccine, with assured financing.

What PneumoADIP has achieved

- (1) Clarification of the disease burden: In collaboration with WHO, multi-country surveillance networks have been created, involving 13 countries. Twenty-seven countries are expected to join the network in 2006. In addition, PneumoADIP has helped to standardize the surveillance methods for pneumonia and meningitis to allow inter-country comparison. This surveillance is demonstrating a significant burden of disease in many Asian countries. It is also showing that the existing 7-valent vaccine is likely to have a greater impact on health in many Asian countries than was expected in 2003, before PneumoADIP began supporting surveillance.
- (2) Demonstration of vaccine impact in developing countries: Field sites in eight Asian countries have been identified for development as sites to study the vaccine’s impact after introduction. Small research and cost-effectiveness studies are also supported.
- (3) Improvement of vaccine supply: To break the vicious circle of low demand-low supply-high price, PneumoADIP has developed a strategic demand forecast for pneumococcal vaccine introduction in the 72-GAVI eligible countries and supply forecasts from 2006 to 2025, including projection of roles for multinational and emerging market suppliers.
- (4) Ensured appropriate financing mechanism to procure the vaccine: PneumoADIP provided a strong case to G7 finance ministers advocating that they invest ~US\$ 1.5 billion in an ‘advance market commitment’ to procure pneumococcal vaccines for developing countries. Efforts to find additional financing sources and mechanisms are under way.

Discussion

In the case of pneumococcal vaccines, country-specific serotypes may need to be identified initially to see the match with existing vaccines. However, the overall disease burden may be so high in developing countries that even the existing 7-valent may provide considerable reduction in morbidity and mortality.

It has been calculated that new vaccines may be profitable for the manufacturers at a price range of US\$ 2.00-5.00/dose. Thus, if demand meets the forecasted targets, the prices are expected to fall in the future.

Countries face a dilemma about which vaccines to choose when they have multiple new vaccines available and limited resources to spend. The international community needs to assist in identifying priorities. GAVI is trying to develop suitable co-financing mechanisms for countries planning to introduce multiple vaccines.

2.2 Overview of regional epidemiology of Hib and pneumococcal diseases

Chairperson: Dr Kim Mulholland
Rapporteur: Dr Maria Knoll

2.2.1 Disease burden and impact studies: challenges in study design and data interpretation (Dr James Watt)

Appreciation of the pneumonia and meningitis disease burden but not of its etiology

Although most people know pneumonia and meningitis as major killers of children, few appreciate the etiology behind them. Hib and pneumococcus are the most common organisms causing these two clinical diseases, but are difficult to diagnose compared with measles, hepatitis B or HIV. First, unlike measles, there is no single sign or symptom that is exclusively the result of pneumococcal or Hib disease, like the rash or Koplik's spots in measles. Second, unlike hepatitis B and HIV, the best diagnostic test for Hib and pneumococcal disease, a blood or cerebral spinal fluid (CSF) culture, is not very sensitive (i.e. it misses many true cases), requires the specimen to be collected during the acute phase of illness, and is easily turned false-negative by the use of antibiotics. The result is that most pneumonia and meningitis patients do not have a known etiology when they are treated.

Difficulties in measuring the Hib/pneumococcal disease burden

Conventional surveillance disease studies are hard to carry out. The current case ascertainment is primarily hospital-based, with biases resulting from underreporting to hospital, and non-inclusion of all hospitals. Besides biases in case ascertainment, lumbar puncture is not done in all cases presenting with meningitis, limiting the availability of key sample to diagnose Hib/pneumococcus. Sample handling for Hib and pneumococcus diagnosis requires special specimen handling and laboratory capacity (e.g. Co2 incubator, candle jar, proper culture media with X and V factor, etc.) that may be inadequate in many developing countries. Widespread prior antibiotic use in many developing countries further limits the sensitivity of culture and may affect antigen detection tests. Defining the etiology of pneumonia is even more complex than meningitis, and just focusing on meningitis in economic analysis or policy decision-making may give a false impression.

The biases in estimation of disease burden are clearly demonstrated in many studies. Several biases could have led to the underestimation of the incidence of laboratory-confirmed

Hib meningitis at 3.8/100 000 under-five population in a Thai study. Some of these key biases included: 8% of children not being enrolled; 24% of enrolled children not having lumbar puncture; 56% of suspected bacterial meningitis cultures testing negative due to prior antibiotic use; and a lack of data on children not attending study hospitals. Adjustment of these biases, except the last one, led to substantial upwards revision of the estimates to 9.5/100 000, compared with 3.8 when measured only on the basis of laboratory confirmation.

Study designs, other than conventional surveillance, to estimate the disease burden

Vaccine impact studies (case control studies and vaccine trials) can be used to estimate the vaccine-preventable burden in a field situation by measuring the difference in disease between the vaccinated and unvaccinated. This method can measure the non-laboratory-confirmed disease (both pneumonia and purulent meningitis). A case-control study has been successfully done in Bangladesh to estimate the proportion of X-ray-confirmed pneumonia and purulent meningitis cases prevented by Hib vaccination. Although case-control studies measure the proportion of disease prevented by vaccine, they can be linked to incidence studies. Vaccine trials or vaccine probe studies, on the other hand, although the most robust approach, are very expensive, long and difficult to conduct. The Hib vaccine probe study conducted in Lombok, Indonesia, suggested a much higher burden than that suggested by only laboratory-confirmed cases.

Understanding the data: a hypothesis

In some places, such as North America and Africa, where the Hib disease burden has been shown to be high even with conventional surveillance methods, Hib may be easier to find. However, in Asia, Hib may be harder to find due to higher levels of prior antibiotic use, better access to care, diverse settings, limited diagnostic testing and laboratory issues. Earlier surveillance studies that failed to address these issues may have substantially underestimated the disease burden, although the recent surveillance studies that addressed some of the problems demonstrated a much higher burden (e.g. in Bangladesh).

Discussion

- (1) Defying the generalizations: In the Western Pacific Region, low disease burden areas appear to span economic stratification and laboratory capacities. While developed countries, such as Japan, Hong Kong (China), the Republic of Korea and Singapore, with some of the best laboratory systems, show a low disease burden with conventional surveillance methods, a low disease burden has also been observed in China and Viet Nam. Papua New Guinea and the Philippines, with no better laboratory systems and no less prior antibiotic use, on the other hand, have shown much higher levels of disease burden.
- (2) What levels of disease burden are considered high and what levels are considered low?
- (3) What exactly is meant by unclear disease burden? Is unclear disease burden~low disease burden?

2.2.2 Overview of existing evidence on disease burden due to Hib and pneumococcus in the Western Pacific Region (Dr Manju Rani)

The Western Pacific Region has 37 countries and areas with a total population of 1.7 billion, accounting for 28% of total global population. Of the total estimated 1.1 million under-five deaths each year, 13% (~137 000) are estimated to be due to acute respiratory tract infections.

Current vaccine introduction status

Hib vaccine has been introduced in 18 countries and areas in the Region, accounting for less than 4% of total regional population. None of the five countries accounting for 95% of the total population (China, Japan, the Philippines, the Republic of Korea and Viet Nam), have introduced the vaccine. Pneumococcal vaccines have been introduced in national schedules in Australia and three Pacific island countries (Guam, Northern Mariana Islands and New Caledonia). The vaccine is also licensed in several other countries and is available in the private market in those countries.

Evidence of Hib disease burden in the Western Pacific Region

There are no data on disease burden from seven countries and areas. Among the five big countries accounting for 95% of the regional population, the disease burden is shown to be high only in the Philippines, with Hib meningitis incidence measured as 28 and 95/100 000 under-five children in two different studies. The annual incidence of Hib meningitis has been shown to be less than 10 in China (1.2 to 10.4) and Japan (3.4 to 9.9), while a recent study in Viet Nam estimated the disease burden to be about 12/100 000 under-five population. The average case fatality rate and sequelae rate have been estimated to be about 25% and 30%, respectively, but seem to vary widely between developed and developing countries.

Evidence of pneumococcal disease burden in the Western Pacific Region

There are no direct estimates of pneumococcal disease burden in the Region, but it is perceived to be the second most important cause of childhood bacterial meningitis, and the most important cause of bacterial pneumonia among children, accounting for almost one-third of all childhood bacterial pneumonia cases. Although, in the case of Hib, a single serotype (type B) is estimated to cause the majority of the disease burden, there are additional issues with regard to pneumococcal vaccine introduction due to the multiple serotypes that may be differentially distributed across countries. In addition, multiple serotypes raise the issue of replacement morbidity, as current vaccines do not include all prevalent serotypes.

Hurdles/issues in Hib vaccine introduction in the Western Pacific Region

- (1) Demonstration of justifiable disease burden only: In five of the high-income countries and areas (Hong Kong [China], Japan, Macao [China], the Republic of Korea and Singapore) that can easily afford the vaccine, Hib meningitis incidence has uniformly been shown to be lower than 10/100 000 under-five population.
- (2) Issues of disease burden and affordability: In four countries (Cambodia, China, the Lao People's Democratic Republic and Viet Nam) there are two issues: demonstration of clear disease burden and affordability. The total per capita public sector health financing in these four countries ranges from ~US\$ 4 in Cambodia and the Lao People's Democratic Republic, to US\$ 6.3 in Viet Nam and US\$ 21 in China. The current Hib vaccine cost per child is ~US\$ 12, excluding programmatic costs. Even without Hib vaccine, EPI programmes account for 4%-6% of total government spending on health, with the EPI programmes being highly donor-dependent in Cambodia and the Lao People's Democratic Republic.
- (3) Issues of affordability only: In Mongolia, Papua New Guinea and the Philippines, the disease burden and the cost-effectiveness of the vaccine have been demonstrated to be relatively high, even with the current studies, but, with overall low public sector spending on health, these countries find it hard to afford the vaccine at the current prices. However,

Mongolia and Papua New Guinea, being GAVI-eligible, will at least be able to overcome this hurdle in the short term.

- (4) Substantial expansion of Hib vaccine coverage will take more than GAVI efforts: The seven GAVI-eligible countries account for only 10% of total regional births and hence substantial efforts will be needed beyond GAVI-eligible countries, with participation of other local, bilateral donors to expand Hib vaccine coverage in the Western Pacific Region.

Discussion

Discussion centred on how to overcome the challenge of affordability in countries with total public health spending in the range of US\$ 3.00-20.00 per capita, and with high levels of external dependence.

2.2.3 Sharing the experience: examples of meningitis and pneumonia studies from South Asian countries (Dr Craig Burgess)

Approximately three million children under five years of age die annually in the WHO South-East Asia Region. Nineteen per cent of these deaths (or approximately 590 000) are from acute respiratory tract infections, although little is known about the exact etiology of these infections, with most interventions focused on syndromic case management under integrated management of childhood illnesses (IMCI) strategies. Although the precise etiology in most cases is unknown, careful trials of the case-management approach have provided important insights into the etiology of fatal pneumonia. In these trials, the use of antibiotics significantly reduced pneumonia-specific mortality, and even overall infant mortality. This observation supports the assumption that the vast majority of pneumonia deaths in the Region are due to bacterial pneumonia. Other studies show that Hib and *S. pneumoniae* are the most commonly identified bacterial causes of pneumonia.

Hib disease burden in the South-East Asia Region

In general, there is low awareness about the Hib disease burden in the South-East Asia Region, with limited surveillance and laboratory capacity. Initial data suggest relatively lower incidence of Hib meningitis (less than 10/100 000 under-five population) compared with other regions. Hypotheses put forward to explain this lower estimation include: inadequate study methods, including lower lumbar puncture rates; prior antibiotic use; and poor laboratory capacity. Besides the methodology issues, other hypotheses put forward include lower genetic predilection; lifestyle issues, including diet and childcare practices; and potential natural immunity from natural exposure to cross-reactive antigens.

Recent data on Hib disease burden from the South-East Asia Region

A lot of data have been generated in the last three to four years from rapid assessments of Hib disease in Bhutan, the Maldives, Nepal and Thailand, using tools developed by WHO: a case-control vaccine trial study in Bangladesh; a vaccine trial in Lombok, Indonesia; and a few small-scale studies and reports in Bangladesh, India, Sri Lanka and Thailand. Data from rapid assessment of the Hib disease burden estimate the Hib meningitis incidence rate to be 5.8, 13, 19, and 29 per 100 000 under-five population in Thailand, Bhutan, Nepal and the Maldives, respectively, much lower than that estimated in four Pacific island countries in the Western Pacific Region using similar tools (more than 70/100 000 under-five population). In Bangladesh, a case-controlled Hib vaccine probe study¹ estimated a 15% to 45% risk reduction for pneumonia and a 50% risk reduction for bacterial meningitis. In Lombok, Indonesia², a prospective cohort Hib vaccine probe study estimated prevention of 47 to 156 cases of clinical meningitis among

children of 11 weeks to two years of age (with an estimated Hib meningitis incidence rate of 61/100 000 under-five population), although the vaccine impact on pneumonia was less clear. However, the incidence of laboratory-confirmed Hib meningitis continues to be low. For example, in India and Thailand, some population-based prospective studies estimated laboratory-confirmed Hib meningitis rates to be lower than 10/100 000 and at 3.6 per 100 000 under-five children, respectively.

Efforts planned to generate more disease burden data

Invasive Bacterial Infections Surveillance (IBIS), a vaccine probe study, is now planned in India to map out the Hib disease burden beyond that identified by laboratory-based conventional surveillance. The results are expected by 2009.

Disease burden due to *S. Pneumoniae*

There is little laboratory capacity for microbiological confirmation in most countries. Very limited studies from India suggest that 32% of all pneumonia cases are caused by *S. Pneumoniae*, with 20.8% caused by Hib (based on latex agglutination). In Thailand, similar estimates include 9.9% and 8.9%, respectively.

Prospects for introduction of Hib/Pneumo vaccines in the South-East Asia Region

The key issues in new vaccine introduction in the South-East Asia Region include: the availability of reliable information on the disease burden; systems' capacities to deliver the vaccine; and availability of sustained financing. Data on the disease burden due to Hib and pneumococcus still remains inconclusive in many countries. In addition, the systems to deliver the vaccine remain weak in many South-East Asian countries, with coverage of the third dose of diphtheria-pertussis-tetanus (DPT3) still less than adequate. Considering the high cost of vaccines, the low overall per capita spending on health and the funding gaps in other cost-effective health interventions, the financing of Hib and pneumococcus vaccines will be a significant challenge to overcome, at least in the short term, despite their demonstrated cost-effectiveness.

2.3 Sharing country experiences

2.3.1 Experiences from the South-East Asia Region

The Lombok Vaccine Probe Studies—Issues (Dr Kim Mulholland)

Study: The burden of Hib disease, either meningitis or pneumonia, had not been well quantified in Indonesia. Hence, a Hib vaccine probe study was designed to provide an estimate of the burden. The study was carried out in Lombok, a rural and agrarian island in Indonesia with a high infant mortality rate of 90 per 1000 live births. The island has three major and two minor hospitals. The main study partners included the Ministry of Health of Indonesia, the Program for Appropriate Technology in Health (PATH) and the Association pour l'Aide à la Médecine Préventive (AMP). The total study cost of US\$ 8 million was jointly financed by the Bill and Melinda Gates Foundation, Foundation Merieux, Aventis Pasteur and the United States Agency for International Development (USAID).

Methodology: A total of 818 hamlets on the island were randomized to receive Hib vaccine (DPT-Hib) or no Hib vaccine (DTP), and 55 073 children, with an average age of 13 weeks at enrolment, were vaccinated between December 1998 and September 2002.

Pneumonia and meningitis episodes were measured in both groups, with the following assumptions:

- 100% Hib vaccine efficacy;
- Hib vaccine only prevents Hib infections;
- all Hib pneumonia and meningitis cases reach the health care system;
- the difference between immunized and non-immunized groups represents the proportion (and number) of pneumonia or meningitis episodes due to Hib.

Measurement of primary outcomes: Pneumonia was measured using five different indicators/outcomes: clinical pneumonia (cough and fast breathing, or lower chest wall indrawing); severe pneumonia (lower chest wall indrawing); very severe pneumonia (evidence of hypoxia); radiological pneumonia; and fatal pneumonia (documented pneumonia and died). Meningitis cases were also measured using five different indicators: confirmed meningitis (signs of meningitis, abnormal CSF and organism grown from CSF); signs of meningitis (abnormal CSF but no organisms grown on culture); signs of meningitis (CSF not taken); possible missed meningitis (presented with fever fits, no further information); fatal meningitis (documented meningitis and died, usually in hospital, or meningitis diagnosed by verbal autopsy [died at home]). All possible cases of meningitis and pneumonia were identified at the primary care level and referred to hospital for investigation and admission.

Results: Hib vaccination had no effect on radiological pneumonia, the primary outcome of the study. However, the investigators hypothesized that this might be attributed to intense surveillance in the study, which may have prevented Hib pneumonia cases from developing X-ray changes. Although the effect on clinical pneumonia was small, with only 3.8% of cases prevented, in absolute terms, a large number of cases were prevented due to an overall very high incidence of clinical pneumonia (1467 cases/100 000).

However, the impact on meningitis incidence was much bigger. The study showed that Hib incidence on the basis of laboratory confirmation only was grossly underestimated. The large number of cases of fever/convulsion prevented suggested that the burden of meningitis in Lombok is very large and many children with meningitis do not receive appropriate care in rural areas. Hence the life-saving impact of Hib vaccines is accentuated in rural areas where health care is poor. The key findings of the study are presented in Tables 1 and 2.

Table 1. Pneumonia results in Lombok study: first episodes in fully vaccinated children only

| | Vaccinated incidence | Control incidence | % cases prevented | Imputed incidence |
|------------------------|----------------------|-------------------|-------------------|-------------------|
| Clinical pneumonia | 36 759 | 38 226 | 3.8% | 1467 |
| Severe pneumonia | 4705 | 4712 | 0.2% | 7 |
| Radiological pneumonia | 859 | 770 | -12% | Negative |
| Fatal pneumonia | 564 | 583 | 4.2% | 19 |

| | Vaccinated incidence | Control incidence | % cases prevented | Imputed incidence |
|----------------------------------|----------------------|-------------------|-------------------|-------------------|
| Proven Hib meningitis (6) | 4 | 23 | 84% | 20 |
| Meningitis cells >10 (52) | 64 | 137 | 54%* | 74* |
| Meningitis admission (243) | 451 | 488 | 7% | 36 |
| Meningitis or seizures at clinic | 527 | 656 | 20% | 129 |

The Sri Lankan Experience (Dr Nihal Abeyasinghe)

Hib burden study: A prospective population-based Hib disease burden study was conducted for one year beginning on 1 January 2004. Only children permanently resident in the Colombo district were included in the study. All five main hospitals in the Colombo district were enrolled. In addition, data were collected from hospitals surrounding the Colombo district, and any Colombo-resident child admitted to those hospitals was included. A total of 64 cases of laboratory-confirmed Hib disease were identified during the study period, of which 36 cases were among Colombo permanent residents, giving an annual incidence of Hib meningitis of 20/100 000 under-five population. In addition, a total of 14 meningitis cases were identified as being due to *S. Pneumoniae*, amounting to an annual incidence of 7.8/100 000 under-five population. Overall meningitis incidence was estimated to be about 90.5/100 000 under-five population.

Hospital-based surveillance data: Data from pneumonia surveillance from the nationwide monthly reporting system of morbidity and mortality between 1998 and 2003 was also presented. The total number of pneumonia admissions ranged from 20 207 to 25 162. The number of pneumonia deaths reported among patients admitted for pneumonia ranged from 1073 to 1475, giving a case fatality rate of 5% to 6.3%. In Lady Ridgeway Hospital for children, admission for pneumonia varied from 1% to 1.5% of all inpatient admissions between 1998 and 2001.

Data from SAPNA: Data were also presented from the SAPNA/Sri Lanka pneumococcal surveillance network. A total of 13 pneumococcal isolates were identified in one year, three in meningitis, nine in pneumonia cases and one case in septic arthritis. Eleven of the 13 were isolated from children two months to five years old, one case from a child less than two months old and one case from a child more than five years old. Approximately 80% of the isolates were due to serotypes included in the 7-valent vaccine.

Future plans: The future plans for pneumococcal surveillance in Sri Lanka include expanding the number of surveillance sites within the Colombo district, including sites from outside Colombo and increasing serotyping efforts to gain a more complete picture of serotype distribution in Sri Lanka.

Bangladesh: pneumonia and meningitis in Bangladesh – What do we know?
(Shams El Arifeen, Samir K Saha and Abdullah H Baqui)

Trends in under-five mortality and the role of acute respiratory infection (ARI): The under-five mortality rate in Bangladesh declined from 133/1000 live births in 1989-1993 to 88 in 2000-2004, still falling short of achieving the MDG goal for under-five mortality. While the rate has gone down substantially in urban areas from 153 to 98 (between 1984-1993 and

1994-2003), the decline in urban under-five mortality has been very insignificant (from 114 to 92 in the same period). Between 1994 and 2003, ARI have been estimated to have contributed to 21% of total under-five deaths, and other serious infections, 31%. Between 1993 and 2004, while ARI prevalence seems to have been increasing, the percentage of children with ARI taken to health facilities for medical care seems to have been declining. However, utilization of immunization services seems to be increasing, with 81% of 12- to 23-month-old children in urban areas and 71% in rural areas receiving all vaccines in 2004.

Hib case-control study: An effectiveness trial of Hib vaccine in the form of an ‘incident case-control study’ was undertaken in Bangladesh by ICDDR-B, Shishu Hospital Dhaka, Johns Hopkins University, funded by the Asian Development Bank (ADB) and USAID. The main objective of the trial was to estimate the proportion of pneumonia and meningitis cases in children under two years of age that are prevented by Hib vaccination. The study was undertaken in three out of 10 zones of Dhaka—the capital city of Bangladesh. The study areas had an estimated population of 1.8 million and a birth cohort of 75 000. The follow-up period was approximately 18 months.

The clinical outcomes measured in the trial included: X-ray-confirmed pneumonia, culture-confirmed Hib pneumonia, confirmed Hib meningitis, probable Hib meningitis and probable bacterial meningitis. Tetravalent vaccine (DPT-Hib) by Aventis Pasteur was used for vaccination through the existing EPI system from June 2000 to January 2002. A total of 31 clinics were assigned to vaccinate with Hib vaccine in their catchment areas, with an expectation of achieving 50% vaccine coverage. Cases with clinical outcomes were identified from six hospitals fulfilling the residency and age criteria through surveillance for pneumonia and meningitis in the study area. Four community controls with no acute respiratory tract infection or meningitis were recruited for each case and matched for age, sex and distance from health facility.

Results: The estimated percentage reduction (95% CI) for X-ray-confirmed pneumonia and meningitis (confirmed Hib and probable bacterial meningitis) by number of DPT-Hib or DPT doses received is given in Table 3.

| Table 3: Estimated percentage reduction (95% CI) for X-ray-confirmed pneumonia by number of DPT-Hib or DPT doses received | | |
|--|---------------------------------------|--|
| Number of Hib-DPT or DPT doses received | Confirmed by study readers N=475** | Confirmed by both study and WHO readers N=343** |
| At least one dose | 5 (-24 to 26) | 24 (-6 to 43) |
| At least two doses | 17 (-10 to 38) | 34 (6 to 53) |
| Three doses | 20 (-10 to 43) | 32 (-2 to 54) |

Note:

* *Adjusted for child's age, number of vaccine doses received and household income*

** *Number of x-ray confirmed pneumonia cases*

| Table 4. Estimated percentage reduction (95 CI%) for confirmed Hib meningitis and probable bacterial meningitis by number of DPT-Hib or DPT doses received | | |
|---|------------------------------------|---|
| Number of Hib-DPT or DPT doses received | Confirmed Hib meningitis N=15** | Probable bacterial meningitis N=41** |
| At least one dose | 90 (34 to 100) | 54 (-21 to 83) |
| At least two doses | 89 (28 to 100) | 71 (-1 to 92) |
| Three doses | 65 (-190 to 100) | 40 (-138 to 85) |

Note:

* For confirmed Hib meningitis, adjusted for number of vaccine doses received; for probable bacterial meningitis, adjusted for child's age, number of vaccine doses received and household income

** Number of cases

The study estimated the incidence of confirmed Hib meningitis to be 40/100 000 and that of probable bacterial meningitis to be 154/100 000. Similarly, it estimated the incidence of X-ray-confirmed pneumonia prevented by Hib vaccine to be 556/100 000.

The study findings have huge public health implications for Bangladesh, with an annual birth cohort of 3.6 million. The study findings suggest about 90 000 deaths due to pneumonia among children under two years of age, of which 17 800 are likely to be due to Hib. Assuming that there is one Hib meningitis death for every four Hib pneumonia deaths, there will be about 22 000 deaths due to Hib meningitis.

Meningitis surveillance data from Dhaka Shishu Hospital: A total of 2410 meningitis cases were admitted to Dhaka Shishu Hospital from 1994 to 2006, and Hib was determined to be the predominant cause, accounting for 48% of cases, followed by *S. pneumoniae* (37%). The main diagnostic methods used were ICT (from 2003 only, which increased the detection rate of *S. pneumoniae*) and latex agglutination on blood/cerebral spinal fluid (CSF) samples.

Case fatality and residual *sequelae* rates in the Hib-confirmed meningitis cases were high, at 22% and 24%, respectively, emphasizing the importance of immunization. Although no differences were found between multiple drug resistance of Hib among children who died, 31% of the children who survived and developed disabilities were infected with Hib resistance to drugs, compared with only 12% of the children who survived and did not develop disabilities.

Conclusions: Twenty per cent of all pneumonia cases, the single most important cause of under-five mortality in Bangladesh, are caused by Hib and can be prevented by Hib vaccine. Meningitis is also a common and serious infection; 50% of cases are estimated to be caused by Hib. Vaccination is becoming all the more important due to the increasing resistance of Hib to common antibiotics and the consequent higher disability rate and higher cost of treatment. The presenters concluded that the immunization programme—which is already a success story in Bangladesh—should be expanded further with inclusion of Hib vaccine without further delay.

2.3.2 Experiences from the Western Pacific Region

Experience from Mongolia

Epidemiology of bacterial meningitis in Ulaanbaatar, Mongolia (Dr Chunt Munkhtsetseg, National Center for Communicable Diseases, Ministry of Health)

Mongolia is a landlocked country with a total population of 2.5 million, with more than one-third (928 531) residing in the capital City, Ulaanbaatar. The country has maintained a very successful immunization programme, with reported DPT3 coverage of more than 90%, since 1998. A pentavalent Hib-containing vaccine (DPT-HepB-Hib) was introduced in a phased manner in January 2005, covering 25% of the population in 2005.

Hib disease burden data: Hib was rarely isolated prior to 2002. Although lumbar punctures were carried out for most children with meningitis, limited culture testing was done on the collected CSF samples.

Hib meningitis surveillance project: Population-based hospital surveillance was started in six paediatric hospitals in Ulaanbaatar in February 2002, with hospital-based case ascertainment. The subject criteria included: aged two months to less than five years; resident of Ulaanbaatar city; and admitted to the study hospital with suspected meningitis with at least one of the following clinical symptoms—fever, headache, stiff neck, bulging fontanel, mental status change. The outcome indicator included probable bacterial meningitis (WBC>100/ml, neutrophyl>80% or protein>100 mg/dl and glucose<40 mg/dl, or cloudy CSF); and confirmed cases (bacterial isolated in CSF, CSF antigen detection test or polymerase chain reaction [PCR] positive, or positive blood culture in a child with clinical meningitis). The surveillance is continuing, with the introduction of pentavalent vaccine in 2005, to monitor vaccine impact.

Results: Based on the surveillance data from 2003-2004, Hib meningitis incidence was estimated to be 36/100 000 under-five population. The incidence was estimated to have fallen to nine per 1 000 000 under-five population in 2005 with the introduction of Hib-containing vaccine in Ulaanbaatar city in January 2005. The importance of vaccination is stressed considering the high levels of antibiotic resistance of the Hib isolates. The proportion of *S. Pneumoniae* isolates ranged from 6% in 2003 to 10% in 2004 and 13% in 2005.

Results from a three-country study—China, Republic of Korea and Viet Nam

Invasive bacterial disease studies in China, Republic of Korea and Viet Nam (Paul Kilgore, Division of Translational Research, International Vaccine Institute [IVI], Seoul, Korea)

IVI undertook the three-country study in China (January 2001 to December 2002); Republic of Korea (September 1999 to December 2001) and Viet Nam (March 2000 to March 2002) to describe the patterns of bacterial meningitis and estimate the incidence of laboratory-confirmed meningitis due to Hib and *S. Pneumoniae*.

WHO's generic Hib meningitis protocol was used, with patient referral from outlying health centres, clinics and hospitals and use of pre-tested case report forms with standardized database management systems.

China (January 2001 to December 2002): The study was carried out in the Nanning area in Guangxi province, with a total under-five population of 168 060. Three cases of Hib meningitis were identified (either by PCR or latex agglutination or culture), all under two years of age, giving an incidence rate of 1.8/100 000 under-five population. The incidence of invasive

pneumococcal meningitis in the same population was estimated to be 2.1 (a total of six cases were identified, all under two years of age). However, almost 32% of the children aged less than five years had evidence of prior antibiotic use in the CSF.

Republic of Korea: The study site was Jeonbuk province, with a total under-five population of 116 894. Surveillance was conducted from September 1999 to December 2001. The overall incidence of probable bacterial meningitis among under-five children was estimated to be 91/100 000. The incidence of laboratory-confirmed Hib meningitis was only six per 100 000. However, the data should be interpreted in the context of use of Hib vaccine in the private sector. The number of Hib vaccine doses distributed increased from 2923 in 1996 to 28 160 in 2001. The incidence of invasive pneumococcal meningitis during the same period and in the same population was estimated to be 2.1 (95% CI: 0.7-6.9). However, 19% of CSF samples collected showed evidence of prior antibiotic use.

Viet Nam: The study was done in urban Ha Noi, with a total under-five population of 94 529 followed up from March 2000 to March 2002. While the overall incidence of probable bacterial meningitis was 88/100 000 under-five population, the incidence of confirmed and probable Hib meningitis was estimated to be 11.6 per 100 000 under-five population, with more than 90% of the cases occurring among children under two years of age. Eighty-eight per cent of invasive pneumococcal meningitis cases also occurred in children under two years of age, with an overall under-five incidence of 1.1/1 000 000. Thirty-nine per cent of CSF samples showed evidence of prior antibiotic use.

Combined results from three countries: Of the total 48 invasive pneumococcal isolates, 19 isolates were resistant to penicillin. Residual neurological *sequelae* were observed in 47% of cases, ranging from 60% in China, to 50% in the Republic of Korea and 43% in Viet Nam. On the other hand, the average case fatality rate in the invasive pneumococcal meningitis cases was 19%.

Discussion

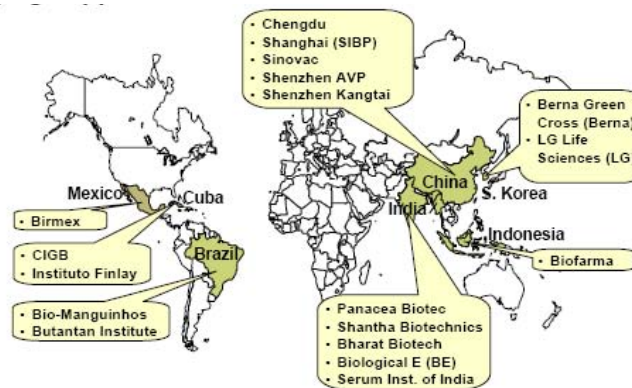
- (1) Use of different methods to demonstrate the disease burden in the country experiences presented: While simple laboratory-based surveillance was able to demonstrate a relatively higher disease burden in Sri Lanka, in Dhaka Shishu Hospital in Bangladesh, and in Mongolia, it failed to demonstrate the high disease burden in China, the Republic of Korea, or Viet Nam.
- (2) Discrepancy between laboratory-confirmed and estimated disease prevented in Bangladesh and Lombok: While the results of the vaccine trial (case-control incident study) corroborate the high meningitis incidence also noted in hospital surveillance data (mainly using laboratory confirmation) in Dhaka Shishu Hospital in Bangladesh, the Lombok study demonstrated a much higher disease burden that was estimated to be vaccine-prevented compared with what was laboratory-confirmed.
- (3) How generalizable are the study results: Although the vaccine probe study methodology is considered to be the most robust method, the localized geographical location means it may not convince policy-makers.

2.4 Session 4: Hib vaccine supply issues, economic evaluations and need for advocacy

2.4.1 Hib vaccine supply issues (Dr Patrick Zuber, Medical Officer, WHO Headquarters)

Multiple emerging suppliers, especially in developing countries (Figure 1), in addition to multinational suppliers (Berna Biotech, Chiron, GSK, Merck, Wyeth and Sanofi Pasteur, etc.) are positioning themselves to be global suppliers of GAVI priority vaccines.

Figure 1. Emerging vaccine suppliers for Hib and other new vaccines in developing countries



Although the GAVI vaccine market has experienced the most rapid growth (84%) in public agency vaccine procurement sales in recent years, global vaccine revenues are driven by sales to high income markets (82%). Sales to public agencies account for only a small fraction of total market revenues (8%). Despite this, public agency markets (e.g. UNICEF) have, in general, been able to offer and negotiate more attractive rates, while assuring the quality of vaccines through a prequalification process. However, constraints have been felt in assuring the quality of vaccines due to weak national regulatory authorities, undersupported post-marketing surveillance systems, and funding gaps for pre-qualification activities, including difficulties in securing qualified technical experts.

The GAVI vaccine demand forecast since 2002, undertaken in collaboration with the WHO/UNICEF/GAVI secretariat, has ensured a regular supply of vaccines to GAVI-eligible countries, managed exceptional cases and provided long-term demand information for the supply strategy. The baseline demand for pentavalent vaccine in 2006 has been estimated to be 40 million doses, increasing to more than 140 million doses by 2009.

A need has been felt for a GAVI supply strategy that can deal with the increasingly complex supply and financial environment, and with maturing GAVI alliances, and build on lessons learnt. A successful GAVI supply strategy should ensure a reliable supply of high quality vaccines in the presentations and volumes needed to meet demand in GAVI-eligible countries at affordable prices. The current GAVI alliance supply strategy is product-based, with a product-specific procurement strategy and implementation plan.

The timeline for the GAVI supply strategy includes two distinct phases: Phase I, characterized by informal signals to suppliers, involves vaccine assessment (i.e. assess the vaccine needs in countries) and strategic demand analysis. Phase I is followed by Phase II, involving more formal signals to manufacturers and suppliers. Phase II involves the development of an integrated supply, demand and financing strategy, pre-launch activities

(commitment of countries, donors and suppliers) and tender issuance, followed by vaccine introduction.

In GAVI Phase II, countries' demands for Hib vaccine are likely to be affected by the proposed Phase II vaccine co-financing policies; clarification of the Hib disease burden in countries and demand from middle-income countries.

In conclusion, the GAVI supply strategy for Hib-containing vaccines is working on a new tender processes, with the expectation of multiple manufacturers by 2007. In addition, the Hib Initiative will further inform long-term demand forecasting by clarifying the disease burden and providing more accurate supply information to countries to facilitate the decision-making process at the country level.

2.4.2 Cost-effectiveness studies for Hib and pneumococcal disease: needs and key issues (Dr Damian Walker)

Economic evaluation is the comparative analysis of alternative courses of action in terms of both their costs and their consequences. The different types of economic evaluation include: cost-minimization analysis (which of the two Hib vaccines, given equivalent effectiveness, is the cheapest); cost-effectiveness analysis (Hib/pneumo vaccines in terms of US\$ per pneumonia/meningitis cases averted); cost-utility analysis (Hib/pneumo vaccines versus other health care in terms of US\$ per DALY averted); and cost-benefit analysis (health care versus education in terms of US\$ benefits).

Hib cost-effectiveness data from five Asian countries at 2002 prices were presented. The US\$ per DALY averted ranged from US\$ 250 in Bangladesh to US\$ 201 in Pakistan. In the Philippines and Papua New Guinea the US\$ per death averted ranged from US\$ 3749 and US\$ 1216, respectively. Rapid Assessment of Cost Effectiveness (RACE) data from Nepal, with Hib meningitis incidence estimated to be above 56/100 000 under-five population, estimated the cost per case averted to be US\$ 530 and the cost per death averted to be US\$ 3050. Similar data from four Pacific island countries estimated the same indicators to be US\$ 300-US\$ 1100 and US\$ 1300 to US\$ 10 135, respectively. However, these data did not include treatment costs and assumed 100% vaccine coverage, with exclusion of vaccine wastage and syringe costs.

Dr Walker presented the data from the Sinha study on cost-effectiveness estimates for pneumococcal vaccination in South Asia. The key model inputs included a vaccine cost of US\$ 5.00 per dose, with a three-dose schedule, and additional vaccination programme costs per dose of US\$ 0.40 to US\$ 0.73. The mortality among children aged three to 29 months was assumed to be four to 42 per 1000, with vaccine efficacy in terms of deaths averted per 1000 children to be 0.1 to 7.4. The model was limited to prevention of mortality and fatal episodes of pneumococcal disease. In this respect the health impact assumptions were conservative. Treatment costs saved were estimated to offset 5% of vaccination costs. These inputs resulted in a computed cost per death averted of US\$ 3516 and a cost per DALY averted of US\$ 107.

Notwithstanding the above, cost-effectiveness data may give different results depending upon the assumptions (e.g. model structure, etc) of the incidence of disease, vaccine cost and effectiveness; assumptions of treatment costs and their inclusion in the model; and assumptions about other programme costs (e.g. surveillance, training, stationary, and social mobilization, cold chain, transportation, etc.). Current cost estimates are being criticized for their lack of transparency, completeness and comparability in terms of inputs, reducing their credibility and application to other settings.

The interpretation of cost-effectiveness data is equally difficult. Following the recommendation of the Commission of Macroeconomics and Health, WHO defines an intervention as highly cost-effective if the cost per DALY averted is less than the gross domestic product (GDP) per capita; cost-effective if the cost per DALY averted is one to three times the GDP; and not cost-effective if the cost per DALY averted is more than three times GDP per capita. Limited evidence-base data suggest Hib and pneumococcal vaccination to be highly cost-effective, with the use of scarce resources in Asia. However, certain issues remain, including the paucity and variable quality of cost-effectiveness data; the lack of reliable data on disease incidence; and the cost of Hib/pneumococcal vaccine introduction. Current data suggest that treatment costs saved are likely to offset a small percentage of vaccination costs, but most studies have not included the cost of long-term *sequelae* and have not assessed how the relationship would change over time, with a possible decline in vaccine prices.

To conclude, cost-effectiveness data should be one of the elements shaping vaccine policy, although it does not tell us anything about affordability in a particular context. Hib/pneumococcal vaccines may be highly cost-effective, as suggested by existing data, but may not be affordable in many countries.

2.4.3 Introducing new vaccines: role of advocacy (Dr Lois Prim-divor)

The presenter opened with a short video documentary illustrating the human toll of Hib disease. The documentary, filmed in Gambia and Bangladesh, had been aired on BBC World.

Advocacy includes any effort to influence policy- and decision-makers, fight for social change, transform public perceptions and attitudes, modify behavior, or mobilize human and financial resources. In the case of introduction of new vaccines, specially designed advocacy efforts can help to accelerate decision-making, including increases in funding for vaccination programmes, building support for improved laboratory capacity and surveillance, and addressing other barriers to vaccination programmes. Advocacy played a key role in the decision to introduce Hib vaccine in Mongolia and Sri Lanka, and in mobilizing resources for poliomyelitis eradication efforts and hepatitis B vaccine programmes worldwide. The goal of the advocacy programme is to use the best available data in providing advice and recommendations directly or indirectly to policy-makers and to ensure that decisions are sustained by demonstrating a clear public health benefit over time.

The first step in designing an advocacy effort is collection of basic facts, comparing local data to regional, national or international averages, where possible. For example, the Hib data in Bangladesh can be compared with global averages: 'Consistent with global data, Hib is the leading cause of childhood bacterial meningitis in Bangladesh'. Similarly, the role of pneumonia can be summarized very well by the powerful statement that 'Pneumonia accounts for one-third of infectious deaths in South-east Asia'.

The next step involves defining and understanding the attitudes/perceptions/priorities of key audiences; identifying the adversaries; and learning to speak the language that convinces both supporters and adversaries. No preconceived assumptions should be made about the key audiences.

A well developed plan, with defined objectives, scope, timeline and budget, which can be presented to key audiences, will be the key to implementing advocacy efforts, including development of advocacy messages and materials for multiple audiences (e.g. donors, government and paediatricians). Messages should be targeted and simple. For example, the key messages for donors may include: 'Pneumonia is the leading infectious killer of children in the country' or 'Hib vaccine is an important part of an integrated approach to reduce childhood

mortality, with potential to reduce childhood deaths by 4%'. Messages for policy-makers may include: 'X per cent of children are dying of meningitis and pneumonia'; 'Hib immunization is needed to help fight pneumonia and meningitis among children'; and 'Hib vaccine programmes are cost-effective and affordable'. Messages for technical evaluators will focus on emphasizing Hib as the leading cause of bacterial meningitis and the impact of Hib vaccine on childhood pneumonia and meningitis. Messages should be developed locally to ensure they address the priorities particular to each country, and should be tested, where possible, with target audiences.

Finally, a coalition involving multiple stakeholders (e.g. health care providers, community leaders, parents, international partners, researchers and policy-makers) builds stronger support and more sustainable decisions. Both the pros and cons of directly involving the media and the public should be carefully weighed and implementers of advocacy efforts should remain prepared for both positive and negative outcomes. Monitoring and evaluation is an important component of any advocacy plan to assess the achievement of desired goals and to document the lessons learnt.

Finally, the presenter informed the participants of the Hib Initiative's communication support. The materials developed by the Hib Initiative include: fact sheets (global and regional); slide presentations (global, regional and for selected countries); bibliography by country; 'Hib Kill or Cure' DVD (three-minute and 20-minute versions available); press backgrounders; and 'answers to frequently asked questions' at www.Hibaction.org. Requests for additional information can be made through the website.

2.5 Session 5: vaccine financing and programme issue

Chairperson: Dr Rana Hajjeh

Rapporteur: Dr Patrick Zuber

2.5.1 The Malaysia experience with Hib vaccine introduction: decision-making process, programme issues and impact assessment (Dato' Dr Narimah Awini)

The Malaysian health care system includes about 45% of practitioners in the public sector and the rest in the private sector. There is no national health care insurance, but government health services are free for all. The Ministry of Health is the custodian and policy-maker for health services. The Maternal and Child Health/Family Health Department provides immunization services, while the Communicable Diseases Department is responsible for disease surveillance, including that for vaccine-preventable diseases. At village level, community nurses provide primary health care.

Although many paediatric associations requested the introduction of Hib vaccine in the early 1990s, evidence on the Hib disease burden in Malaysia was not convincing at that time. In addition, the cost of vaccine was a major barrier to considering its introduction. Nonetheless, the vaccine was available in the private sector, which put additional emphasis on the need to look for data. The Ministry of Health is strongly oriented towards evidence-based decision-making and recognized that the paucity of evidence could not paralyze it into inaction. With the urging of key stakeholders, it organized a thorough literature review and led several hospital studies to clarify the Hib disease burden in the country. The studies noted that almost 1000 bacterial meningitis cases per year were due to Hib. A national child health conference was held in August 2000. Hib vaccine introduction was recommended, with three doses in infancy and a modification of the DTP schedule starting at two months of age. A key factor was the part played by Hib vaccine champions and their passion and persistence in supporting the decision-making process and the need to reach decisions sooner.

The cost of DTP was RM 47.5 million (1 US\$~3.74 RM) and went to RM 650 million with DTP+Hib. The cost was a concern, and the initial tendency was to delay the delivery of DTP. Fortunately, advocates such as the speaker pointed out the value of saving lives. Manufacturers' competition was handled by a tender board. In 2006, the country will be switching to pentavalent vaccine. Because of funding shortages, other programmes such as breast cancer education and hypothyroid screening have had to be postponed.

One lesson learnt, and expressed by the speaker, was the importance of looking for ways for the Ministry of Health "to end up on the front page". Informing the public is one way to help ensure sustainability for programmes.

Impact assessment is challenging in Malaysia because the disease surveillance system does not include meningitis among its reportable conditions. A hospital-based surveillance system is being put in place. The programme is now looking at pneumococcal vaccine, but might not be able to afford it in the immediate future.

Discussion: More needs to be done to get to the decision point on vaccines sooner, while not necessarily pushing any particular vaccine.

2.5.2 GAVI Phase II: what it means to countries in the Region (Dr Abdallah Bchir)

GAVI will provide support to 72 countries in Phase II instead of 75 as in Phase 1. This was determined based on gross national income (GNI) per capita for 2003 and may possibly be revised over time. One country, India, is under a specific arrangement with a US\$ 100 million cap. In addition to the support provided in Phase I (immunization strengthening support, injection safety), there will be new windows of support for health system strengthening, the introduction of the second dose of measles and yellow fever in Africa.

Bridge financing for new vaccine (Hib/HepB) containing combination vaccine introduced in Phase I

Bridge financing is a mechanism to sustain the support that was provided to countries during the first phase of GAVI for combination vaccines. The introduction of new vaccines has increased the cost of immunization programmes in GAVI-supported countries by almost 120% to 430%. The objective of the bridge financing will be to stimulate the downward pressure on vaccine prices while supporting countries on the trajectory towards financial sustainability, and to support integrated planning and budgeting at country level.

The general principles of the bridge will include: respecting the country-driven decision-making process, being compatible with national budgeting cycles, being flexible and allowing for monitoring and evaluation. Bridge financing will start when Phase 1 is ending. Its duration will be five years for tetravalent DTP-HepB and up to 2015 for countries using pentavalent vaccine. Six or seven countries in Asia are eligible for bridge financing (depending on Papua New Guinea approval for Hib introduction).

All countries with GAVI support ending in 2006 will receive one additional year of full support for vaccine procurement. Afterwards, countries will have to start contributing to the financing of subsidized vaccines, on an increasing scale over time and with a maximum level of target payment. For pentavalent Hib vaccine, that target has been set at US\$ 1.85 per dose and, for DTP-Hib, US\$ 1.77 per dose up to 2015. For tetravalent vaccine the target is US\$ 0.65 per dose after five years. Contributions to vaccine procurement prior to the bridge will be banked. The bridge contractual agreement will be conducted through two mechanisms: one general

framework for the whole duration of the support and another for the short term to fit country planning cycles.

New vaccine support in Phase II

New vaccine support is currently limited to 2015 for combination vaccines. Support for hepatitis B monovalent vaccine and measles second dose will be limited to five to seven years and five years, respectively. Countries will be required to pay a subsidized price from the onset. Several points are still under discussion, including the level of the minimum starting contribution, the level of the target payment according to GNI, etc.

The general principles for application for new vaccines will be at least 50% DTP3 coverage, alignment with the country planning cycle through the cMYP process, and requirement of a signed agreement with GAVI.

2.5.3 Pneumococcal vaccines: current status of development and evaluation (Dr Thomas Cherian)

Invasive pneumococcal disease corresponds to a variety of diseases resulting either from bacteraemia or colonization of a secondary site (pneumonia, meningitis, arthritis, etc.). The burden of invasive pneumococcal disease is higher in Africa than in industrialized countries. Historically, efforts to detect pneumococcal disease in Asian countries have been characterized by low yields from blood and CSF cultures. However, recent data from Bangladesh have suggested that a high burden of pneumococcal disease (as high as observed in some African settings) can be demonstrated if early blood cultures are drawn.

Around 800 000 child deaths are estimated to occur from pneumococcal infections every year, most of them in Africa and Asia. Although the proportion of pneumococcal serotypes responsible for invasive disease varies across countries, 11 serotypes account for 80% or more of pneumococcal disease in children worldwide.

It is difficult to measure vaccine effectiveness against pneumococcal pneumonia because of the non-specificity of the etiological diagnosis. However, clinical trial results are remarkably consistent about vaccine effectiveness against paediatric pneumonia, with the vaccine leading to a 25% to 37% reduction. The vaccine has also proven to be effective in children with HIV infection. A clinical trial in South Africa showed significant protection against invasive pneumococcal disease and against clinically defined pneumonia, regardless of etiology. In the United States of America, use of the 7-valent vaccine has dramatically reduced the incidence of pneumococcal disease in children. In addition, the vaccine's herd immunity effect has been substantial. Vaccination of children has actually 'indirectly' prevented twice as many cases of pneumococcal disease among unvaccinated adults – through reduced transmission from children – as it has prevented directly in immunized children. It has also reduced the incidence gap across socioeconomic groups.

Many new pneumococcal vaccine candidates are in the pipeline. A 10-valent vaccine is expected to be launched by 2008. A 13-valent vaccine is expected shortly after that. Recent trials suggest that additional benefits can be expected from the use of pneumococcal vaccines. The 10-valent pneumococcal vaccine candidate includes a component of non-typeable *Haemophilus influenzae* that has shown promise in preventing *H. influenzae* otitis media, and may ultimately help to prevent other *H. influenzae* infections. The potential for this vaccine to prevent pneumonia and invasive disease caused by Hib remains to be explored.

Additional data on vaccine effectiveness in Asia and serotype distribution, as well as clearer disease burden estimates are being developed and will contribute to policies regarding the use of pneumococcal vaccine in global programmes.

2.6 Session 6: group work and individual country presentations

All 13 participant Member States were categorized into four groups, based on country size, Hib vaccine introduction status and GAVI eligibility status, to discuss key issues related to the introduction of Hib and pneumococcal vaccines in their respective countries. A moderator and rapporteur were assigned for each group.

Each country prepared a five-minute presentation for the whole group, summarizing its status in four areas: perceptions of the disease burden and vaccine cost; the status of new vaccine introduction; country capacity and needs for decision-making and sustainability; and proposed next steps for decision-making. Presentations were followed by discussions.

Participating countries may be grouped according to Hib vaccine introduction status: (1) already introduced (three countries – Australia, Malaysia, Mongolia); (2) preparing to apply for GAVI support to introduce Hib vaccine (four countries – Bhutan, Papua New Guinea, Sri Lanka, Viet Nam); (3) considering introduction within the next few years (two countries – Bangladesh, India); and (4) not currently considering Hib vaccine introduction (four countries – China, Indonesia, the Philippines, Thailand).

Among the countries that have introduced Hib vaccine, all have documented a high Hib disease burden through specific surveillance or disease burden studies, have resolved implementation issues, and are in various stages of considering pneumococcal vaccine introduction (Australia introduced; others beginning to measure disease burden).

Countries that are preparing to introduce Hib vaccine have also documented the disease burden, are all GAVI-eligible, and are in the process of or planning to apply for GAVI new-vaccine support. Key issues include consideration of financial sustainability and government commitment to vaccine co-funding, strengthening surveillance and laboratory capacity, and better documenting cost-effectiveness to support financial sustainability. Proposed next steps include completing comprehensive multiyear plans and financial sustainability plans; resolving the operational aspects of introducing the new vaccine; enhancing surveillance to document vaccine impact; and consideration of local vaccine production (Viet Nam).

Among the two countries considering future Hib introduction, both are GAVI-eligible and studies of their disease burdens have been completed or are under way (India probe study). However, additional information and better documentation of the disease burden, as well as vaccine cost and cost-effectiveness are needed, as is consensus-building among key policy-makers and the public. Next steps include completing key disease burden studies (India vaccine probe study), holding workshops to review the available information and preparing the vaccine introduction case for their national vaccine advisory committees.

Countries that are not planning to introduce Hib vaccine immediately are uniformly less certain about their disease burden, except the Philippines, and perceive high vaccine cost as being an impediment to vaccine introduction. Most recognize a high ARI disease burden, but have limited documentation of Hib in contributing to that burden. However, in all countries, Hib vaccine is being used in the private sector. All these countries also note competing priorities, including other EPI programmes (poliomyelitis, measles, hepatitis B, maternal and neonatal tetanus); injuries; and other maternal and child health issues. Countries not yet considering vaccine introduction include three countries not eligible for GAVI funding. Key issues are the

uncertain disease burden (particularly in China), the high vaccine cost, many competing health priorities, low overall health spending, and concerns about how Hib vaccine use might shift vaccine purchase away from locally produced vaccines. These countries desire to better document their disease burden, establish better disease surveillance, and examine vaccine cost-effectiveness and affordability, but some are limited by a lack of resources to complete such studies. Next steps include establishing surveillance for meningitis/ARI and better defining the disease burden, identifying hurdles to strengthening health care spending (the Philippines); building better appreciation of the disease burden among the public and policy-makers, and facilitating local vaccine production to ultimately reduce vaccine prices (China, Thailand).

Discussion

- (1) There is a need to emphasize surveillance, and to document both meningitis and pneumonia burdens. Consideration has to be given on how to strengthen surveillance using the polio infrastructure.
- (2) Issues regarding vaccine probe studies: Why has Indonesia not considered the results of the Lombok vaccine probe sufficient information on the disease burden – controversial results with relatively lower impact on pneumonia, huge archipelago with differing conditions. India should be cautioned against relying only on the ongoing vaccine probe study for decision-making.
- (3) Why was vaccine introduction phased in some countries – programmatic choice. Why are Viet Nam and Papua New Guinea not planning to use combination pentavalent hepB containing vaccines – need for a monovalent hep B birth dose.
- (4) It was noted that, among countries with comparable disease incidence, some are ready to introduce Hib vaccine (e.g. Viet Nam), while others are not (e.g. Thailand). Discussion of the reasons centred on funding source (GAVI eligibility) and other health priorities.
- (5) Bhutan's application for Hib vaccine introduction on the basis of rapid assessment tool (RAT) results was rejected by GAVI in Phase I. However, it plans to reintroduce it in Phase II with the same data. Due to changes in the global policy environment with the new SAGE recommendation, the application is likely to be accepted with the same disease burden data presented as before.

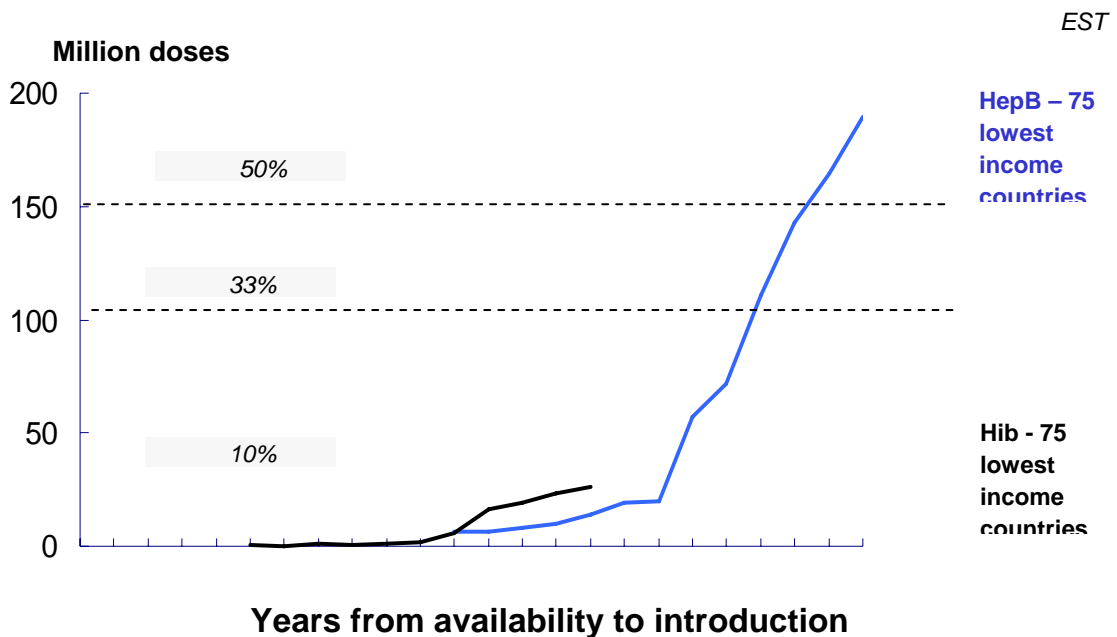
In summation, several important themes were emphasized. First, the importance of establishing strong surveillance to document disease burden and monitor the impact of vaccination programmes. Surveillance both establishes the need for vaccine and provides the strongest data for advocacy for continuing vaccination programmes. Second, the importance of national advisory committees to objectively review information about new vaccines and make recommendations to the government. These will be increasingly important as additional new vaccines become available and countries may need to choose between several effective new interventions. Third, there is a need for increased advocacy for decision-making and funding systems to gather needed evidence, but this must be balanced with many competing priorities from other EPI and public health programmes. Efforts should be made both to work with countries to define highest priorities and to increase national and international commitment to preventive health on the part of donors, suppliers and partners.

Final discussions noted the importance of regional working groups to coordinate new vaccine introduction efforts; the need to make the health care funding pie bigger rather than have new vaccines compete with each other or extant programmes; and the need to keep a long perspective – what seems expensive today may not seem so in a few years.

3. CONCLUSIONS AND RECOMMENDATIONS

3.1 Conclusions

- (1) There is a need for special visible and focused efforts to expedite the use of new vaccines. Past experience with slow and inequitable uptake of hepatitis B and Hib vaccine is justification for the global Hib initiative and PneumoADIP.



- (2) Hib and pneumococcal disease burdens are difficult to measure and conventional laboratory-based surveillance may underestimate them. More clarity is needed as regards the overall burden of pneumonia and meningitis attributed to Hib and pneumococcus in countries. While the overall morbidity and mortality due to bacterial pneumonia and meningitis may be low in some countries in the Western Pacific Region (e.g. Hong Kong [China], Japan, Republic of Korea), laboratory-based surveillance may underestimate them due to difficulties in isolation of Hib and pneumococcus.

However, this conclusion is not justified in all the country case studies presented.

Use of different methods to demonstrate the disease burdens in countries: While simple laboratory-based surveillance was able to demonstrate relatively higher disease burdens in Dhaka Shishu Hospital in Bangladesh, and in Malaysia, Mongolia and Sri Lanka, it failed to demonstrate the high disease burden in China, the Republic of Korea and Viet Nam.

Discrepancy between laboratory-confirmed and estimated disease prevented in Bangladesh and Lombok: While the results of the vaccine trial (case-control incident study) corroborate the high meningitis incidence also noted in hospital surveillance data (mainly using laboratory confirmation) in Dhaka Shishu Hospital in Bangladesh, the Lombok study demonstrated a much

higher disease burden that was estimated to be vaccine-prevented compared with what was laboratory-confirmed.

- (3) Even the best and most expensive studies, such as vaccine probe studies, may not yield conclusive data to convince policy-makers, as demonstrated in Indonesia. Whereas the Lombok study showed that the burden of bacterial meningitis was highly underestimated by standard laboratory tests, the magnitude of pneumonia cases prevented was much smaller than anticipated earlier. Hence, while the decision to introduce Hib vaccine in another big country, India, rests on the results of an ongoing vaccine probe study, the country may still need to consider other factors before introducing the vaccine.
- (4) The current cost of the vaccine still remains a formidable challenge for vaccine introduction in many countries. Although standard cost-benefit and cost-effectiveness analyses may show the vaccine to be cost-effective, developing countries may still find its introduction unaffordable. In addition, introduction of the vaccine may compete with many other cost-effective public health interventions (such as provision of clean water, sanitation, expansion of other health services) that are also underfunded.
- (5) Introduction of vaccines by GAVI-non-eligible countries in the Western Pacific Region may be critical to expanding vaccine use, as GAVI-eligible countries only constitute 7% of the total regional population. In addition, it was noted that countries not eligible for GAVI are at a great disadvantage, not only for introduction of new vaccines, but also for identifying resources to determine disease burden, establish surveillance, etc. Participants suggested that GAVI should reconsider the criteria for country eligibility for support.

3.2 Recommendations

Based on the assessments by each country, plans should be put in place to put more emphasis on the decision-making process for Hib and pneumococcal vaccines to expedite the process and avoid unnecessary delays, unless overwhelming impediments exist.

- (1) Novel ways of measuring the disease burdens of Hib and pneumococcus should be implemented where the disease burden data are still not conclusive and where the traditional laboratory-based surveillance of pneumonia and meningitis has shown a relatively low disease burden. Some of these may include case-control studies, with the introduction of vaccine in one of the pilot areas.
- (2) Continuous efforts should be made at the global level to increase the downward pressure on vaccine price to make it affordable for low-income countries. Countries will also need to demonstrate that they are evaluating vaccine decisions on a timely basis to signal to suppliers that there is a more predictable demand.
- (3) Efforts related to the disease burdens of Hib and pneumococcus should be integrated at the country level. The PneumoADIP and Global Hib Initiative should coordinate efforts.
- (4) The ADIPS and Hib Initiative might/should mobilize funds from other organizations to enable expansion of their support for determining disease burden and advocacy to other non-GAVI countries, especially countries that are demographically very important in the Region, such as China and the Philippines.
- (5) The organizers should recommend to GAVI that they should reconsider the eligibility of the Philippines for funding.

(6) Country action plans:

Australia, Malaysia and Mongolia

Australia, Malaysia and Mongolia have already introduced the vaccine. Disease is mostly based on disease burden generated by laboratory-based surveillance. Future action: Continue regular disease surveillance to further demonstrate vaccine impact.

Bangladesh

Bangladesh considers existing data from the case-control study and hospital-based surveillance data to be sufficient to warrant vaccine introduction. However, financial affordability is still the issue. Future action: Conduct a workshop to review the disease burden, competing priorities and financing to make recommendation to the Interagency Coordinating Committee. If positive, introduce Hib in the next couple of years.

China

China is not GAVI-eligible. All the existing studies suggest a low disease burden. Policy-makers are not considering the introduction of vaccine in the immediate future. Further action: Carry out more studies using a different methodology from before and also use data generated by the Global Disease Detection studies. Have more dialogue on this issue within the country with different policy-makers and researchers. Work with Chinese suppliers to help develop vaccines at a lower price

India

India wants to wait for the results of the ongoing vaccine probe study (although the results from a similar study did not lead to vaccine introduction in Indonesia). The results from this study may not be available for the next two to three years. In addition, the US\$ 100 million GAVI cap may mean that India has to set aside substantial co-financing if it takes a decision to introduce the vaccine. Future action: Wait for the results of the vaccine probe study.

Indonesia

In Indonesia, although the study investigators consider the data generated by the Lombok vaccine probe study to be very convincing and sufficient evidence to warrant vaccine introduction, the Ministry of Health do not agree. Indonesia, although GAVI-eligible, is not considering vaccine introduction in the near future. Future action: Generate more disease burden data from other parts of the country that can be more easily generalized nationally.

Papua New Guinea

Papua New Guinea considers the burden demonstrated by existing studies to be high. The decision to introduce Hib vaccine was undertaken in 1999 with the drafting of a 10-year national health plan (2000-2010). Papua New Guinea made an application to GAVI for the introduction of vaccine in 2005 under Phase I and got conditional approval. Future action plan: Address GAVI concerns to get unconditional approval. Formulate and implement a plan to introduce Hib-containing vaccine in mid-2007.

The Philippines

The Philippines considers the existing disease burden to be high, but affordability is a major issue. The country is not even able to provide regular funding for hepatitis B vaccine in the first 12 hours, despite the price of hepatitis B vaccine being almost one-tenth of Hib-containing vaccines. Future action: Conduct more dialogue and advocacy with policy-makers to convey the disease burden data; mobilize donor support.

Thailand

Thailand is not GAVI-eligible. Thailand does not consider the current disease burden (Hib meningitis rate ~10/100 000 under-five population, almost the same as that of Viet Nam) to be high enough to warrant vaccine introduction. Thailand considers the expansion of flu vaccine to be a higher priority than Hib vaccine. Future action: No action planned.

Viet Nam

Viet Nam considers the existing disease burden (Hib meningitis incidence at 10-12/100 000) to be high. Future action: Conduct a cost-effectiveness study to assess whether vaccine introduction is cost-effective at current disease levels and apply to GAVI in 2006/07 for introduction of DPT-Hib vaccine.

Bhutan and Sri Lanka

Bhutan and Sri Lanka both consider the disease burden suggested by current studies (RAT in Bhutan and hospital-based surveillance in Sri Lanka) to be high enough to warrant vaccine introduction. Future action: Apply to GAVI in 2006/07 for new vaccine introduction.

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Provisional Agenda

Day 1, Thursday, 30 March

Session 1: Introduction

- (1) Opening of the session
- (2) Opening remarks
- (3) Administration of a baseline questionnaire
- (3) Overview of Global Hib initiative
- (4) Overview of PneumoADIP

Session 2: Overview of regional epidemiology of Hib and pneumococcal diseases

- (5) Disease burden and impact studies: challenges in study design and data interpretation
- (6) Overview of existing evidence on disease burden due to Hib and pneumococcus in Western Pacific Region
- (7) Overview of Hib and pneumococcal disease burden in South East Asian Region

Session 3: Sharing the experience: examples of meningitis and pneumonia studies from Asian countries

- (8) From South East Asian Region (each presentation 20 minutes each)
 - a) The Lombok study – the issues
 - b) The Sri Lanka experience
 - c) Bangladesh
- (9) From Western Pacific Region
 - a) The experience from Mongolia
 - b) Results from three country studies– China, Viet Nam and the Republic of Korea

Session 4: Update on vaccines

- (10) Hib vaccine supply issues
- (11) Pneumo vaccines update
- (12) Cost-effectiveness studies for Hib and pneumococcal disease: needs and key issues
Announcement of groups for group work for the 2nd day

Day 2, Friday, 31 March

Session 5: Vaccine financing and programme issues

- (12) The Malaysia experience with Hib vaccine introduction: decision-making process and programme issues
- (13) GAVI phase II: and Bridge financing issues
- (14) Introducing new vaccines: role of Advocacy

Annex 2

- (15) Working Group Discussions: Assessment of country needs for decision-making regarding new vaccine introduction (burden of disease, information on financing and supply, communications, etc.)
- (16) Presentation of individual country report based on their group work laying down the gaps in information and identified future activities
- (17) Summary of overall issues and action plan and closure of the session