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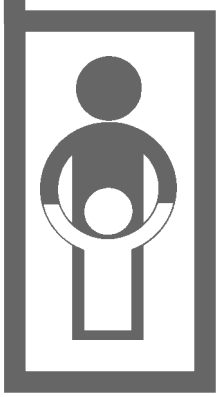
Expert review of a tool for rapidly assessing *Haemophilus influenzae* type b (Hib) disease burden

Geneva, 19–20 October 2000



DEPARTMENT OF VACCINES AND BIOLOGICALS

World Health Organization
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Contents

Abbreviations

ARI	acute respiratory infections
CDC	Centers for Disease Control and Prevention (USA)
CFR	case fatality rate
CSF	cerebrospinal fluid
EPI	Expanded Programme on Immunization
GAVI	Global Alliance for Vaccines and Immunization
Hib	*Haemophilus influenzae* type b
HIV	human immunodeficiency virus
NIH	National Institutes of Health (USA)
WBC	white blood cell

Executive summary

An expert meeting to review a draft tool for rapidly assessing the local burden of disease due to *Haemophilus influenzae* type b (Hib) was held in Geneva from 19–20 October, 2000. The meeting was organized by the WHO Department of Vaccines and Biologicals with financial support from the US National Institutes of Health and Centers for Disease Control and Prevention.

Before the introduction of Hib conjugate vaccine in the late 1980s, Hib was the leading cause of bacterial meningitis and one of the leading causes of bacterial pneumonia and sepsis among young children worldwide. In many developed countries where Hib conjugate vaccine is routinely used, the burden of Hib disease has been virtually eliminated. Most developing countries, however, have not added the Hib vaccine to their routine childhood immunization schedules (Figure 1: Global status of Hib immunization policy). Consequently, an estimated 350 000 – 700 000 children worldwide still die of Hib disease each year (Figure 2: Estimated rate of Hib meningitis and pneumonia).

Several important obstacles have prevented most developing countries from adopting Hib vaccine. One important obstacle is its high cost relative to other routine immunizations. Equally important, health officials in many countries have not seen convincing evidence of the burden of Hib disease in their own countries, and consequently, there are few local advocates for the introduction of Hib vaccine. Without recognition of the burden of Hib disease in their own country, health officials may underestimate the value of Hib vaccination and have little incentive to spend the financial and other resources necessary to introduce the vaccine.

The Rapid Assessment Tool reviewed at this meeting was specifically designed to enable people in developing countries to rapidly estimate the local burden of Hib disease using as much of their own local data as possible. An explicit goal of the tool is to engage local decision-makers in the process of developing disease burden estimates so that the information gathered will be most likely to increase local awareness of Hib disease. Using the rapid tool will also focus attention on the issues of surveillance for Hib disease, the difficulties in estimating Hib disease burden, and the steps that would be required to monitor vaccine effectiveness.

No one tool or technique for assessing the burden of Hib disease will be appropriate for all countries and all situations. Available techniques include routine surveillance, prospective studies, clinical trials, and the Rapid Assessment Tool. The first three of these techniques are expensive and all require laboratory facilities that can identify Hib. The meeting participants agreed that because of its low cost, rapid results and flexibility, the Rapid Assessment Tool fills an important place in the spectrum of options for assessing Hib disease burden. This Rapid Assessment Tool will be

particularly useful for countries that do not conduct routine surveillance for Hib disease and are considering vaccine introduction or are preparing requests for vaccine funding through the Global Fund for Children's Vaccines or other sources. The participants also made the following recommendations for improving the technical aspects of the two methods used in the tool to estimate the burden of Hib disease and for implementation of the tool.

Figure 1: Global status of Hib immunization policy

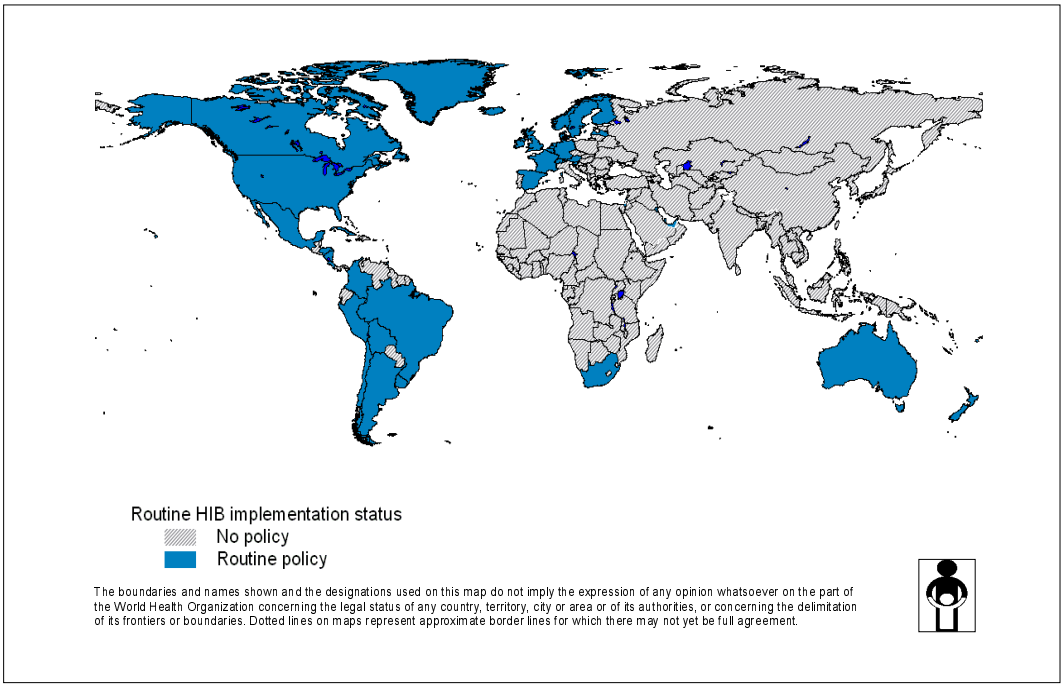
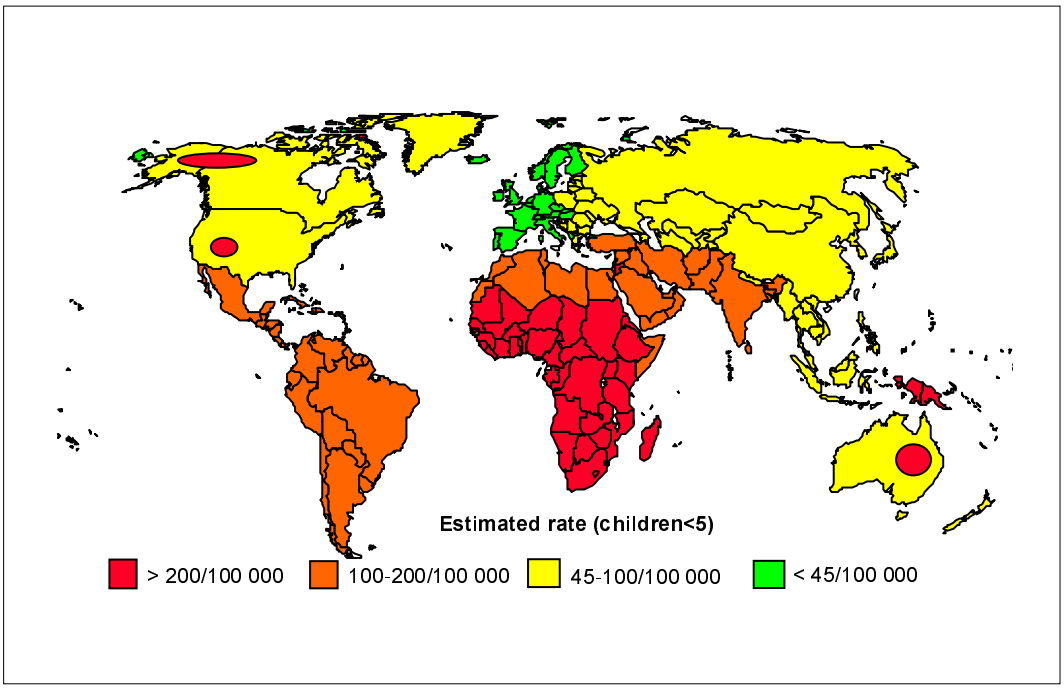


Figure 2: Estimated rate of Hib meningitis and pneumonia



Recommendations

1) Whenever possible, the tool should be used in several areas within a country. These sites should be selected to capture the possible diversity of Hib disease epidemiology. For example, Hib disease burden in urban areas may differ from that in rural areas.

2) Whenever the tool is used, it should be emphasized that the results provide only estimates of the true Hib disease burden.

3) Training should be available to persons interested in using the tool. The training should include:

   - implementation issues
   - the impact of assumptions and the limitations of the tool,
   - assistance with interpreting the results of the tool in different situations.

4) The assumptions in the tool should be evaluated for the strength of the underlying data and the relative impact on the final results. Data from ongoing intensive studies of Hib disease should be reviewed to help evaluate the assumptions made in this tool. Assumptions which are based on limited data and which have the largest impact on the results should be discussed in the tool.

5) The tool should be validated in areas where population-based surveillance studies of Hib disease are under way.

6) Several technical points should be reviewed to determine their impact on the accuracy of the Hib disease burden estimates calculated with the tool. Existing data sources should be used to assess the following suggested changes:

   - The definition of purulent meningitis could be expanded to include cerebrospinal fluid (CSF) specimens with 10–99 white blood cells/ml and abnormal protein and glucose levels.
   - The infant mortality rate could be used in the estimation of Hib pneumonia burden (worksheet 3) instead of the under-five mortality rate.
   - The Hib pneumonia case-fatality ratio is likely to vary between countries and additional data is needed to determine the range of possible values.

7) Cases of clinical or purulent meningitis in children under one month of age are unlikely to be caused by Hib and should not be used to estimate the number of cases of Hib meningitis (worksheet 1).

8) The tool should be simplified by eliminating blood culture information in the calculation of Hib meningitis incidence (worksheet 1).

9) The section in the tool that deals with laboratory issues should be expanded to include specific criteria for assessing the ability of local laboratories to identify Hib.

10) An example of a one page executive summary should be added to the tool to assist with the presentation of results in a concise manner.

11) A standardized reporting format for the results of the tool should be developed and maintained by WHO.

12) The method for calculation of Hib disease burden from the under-five mortality rate (worksheet 3) is most useful for providing an additional estimate of the burden of Hib pneumonia, which is impossible to determine by surveillance methods. Extension of the method to estimate the burden of Hib meningitis relies on additional assumptions, and the results should be interpreted with caution. Whenever possible, the method which is based on the number of bacterial or purulent meningitis cases (worksheets 1 and 2) should be used to estimate the Hib meningitis burden.

Opening statement

Dr Maureen Birmingham opened the meeting by welcoming the participants and noting that the meeting was cosponsored by WHO and the US National Institutes of Health and Centers for Disease Control and Prevention. She went on to make the following observations.

This meeting represents a milestone in the process of developing tools to gather information on the burden of disease due to *Haemophilus influenzae* type b (Hib). There is an urgent need for local data on Hib disease burden to enable evidence-based decision-making. Countries are facing important questions about how to prioritize new vaccination efforts including the introduction of hepatitis B vaccine, the introduction of Hib vaccine and measles elimination. Also, countries must weigh new vaccination efforts against other health priorities. The information that Hib disease burden estimates provide will help countries make rational decisions about the introduction of Hib vaccine. There is some data on the burden of Hib disease from special studies and population-based surveillance in a handful of countries. However, local data are very important for decision-makers. Many countries do not have the time or the resources to embark on long- term studies. Therefore, a tool to rapidly estimate the local burden of Hib disease is needed.

Dr Birmingham then proposed that the Chairman and Rapporteur be Dr Mark Steinhoff and Dr James Watt, respectively.

The list of participants is attached as Annex 1.

Objectives and expected outcomes

Dr Christopher Nelson reviewed the agenda (attached as Annex 2) and outlined the objectives and expected outcomes of the meeting.

Objectives

The main objectives of the meeting were to critically review:

- the design of the tool;· the methodologies used to estimate Hib disease burden;
- the technical bases for the assumptions used in the tool.

Expected outcomes

The meeting was expected to produce recommendations for how to improve the tool and how to proceed with development and implementation of the tool.

In addition, several documents were to be written following the meeting. These include:

- the minutes of the meeting;
- the finished tool; and, if needed,
- a supplementary document reviewing the technical bases of the tool.

The importance of disease burden data in the process of vaccine introduction

Introduction

The process of new vaccine introduction (Dr Jay Wenger)

Dr Wenger began by presenting the WHO framework for evaluating a new vaccine for inclusion in the Expanded Programme on Immunization (EPI). Important issues are the priority of the disease and its control, the characteristics of the vaccine, the feasibility of introducing the vaccine, and vaccine supply. He reviewed how these issues impacted the introduction of hepatitis B vaccine. Hepatitis B causes over one million deaths a year, and the prevalence of chronic infection is highest in parts of Asia and Africa. In 1992, the World Health Assembly urged Member States to introduce cost-effective new vaccines such as hepatitis B vaccine wherever feasible. This statement by the Assembly highlights the importance of cost-effectiveness in national decisions about vaccine introduction.

Despite the heavy burden of hepatitis B, only 110 countries representing just under 50% of the childhood population worldwide are using hepatitis B vaccine. One important reason why many countries have not introduced the vaccine is cost. The introduction of new vaccines, including hepatitis B vaccine and Hib vaccine, is related to per capita gross national product (GNP). Countries with higher GNP are more likely to have introduced these new vaccines. For countries with low GNP, the cost of new vaccines relative to GNP has been prohibitive. Because vaccines are obtained and distributed by government agencies in most countries, the introduction of a new vaccine is essentially a political decision which must weigh vaccine costs and benefits against other priorities.

A meeting was convened in May, 2000 at the Academy for Educational Development in Washington, D.C., USA to review data on why some countries have adopted new vaccines and others have not. This meeting developed a paradigm to explain how decisions about new vaccines are made. At the centre of the paradigm are political decision-makers. On one side there is a problem (a vaccine-preventable disease) and on the other side a solution (the vaccine). According to this paradigm, the key to solving a problem is bringing an awareness of the problem and the potential solution together for decision-makers, who in turn generate the political action needed for vaccine introduction.

Decision-makers need to understand the magnitude of the disease burden and the cost of the disease to society. Decision-makers are often unaware of the burden of disease. Local advocacy for addressing a disease can play an important role in increasing this awareness. With respect to the vaccine, decision-makers also need information about cost, supply, the feasibility of introduction, safety, efficacy and

manufacturing issues. Recent studies have shown that vaccine cost is the most important concern while vaccine safety and efficacy are significant but somewhat less important. Some of the political issues which must be weighed in making a decision about vaccine introduction are competing priorities, existing organization structures, donor influence, health sector reform efforts, and the need for coordination of public health efforts.

Recently, Dr Mark Miller, NIH, developed an analytical model to determine the factors which predict the introduction of a new vaccine. The most important factors were the cost of the vaccine compared to per capita gross national product, the existence of data on the burden of the disease, and the presence of a well functioning national vaccination programme. Recent experience has shown that local and regional advocacy for Hib vaccine introduction and sources of funding for the vaccine have been important in many countries. Information about the burden of Hib disease and public concern about Hib disease and its sequelae have also been important. Decision-makers are asking two key questions: is the vaccine accessible, and is the disease important? Information about the burden of disease helps to answer the latter question.

Hib conjugate vaccine is both safe and effective. There is good evidence that Hib is a serious cause of illness worldwide. While gathering data on the burden of Hib disease is difficult, several studies have found that Hib is the most common cause of childhood meningitis, and the second most common cause of serious bacterial pneumonia. However, scientific data on disease incidence only give part of the picture of the impact of Hib disease. The severity of disease and sequelae of infection are also important measures of impact on society. Public awareness of, and concern about, Hib disease as well as interest in the medical community are important to persons making decisions about vaccine introduction. Often these decision-makers have high, political positions in the government.

The amount of information about Hib disease varies from one place to another. In Latin America there is widespread recognition of Hib as an important problem. Most countries have the laboratory capacity to identify the organism and meningitis is perceived to be a major public health problem. Baseline data on Hib incidence is available in many countries. The Pan American Health Organization supports the introduction of Hib vaccine, and most countries in the region have the financial resources to purchase the vaccine. In this region, most countries have introduced Hib vaccine.

In contrast, most countries in Africa have limited laboratory and medical infrastructure. Hib may never have been isolated in some places, which poses a major barrier to awareness of Hib disease burden. In some African countries, there is greater awareness of meningococcal disease and for this reason it competes with Hib as a health priority. Further, many African countries have other public health concerns that eclipse meningitis, including tuberculosis, malaria and HIV. Regional health organizations have been focused on other priorities and have given less attention to Hib. There is also less regional data available about Hib disease burden. Perhaps most importantly, the financial situation in many African countries is difficult and Hib vaccine represents a prohibitively large percentage of total health expenditures per child per year. Consequently, few African countries have introduced Hib vaccine.

There are several ways to address a lack of awareness of Hib disease burden. Data from special studies in the region can be used to show that Hib is a problem in other countries. Local laboratory capacity can be supported so that countries can begin to identify Hib. Special studies can be undertaken to measure Hib disease burden and finally, existing local data can be used to estimate the disease burden. The Rapid Assessment Tool being discussed takes the latter approach. It helps countries use available data to make a rational decision about Hib vaccine. This is particularly important now that additional funding sources for new vaccines are available.

The WHO officially recommends that "Hib vaccine should be included in routine infant immunization programmes as appropriate to national capacities and priorities." Also, "in geographical regions where the burden of Hib disease is unclear, efforts should be made to evaluate the magnitude of this problem." Some countries, primarily in the Americas and western Europe, have already introduced Hib vaccine. However, in many countries with a high incidence of Hib disease, especially those in Africa, the vaccine is not being used. The driving force behind the decision to introduce Hib vaccine will be the balance between disease burden and cost, and this tool enables countries to evaluate that balance in a rational way.

Summary of the discussion following Dr Wenger's presentation:

Dr Orin Levine began by asking how much disease burden data is needed by decision-makers in developing countries.

Dr Wenger replied that an estimate of both the number of deaths due to Hib and the number of cases of severe illness due to Hib would be important. In addition, the data need to be comparable to those used to make decisions about other health interventions.

Dr Keith Klugman asked about the importance of the cost-effectiveness of Hib vaccine. Is there a critical point for cost-effectiveness that decision-makers are interested in? He observed that there is evidence that fractional doses of Hib vaccine could be effective and that the use of fractional doses could decrease the cost of a vaccine programme.

Dr Wenger replied that attempts have been made to quantify the importance of cost. Fractional dosing would help decrease vaccine cost, but Hib vaccine remains relatively expensive, even at one half or one third of the current price.

Dr Samir Saha observed that many countries are implementing hepatitis B vaccine with little data about disease burden, perhaps because there is a perception that hepatitis B is a larger threat because it affects people of all ages.

Dr Wenger added that disease burden is easier to measure for hepatitis B.

Dr Tony Measham observed that the vaccine market in developing countries has become distorted because other vaccines have been provided for free. Therefore, Hib vaccine appears to be expensive, even though it is extremely inexpensive when viewed in terms of the cost per life saved. He asked what the optimum cost for Hib vaccine might be.

Dr Wenger replied that production costs are about US$ 0.30-0.40 per dose.

Dr Kim Mulholland noted that the burden of a disease and the public perception of a disease are linked to the severity of disease. He asked whether decision-makers were more interested in knowing the number of deaths due to a disease or the number of cases of the disease.

Dr Wenger replied that decision-makers usually ask about the number of deaths. He agreed that mortality rate takes both disease severity and disease incidence into account.

The importance of local data in the process of estimating disease burden (Dr Ezzedine Mohsnie)

Dr Mohsnie began by discussing the importance of local data for decision-making drawing on his experience as the EPI manager for Tunisia. In Tunisia, vaccines are provided to the public for free, and 100% of EPI vaccine costs are paid out of the national budget. Decisions about the introduction of new vaccines must be rationally weighed against other national priorities. Local data on cost-effectiveness was very important to convince the Minister of Finance to buy hepatitis B vaccine. Although disease burden data were available in 1990, the Minister rejected the first request for vaccine because there was no information on the local economic impact of a vaccination programme. A cost-effectiveness study was therefore undertaken, and the results of that study were included in a second request for vaccine. That second request was approved, demonstrating that the Minister needed local data on both disease burden and costs to take a decision.

Based on the experience with hepatitis B vaccine, the Tunisian EPI decided to begin the process of Hib vaccine introduction with a review of the local Hib disease burden using the Rapid Assessment Tool. The results of that assessment showed that the Hib disease burden was likely to be similar to other countries in the region. The EPI then implemented population based surveillance in order to gather additional disease burden and economic data for a proposal that would be acceptable to the Minister of Finance. Part of the rationale for beginning population based surveillance was that the use of data from another country could underestimate the disease burden in Tunisia and jeopardize the Hib vaccine request. As an example, Dr Mohsnie presented data from a recent assessment of disease burden in Oman. Using the Rapid Assessment Tool, the team found a higher Hib disease burden than in neighbouring countries. The estimated disease burden was also higher than that reported by the routine surveillance system in Oman. Dr Mohsnie added that local data will be important for monitoring the impact of the vaccine once it is introduced in Tunisia. Being able to demonstrate the success of Hib vaccination will be important for the credibility of the EPI and its ability to introduce new vaccines in the future.

Dr Mohsnie then discussed the use of Hib vaccine from the perspective of his current role as a Regional Officer in Eastern Mediterranean Region (EMR). EMR has countries with a wide range of income levels. For the six countries in the high-income group, vaccine costs are not a limiting factor, and some are already using Hib vaccine. There are 11 countries in the middle income group which have fewer resources for purchasing vaccine. None of these countries are using Hib vaccine, and cost-effectiveness studies will be important as they consider vaccine

introduction. Most countries have either undertaken or requested studies of Hib disease burden. Also, there are six countries in the low-income group which are eligible for funding through the Global Fund for Children's Vaccines. Of these countries, only one has expressed an interest in Hib vaccine. Information on Hib disease burden is therefore an important part of vaccine funding requests in some regions.

In summary, local data will be decisive for Hib vaccine introduction in countries in all three-income categories. Those in the high-income category will need local data to evaluate their vaccination strategy, those in the low-income category to convince donors that Hib vaccine is needed and to monitor the impact of vaccination. As for middle income countries they will need local data to understand the disease burden, assess the cost-effectiveness of vaccination, and convince national authorities that Hib vaccination is a good investment. In all countries, assessment of local Hib disease burden will be important for developing an appropriate Hib disease control strategy, increasing the capacity of the national EPI team and engaging clinicians and epidemiologists in the issues surrounding Hib disease.

At a regional meeting in 1997, EMR countries agreed that assessing disease burden should provide the basis for decisions about Hib vaccine introduction and would be important for evaluating vaccine effectiveness. It was recommended that countries which did not have local data on disease burden should develop an assessment plan with WHO assistance in study design.

In summary, Dr Mohsnie highlighted the following points:

- Local data on disease burden should be a basic element in decisions about vaccine introduction.
- Disease burden estimates based on local data provide a stronger argument for national decision-makers and external donors.
- Baseline local disease burden data will be important for measuring the success of the Hib disease control programme.
- Demonstrating the success of the Hib vaccination programme will be important for future vaccine introductions and establishing the credibility and reliability of the national EPI.
- The process of using the Rapid Assessment Tool is a valuable exercise for national EPI teams and it increases the awareness of Hib disease among EPI staff, clinicians and the Ministry of Health.

Summary of the discussion following Dr Mohsnie's presentation:

Dr Steinhoff began the discussion by noting that the type and level of Hib disease burden information required will vary by income level of the country. Wealthy countries may be content with confirmation that disease exists because the financial barriers are less pressing. Less wealthy countries may actually need more data to convince ministries of finance and donors that Hib vaccination is appropriate.

Dr Richard Adegbola asked whether the high-income countries had surveillance systems in place.

Dr Mohsnie replied that they do, but often this surveillance is incomplete, as was seen in Oman. Additional information about Hib disease burden may be needed, even in countries with surveillance.

Dr Paul Kilgore asked if data from neighbouring countries was important to Oman.

Dr Mohsnie replied that it was important in getting them to consider Hib disease, but local data was still needed.

Dr Daniel Feikin observed that Tunisia decided to implement population-based surveillance, even though good data was available from neighbouring countries. Why was this necessary?

Dr Mohsnie reiterated that the experience with hepatitis B vaccine suggested that the Minister of Finance would want local data. Also, local data was needed to establish a baseline against which to measure the impact of the vaccine.

Dr Thomas Cherian noted that surveillance systems may not be adequate for making a decision about Hib vaccination because they might underestimate disease burden. Independent assessment of Hib disease burden could serve to evaluate existing surveillance systems.

Dr Mulholland added that the cost of vaccination should not be expected to be less than the cost of treating Hib disease in developing countries. In developing countries where the cost of health care is very low the vaccine will not be cost-saving. However, there is no question that there is a value in disease prevention.

Dr Jose Di Fabio underlined the difficulty in estimating the burden of respiratory disease due to Hib. Usually this is extrapolated from the burden of Hib meningitis using assumptions which may not be accurate.

Dr Bradford Gessner asked if each country needed to do a study before introducing Hib vaccine. If doing so, when would be the best time to do it? Should countries wait until funding was available?

Dr Mohsnie replied that some countries might not need to assess Hib disease burden locally. Smaller countries might be more willing to accept data from neighbouring countries. Also, countries might accept reliable data from neighbouring countries with similar populations. Larger countries are most likely to want local data.

Dr Jesus Feris observed that the cost of sequelae is important to consider when estimating disease burden.

Dr Y.L. Lau agreed, noting that Singapore rejected Hib vaccine because the burden was not perceived to be large enough. In Hong Kong a cost-effectiveness study is being done to support a decision, and the cost of sequelae will be important.

The World Bank Perspective on the need for Hib disease burden data (Dr Measham)

Dr Measham began by noting that the World Bank (the Bank) is a member of the Global Alliance for Vaccines and Immunization (GAVI) and is interested in investing in vaccines programmes. Several events have focused the attention of the Bank on vaccination including the high cost of polio eradication, the decrease in bilateral aid for health, and the encouragement of WHO and the United Nations Children's Fund (UNICEF). From the perspective of the Bank, this Rapid Assessment Tool is necessary but not sufficient for decisions to introduce Hib vaccine. Other factors, particularly cost, are important for these decisions. Consequently, the Ministry of Finance will often play a key role, and the World Bank has credibility with finance ministers. The Global Fund for Children's Vaccines has played an important role in increasing funding for vaccines, but additional funds will eventually be needed, and finance ministers are aware of this.

The mandate of the World Bank is both to reduce poverty and to promote economic growth. To accomplish these goals, the Bank makes loans to countries. Currently, the Bank provides approximately US$ 29 billion in loans annually, of which 7% is for health projects. Lending for health has increased rapidly since the 1980s. The conditions of World Bank loans depend on the financial situation in the recipient country. For poorer countries, the loans are interest free for a 30 year period and repayable over a long term. Therefore, approximately 70–80% of the loan is actually a grant. Nevertheless, countries have been reluctant to borrow for immunization programmes. They are often accustomed to receiving vaccines for free which makes any expenditure for vaccines seem high.

Often country demand is a missing element in the development of new health projects. The Ministry of Health may be weak compared to the Ministry of Finance, so health projects are not put forward. He noted that the Bank often advocates for vaccination projects and the introduction of new vaccines. He also discussed the process by which World Bank loans are approved. This begins with the identification of a project and the preparation of a proposal. The proposal is then appraised and reviewed and the loan is granted. The Bank then plays a role in supervision and evaluation of the project. Development of an application and approval of the loan can take several years, but some loans are made on an "emergency" basis when the process is speeded up.

Cost and disease burden data are both very important in the preparation of applications. The application is reviewed by a task leader who is usually not a physician and is responsible for dealing with the whole health sector. Hib is one of many health issues under consideration. Data from the Rapid Assessment Tool can play an important role in focusing attention on Hib. It needs to be user friendly and easy to understand. The task leader needs a brief summary of the tool and the results to understand how to evaluate Hib disease burden. Dr Measham provided a recent proposal as an example of the type of documentation needed. He concluded by saying that other donors and the Ministry of Finance will also be able to use the tool to weigh competing health priorities.

Summary of the discussion following Dr Measham's comments:

Dr Levine asked about the time constraints of the project approval process.

Dr Measham replied that it usually takes 12–18 months for a proposal to be developed and approved.

Dr Kilgore asked about the impact of recent financial crises on the openness of countries to borrow for health sector projects.

Dr Measham noted that the International Monetary Fund has been trying to exempt the health sector from structural reform requirements.

Dr Mulholland observed that when funding from the Global Fund for Children's Vaccines runs out, countries will have to turn to the World Bank for continued support. It is easy to understand why countries are reluctant to borrow for recurrent costs.

Dr Measham replied that investments in human development are among the most effective in decreasing poverty and increasing growth. Countries often underestimate the potential economic benefits of improving the health sector. This is due in part to the fact that it is difficult to measure the return on investments in health.

Dr Cherian added that the savings that the Ministry of Health realizes from a vaccination programme may not cover vaccine cost, but there may be other savings outside the health budget which make the programme attractive.

Tools for Hib disease burden estimation (Dr Levine)

Dr Levine began by observing that disease burden data is the key to the adoption of new vaccines. Countries need to know that a disease is present before they will consider the cost of the disease or vaccine. The availability of funding for new vaccines will be based on the burden of disease. All countries need some local disease burden data in order to introduce a new vaccine, but not all countries will need the same type of data. Several techniques exist to estimate local disease burden. These differ widely with respect to their cost, the time required to implement them, and the accuracy of the estimates that they can produce.

At the more expensive end of the spectrum are "vaccine probe" studies. These yield the most comprehensive and accurate data on Hib disease burden, but they are very difficult and time consuming. To date, only two have been done worldwide (one in The Gambia, one in Chile). Clearly, these studies are not appropriate for every country. In the middle of the spectrum are prospective surveillance systems. These have variable cost and time requirements and moderate accuracy. The Rapid Assessment Tool represents an inexpensive, timely option for collecting Hib disease burden data, albeit with less accuracy. No tool will be appropriate for all situations. The question is how to choose the most appropriate tool for each particular case.

The choice of tool will depend on a number of factors. The regional situation will be important. Countries in regions where Hib vaccine is not being used will need more data than those in regions where the vaccine is widely used. Similarly, countries in

regions with good regional data on Hib disease burden may need less local data to justify a vaccination programme. Local perceptions and priorities also need to be considered in choosing a tool. If Hib disease is not perceived as a problem, more data will be needed to demonstrate the importance of vaccination. Local capacity, such as laboratory facilities, needs to be considered as well as time constraints. The Rapid Assessment Tool might be particularly useful when data are needed quickly, to support a funding proposal for example.

The Rapid Assessment Tool complements other methods for assessing disease burden. It can serve as a bridge to more intensive studies in the region by showing countries that they have a Hib disease burden of a similar magnitude as countries which have conducted in depth assessments. The Rapid Assessment Tool also depends on other more intensive studies for its assumptions and validation. The rapid tool is best suited for estimation of disease burden prior to the introduction of vaccine. The process of using the tool increases awareness of Hib disease and the value of surveillance and creates advocacy for the introduction of Hib vaccine. By going through the rapid assessment process, countries can also identify possible surveillance sites for monitoring vaccine effectiveness. Prospective surveillance will be better than the Rapid Assessment Tool for the evaluation of vaccine impact.

In summary, no one tool is right for all situations. The effective assessment of local disease burden will depend on matching the right tool to the right situation. Various factors will determine which tool is best. The proposed Rapid Assessment Tool for Hib disease burden is one of those tools.

Summary of the discussion following Dr Levine's presentation:

Dr Cherian noted that disease burden data can be used to "market" the importance of a new vaccine.

Dr Levine agreed and said that the precision of the data may not always be critical. The important thing is to present data so that it generates advocacy.

Dr Saha asked how the tool could be used in areas where access to health care is limited and people die outside of hospitals.

Dr Levine answered that there is a need to calibrate the tool for different sorts of situations so that it can be broadly applied.

The Rapid Assessment Tool

Introduction (Dr Nelson)

At the core of the Hib Disease Burden Rapid Assessment Tool are two methods for estimating Hib disease burden: one method is based on an estimate of Hib-related childhood meningitis (the meningitis incidence method) and a second on estimating the proportion of under-five pneumonia mortality attributable to Hib (the under-five mortality method). Both use local estimates of meningitis and pneumonia case fatality in addition to other local data. The outcome of either method is an estimate of the annual number of cases and deaths attributable to Hib-related meningitis and pneumonia.

To facilitate the use of these models and the calculation of the morbidity and mortality estimates, the tool includes pre-formatted Microsoft Excel™ spreadsheets that provide a step-by-step method for entering local data. Estimates of cases and deaths are then calculated automatically with all intermediate steps shown clearly on the spreadsheets. A substantial part of the accompanying document explains how to use the spreadsheets and how the calculations are made.

The major strength of this tool is the use of local data in the calculation of disease burden. To facilitate the collection of this data the tool includes three forms. The first of these (A) lists criteria for selecting an appropriate region for evaluation. The second (B) is a series of interviews to assist in data collection and includes interviews targeted at Ministry of Health personnel as well as paediatricians and microbiologists. The last form (C) is a case register that can be used for organizing data collected from paediatric ward and microbiology lab log books.

One advantage of the Hib Disease Burden Rapid Assessment Tool is that local estimates of Hib-related cases and deaths can be made with 1–2 weeks of fieldwork. To facilitate this, the tool needs to be reviewed by the national focal points and all members of the assessment team several weeks prior to the planned fieldwork. Members of the assessment team may include a regional Rapid Assessment Tool consultant, local WHO EPI personnel, the national EPI manager and others with a specific interest in Hib disease from the clinical and academic community. The review should start with the two-disease burden methods, followed by the spreadsheets and supporting documentation, and then finish with the three forms.

Once the review has been completed, attention should turn to selecting appropriate sites for assessment (Form A). In addition to visiting the largest paediatric ward and its associated laboratory in the capital, two sites outside the capital should be selected.

These sites should have a well-defined catchment population of at least 250 000 people and be served by only a few hospitals with supporting laboratories that are capable of culturing Hib. Once the sites are selected, an introductory letter describing the proposed activity (Appendix B) should be sent to the paediatric ward and laboratory chiefs.

Once the assessment team has been identified, the tool has been reviewed, and the sites for assessment have been selected, field activities can begin. This work typically begins with a day of discussions at the Ministry of Health where available surveillance data and local research should be collected and the appropriateness of the selected sites reviewed. After the field sites are accepted, the final itinerary should be forwarded to a contact at each of these sites and arrangements confirmed.

Each site visit should take 1–2 days and involves contacting key personnel such as the local EPI manager, chief of paediatrics, and laboratory chief. At each site, meningitis related clinical and laboratory data are abstracted from paediatric ward and microbiology lab log books. If necessary, medical records should also be consulted.

Following the site visits a further 1–2 days will be needed to calculate the disease burden estimates using both the meningitis incidence and the under-five mortality methods and to write a preliminary report. An outline for the report is provided as part of the Tool (Appendix D).

At the end of the visit, a day is devoted to debriefing and presenting the results to Ministry of Health personnel. A substantial amount of technical material that is useful for these discussions is provided as part of the Tool. In all, the assessment can be completed within 1–2 weeks.

Summary of the discussion following Dr Nelson's presentation:

Dr Cherian asked when the best time would be to select the sites for the visit and do preparatory work.

Dr Nelson replied that it is best to do as much planning and preparation in advance of the fieldwork as is possible. As mentioned, it is particularly important to contact the paediatric ward and laboratory chiefs in each of the proposed assessment sites so that the hospital and laboratory criteria listed in Form A can be reviewed and the appropriateness of the sites for assessment can be evaluated.

Ms Ulla Kou asked why the tool was written for consultants coming in from outside the country.

Dr Nelson replied that the goal was to have a tool that could be used by local staff. However, because the tool requires substantial knowledge in the subject area in order to place the disease burden estimates in the proper context and judge their accuracy, it is expected that the Tool will be used by local staff working together with regional consultants. At this time regional staff were being trained in WHO's Eastern Mediterranean, African and Western Pacific regions.

Dr Feikin noted that it is very important that local personnel from the Ministry of Health and the clinical community be involved in the assessment so that by the end of the process they can act as advocates for Hib vaccination, if appropriate.

Technical bases for estimating Hib disease burden (Dr Feikin)

Dr Feikin began by defining the concept of disease burden. Epidemiologists are used to looking at incidence rates, but persons making decisions about vaccine introduction will want to know the raw numbers of cases of Hib disease and deaths due to Hib. The worksheets in the tool are designed to give these outputs as well as incidence rates.

Dr Feikin acknowledged that some of the assumptions used in the calculation of Hib disease burden estimates could be contentious. He hoped that the group would be able to make recommendations about how to strengthen these assumptions. His presentation began with an overview of the worksheets.Worksheet #1 is used to calculate Hib meningitis incidence using local data. Collecting data about meningitis cases in local hospitals represents the bulk of the work in the site visits. The data available at each hospital will be different, and the data collection strategy may need to be adapted for situations where important data are missing. The first step in worksheet #1 is to estimate the number of Hib meningitis cases diagnosed by CSF analysis during a defined time period. First, purulent CSF specimens are counted. Neonatal specimens (those from children 0–30 days of age) should not be included because Hib is an uncommon cause of neonatal meningitis. The definition of "purulent CSF" is an important assumption made by the tool that needs to be discussed by the group. Next, the numbers of CSF specimens from which any bacterial pathogen was identified and the number of specimens from which Hib was identified are counted. These data are then entered into the worksheet. An important assumption made at this point is that the percentage of purulent, culture-negative cases due to Hib is the same as the percentage of culture positive cases due to Hib.

Step 2 in worksheet #1 calculates the number of Hib meningitis cases diagnosed by blood culture. Cases of Hib bacteremia need to be checked to determine if meningitis was present and to make sure that they are not double counted. Step 3 adjusts for children with meningitis who did not have a lumbar puncture. Step 4 adds population data (the denominator), and step 5 calculates the incidence of Hib meningitis.

Worksheet #2 picks up where worksheet #1 leaves off. Steps 1 and 2 use the incidence rate determined in the region to estimate the number of cases of meningitis and the number of deaths due to meningitis in the whole country. An important assumption is that the national meningitis incidence rate is similar to that estimated from the regional site visits. In steps 3 and 4, the number of cases of deaths due to Hib pneumonia are estimated. Two important assumptions are made in these steps. First, it is assumed that the ratio of Hib pneumonia cases to Hib meningitis cases will be the same as that found in two special studies of Hib vaccine. No other data about this ratio is available. Second, the Hib pneumonia case fatality rate must be estimated. This is very difficult to determine, and local data is unlikely to be available.

Dr Feikin added some additional observations about the first two worksheets. First, other types of invasive Hib disease, such as cellulitis and epiglottitis have been excluded. These are difficult to measure, and are likely to be much less common than

Hib pneumonia. Second, some of the data needed for the first two worksheets may be unavailable. If necessary, regional data can be substituted for local data. If that is not possible, the second method using the under-five mortality rate may still be useful.

Worksheet #3 details the under-five mortality method. This method uses local data for under-five mortality as well as the proportion of childhood deaths due to acute respiratory illness (ARI). Two important data for this method, the percentage of ARI deaths which are due to Hib and the Hib pneumonia case fatality ratio (CFR), will not be available from local data. Suggested values are therefore given in the tool. Dr Feikin noted that in some places the under-five mortality method may give very different results than the meningitis incidence method. He asked the meeting participants to consider whether this was a significant problem.

Dr Feikin then asked for specific recommendations and comments on the methods used to estimate Hib disease burden.

He asked whether neonatal cases of meningitis or purulent CSF specimens from neonates (children under one month of age) should be included in the count of possible Hib meningitis cases. In the Young Infants Study (The Young Infants Study Group. Bacterial etiology of serious infections in young infants in developing countries: results of a multicenter study. *Pediatric Infectious Disease Journal* 1999;18:S17-22) very little Hib disease was seen in children under one month of age.

Dr Slack and Dr Levine agreed and noted that *H. influenzae* disease in neonates was almost always caused by unencapsulated (non-type b) strains which colonize the genitourinary tract. On this basis, the meeting participants agreed that neonatal meningitis cases should be excluded from the calculation of Hib meningitis incidence.

Dr Feikin then asked about the definition of purulent CSF. This is an important element because children often receive antibiotics before presenting to the hospital. Also, laboratories may not have the capacity to routinely isolate Hib. Both of these factors could lead to false negative culture results. In determining the definition of purulent CSF the tool does not use the white blood cell (WBC) differential count because this is often unavailable. The draft tool proposes that a WBC count of >=100 cells/ml be used as one criteria for purulent CSF. The data of Spanos et al. (Spanos A, Harrell FE, and Durack DT. Differential diagnosis of acute meningitis—an analysis of the predictive value of initial observations. *Journal of the American Medical Association* 1989;262:2700-7), suggest that a count of >100 WBC is a sensitive, but non-specific cut off. However, this study included adult patients as well as children, and bacterial meningitis is more likely in children. Therefore it is difficult to apply the Spanos data to this tool.

Dr Slack noted that pre-treatment with antibiotics can lower CSF WBC counts.

Dr Cherian noted that the Spanos data is from the United States, and would not include tuberculous meningitis which is an important problem in many developing countries. Several members of the group felt that the tool should take tuberculous meningitis into account.

Dr Klugman expressed the opinion that a WBC count of 100 was too high. He has often seen Hib meningitis with fewer than 100 WBC in the CSF. He suggested that it would be important to review the CSF characteristics of documented Hib meningitis.

Dr Feikin noted that this would be valuable for determining the sensitivity of a definition, but unless the CSF characteristics of documented viral and tuberculous meningitis were available, the specificity of any definition could not be determined.

Dr Steinhoff and Dr Wenger agreed that a cut off of 100 would exclude approximately 15% of Hib meningitis cases. Dr Wenger noted that lowering the cut off would capture more Hib cases but would also increase the number of false positives. He asked if it would be possible to adjust the model to account for other causes of meningitis with lower WBC counts.

Dr Steinhoff noted that it would be important to provide some discussion of the possible impacts and biases of the definition of "purulent" in the tool. Any definition will have trade-offs. It is important to pick a level that end users will find acceptable and then discuss the implications of that choice.

Dr Feikin presented data from Egypt where 17% of documented Hib meningitis cases had a CSF WBC count less than 100. Also, this cut off would exclude 75% of culture-negative cases.

Dr Levine observed that this seemed to be a conservative cut off when applied to the Egyptian data. He asked whether the tool should prefer sensitivity or specificity. It is important the results be credible and an overly sensitive definition may diminish the credibility of the results by making it look like the tool overestimates the burden of Hib disease.

Dr Measham responded that decision-makers are likely to be non-technical and would prefer a bias towards more specificity. Over-estimates of the disease burden would undermine the credibility of the tool.

Dr Klugman suggested that other factors such as protein and glucose levels be considered for specimens with WBC counts less than 100. This would increase the specificity of the definition for specimens in this category. He proposed that the definition of a purulent CSF specimen could be either 100 or more WBC or 10-99 WBC with either an elevated protein or low glucose. Currently the tool defines a specimen as purulent if either the protein or glucose is abnormal. This seems too loose. Abnormal protein or glucose values should not be used alone.

The group discussed the problem of missing data and Dr Levine noted that in some cases a description of CSF appearance would be available.

Dr Mulholland supported Dr Klugman's suggestion. He noted that the most important objective of the definition of purulent meningitis is to exclude viral meningitis which will vary from country to country and time to time. Tuberculous meningitis does occur in this age group, but it is usually a small percentage of cases.

Dr de Chabalier asked if different definitions should be used for children who had been pretreated, but it was agreed that this would add too much complexity to the model.

The group agreed with the following revised proposal for purulent CSF by Dr Klugman and suggested that it be tested with existing data sets:

- turbid appearance; or
- 100 or more WBC/ml; or
- 10–99 WBC/ml with both elevated protein (greater than 100 gm/dl) and low glucose (less than 40 mg/dl).

The discussion then moved to step number two in the first worksheet. The group agreed that this step should be dropped to simplify the tool because CSF analysis is much more common than blood culture in developing countries. Cases of positive blood culture with negative CSF findings are also rare.

The participants agreed with the current formulation of the remainder of worksheet #1. Dr Klugman observed that it would be important to carefully probe about how often lumbar puncture is not done in children with suspected meningitis.

Dr Feikin noted that the first important assumption in worksheet #2 is that data from the regions where the assessment is done can be applied to the whole country. Several members of the group observed that there are likely to be significant differences in Hib disease incidence within a country. Hib incidence can vary with socioeconomic status, rural or urban residence, access to health care, use of antibiotics, and other factors.

Dr Mansoor observed that because of this assumption it may be important to conduct the assessment in more than one place. The participants agreed that, despite the potential problems, this assumption is necessary.

Dr Feikin then asked for discussion about the Hib meningitis CFR. He noted that local data may be available. If it is not, the draft tool offers a range of 10–40%. How should users decide which value to use?

Dr Klugman observed that it would be important to use the CFR for Hib meningitis rather than the CFR for all bacterial meningitis because different pathogens are more likely to cause death.

Dr Mulholland noted that published studies or locally available data usually come from clinical centres where the care for Hib meningitis is likely to be the best available. Therefore, any available data may underestimate the true CFR.

Dr Levine observed that a key objective of the tool is to use as much local data as possible. If local data is available, it should be used, and the possible biases should be discussed in the presentation.

Dr Steinhoff suggested that the tool be updated with additional data on possible values for the Hib meningitis CFR. Then a discussion of how to choose a likely value and possible biases should be added.

Dr Feikin reviewed step 3 of worksheet #2 which estimates Hib pneumonia cases from Hib meningitis cases. This estimate is based on a ratio of Hib pneumonia cases to Hib meningitis cases (5:1) derived from vaccine trials in the Gambia and Chile and published in an article by Dr Mulholland (Mulholland K, Levine O, Nohynek H, and Greenwood BM. Evaluation of vaccines for the prevention of pneumonia in children in developing countries. *Epidemiological Review* 1999; 21:43-55).

Dr Diaz Ortega added that a similar ratio has been found in Mexico.

Dr Mulholland and Dr Steinhoff observed that this ratio is likely to vary in different places, and the concordance of the data from the studies to date may just be coincidence.

Dr Cherian noted that the ratio is also likely to be age-specific. The studies from the Gambia and Chile measured the ratio for children under two years of age, but the Rapid Assessment Tool looks at children under five years of age.

The group agreed that the ratio used in the tool is based on limited data that may not apply to all countries. However, it is the best data available. The limitations of the data should be discussed in the tool. Additional data may be available soon from a trial of Hib vaccine in Lombok.

Dr Feikin then asked about the Hib pneumonia CFR used in step 4 of worksheet #2. Data for this are difficult to find due to the difficulty in diagnosing Hib pneumonia. A review of published studies carried out by Dr Ben Schwartz, CDC, suggests a range of 5-20%. The community-based case management study by Bang et al. (Bang AT, Bang RA, Tale O, Sonpakke P, Solanki J, Wargantiwar R, and Kelzarkar P. Reduction in pneumonia mortality and total childhood mortality by means of community-based intervention trial in Gadohiroli, India. *Lancet* 1990;336:201-6) suggests 13%. This data is unlikely to be available locally.

Several participants noted that data from clinical settings would not be applicable to all cases in the community because children could die at home without treatment, and children who go to the hospital may not be representative of all children with Hib pneumonia. The group agreed that the tool should present a range of possible values since the available data are limited.

Dr Cherian asked if it would be possible to link Hib pneumonia CFR to childhood mortality rate.

Dr Mulholland noted that the age of the patient was important. Most pneumonia deaths are due to non-treatment and are more common in children under 12 months of age. The range of 5-20% represents ideal conditions and is likely to be an underestimate.

The group then considered worksheet #3. Dr Feikin asked which mortality rate should be used in the first step.

Dr Lau noted that neonates have been excluded from the meningitis incidence method, and, therefore, neonatal mortality should be excluded from this method to make the two consistent.

The group agreed that most deaths due to Hib occur under two years of age. There was also concern that detailed data on different mortality rates by age might not be available. Also, there is limited data on the percentage of mortality due to ARI in different age groups. The group agreed that the tool should eliminate neonatal mortality by subtracting the neonatal mortality rate from the under-five mortality rate.

Dr Feikin presented background information on the proportion of childhood death due to ARI (step 1B of worksheet #3). Garenne et al. (Garenne M, Ronsmans C, and Campbell H. The magnitude of mortality from acute respiratory infections in children under 5 years in developing countries. *World Health Statistics Quarterly* 1992; 45:180-191) reviewed a number of studies from different areas with different designs. His article suggests that the proportion of deaths due to ARI varies with the childhood mortality rate and ranges from 10–25%.

Dr Mulholland agreed that the data from the Garenne article have limitations.

Dr Klugman observed that the range of 10–25% may be conservative.

Dr Mansoor noted that local data is often available for the percentage of childhood mortality due to ARI from the national ARI programme.

The group concluded that local data should be used if possible, but if not, the 10–25% range, which varies with childhood mortality rate, could be substituted as a conservative estimate.

Dr Feikin then presented the derivation of the estimate of the proportion of ARI deaths due to Hib (step 1D of worksheet #3). In 1990 the WHO estimated that there were 12.9 million childhood deaths worldwide. Of these, approximately 4.3 million were due to ARI. Subtracting 1.55 million ARI deaths which occurred in neonates or were due to measles or pertussis leaves 2.75 million (64%) ARI deaths that are likely to be due to bacterial pneumonia. Using data from the Gambia and Chile, 20% of these deaths or 0.55 million deaths can be attributed to Hib ARI. By dividing 0.55 million by 4.3 million, estimate that 13% of all ARI deaths are due to Hib pneumonia is obtained.

Dr Mulholland recommended that this calculation be updated with more recent numbers.

Dr Mansoor noted that the data would need to be adjusted depending on whether neonatal mortality is included in the first step.

Several participants noted that the percentage of ARI deaths due to Hib is likely to vary from country to country. Places with high vaccination coverage might have a higher percentage as measles and pertussis deaths are decreased. Also, countries with good ARI case management programmes might have decreased the percentage.

Dr Wenger noted that the method used to estimate this percentage assumes that the percentage of pneumonia deaths due to Hib would be the same as the percentage of pneumonia cases due to Hib.

The group concluded that there is very little data available to help make this estimate. The number used should have an understandable derivation, even if based on limited data. At this time, the participants were not aware of any better approaches for deriving the estimate and recommended that this estimate continue to be used.

Dr Feikin then asked for discussion of step 2A in worksheet #3. This step uses an estimate of the Hib pneumonia CFR. He pointed out that this value is likely to have wide variation and could explain why the estimates of Hib meningitis burden have differed between the under-five mortality method and the meningitis incidence method. One alternative would be to only use the under-five mortality method to calculate pneumonia burden.

Dr Gessner noted that the Hib pneumonia CFR would vary based on many factors in a country. He suggested that each assumption in the method should be examined to determine which ones contribute the largest amount of possible variability. The group agreed with this suggestion.

Experience with the tool in the field

Tunisia (Dr Mohsnie)

In September of 1999, an assessment of Hib disease burden in Tunisia using the Rapid Assessment Tool was conducted at the request of the Ministry of Health. Field visits were made to Tunis and two other governorates. After a review of these sites, one governorate was chosen as the best site. This governorate had a single hospital that treats childhood meningitis cases, and it was unlikely that children from outside the governorate came to that hospital or that children from the governorate sought care elsewhere. Data on meningitis cases at this hospital for a 44-month period were reviewed.

Dr Mohsnie reviewed the tool worksheets showing the data used to estimate Hib disease burden. The Hib meningitis incidence rate calculated from worksheet #1 was 19.4 cases per 100 000 children under age five years. Worksheet #2 was used to estimate that there are 1164 cases of Hib meningitis and pneumonia and 76 deaths due to Hib each year in Tunisia. Worksheet #3 used local data for childhood mortality and the percentage of childhood deaths due to ARI. This led to an estimate of 2621 annual cases of Hib meningitis and pneumonia and 170 deaths due to Hib. Possible limitations of this assessment included the use of antibiotics before admission to the hospital, cases hospitalized outside the region, and use of Hib vaccine in the private sector. On the basis of the data from the rapid assessment, the Ministry of Health decided to implement population based surveillance to gather additional data. Other studies in large hospitals were set up to measure CFR and cost of hospitalization due to Hib disease.

Summary of the discussion following Dr Mohsnie's presentation:

Dr Klugman asked if there was a systematic bias which caused the under-five mortality method to overestimate the burden of Hib disease. He asked if the percentage of ARI deaths due to Hib might be incorrect. Perhaps it is not appropriate to assume that the proportion of pneumonia due to Hib is the same as the proportion of pneumonia deaths due to Hib.

Dr Levine asked if the difference between the two methods was significant. Perhaps a two-fold difference is acceptable.

Dr Mansoor observed that perhaps the meningitis method is an underestimate.

Dr Klugman replied that the two methods should be reassessed to determine if any systematic biases are responsible for the different results.

Oman (Dr Nelson)

Dr Nelson reported the experience using the Rapid Assessment Tool in Oman. Oman is a relatively wealthy country near the Persian Gulf. Several other Persian Gulf countries have already introduced Hib vaccine. Life expectancy in Oman is over 70 years, and the infant mortality rate is low (17 per 1000 live births). Oman has a routine surveillance system for meningitis, and 31 cases of Hib meningitis were reported in 1999. There were large differences in the incidence of Hib meningitis reported in different regions. The assessment team chose two regions with well-defined populations to visit, one of them specifically because it reported higher meningitis rates than other regions.

The main teaching hospital in the capital city was visited to gather information about health care services in Oman and to help increase awareness of Hib disease in the country. It was learned that many children receive antibiotics prior to hospitalization and that lumbar puncture is refused in about one third of cases due to parental fear of the procedure. Next, the selected regions were visited. One region is near the capital and it was felt that some children might go outside of the region for care. In both regions, blood cultures are done on all suspected cases and laboratory capacity is good.

Using the first worksheet, the region near the capital had an estimated Hib meningitis incidence of 23.5/100 000 children under age five, while the other region had an estimated rate of 41.2/100 000 children under age five. This second region was the one which consistently reported higher rates of meningitis to the routine surveillance system. The under-five mortality method gave results approximately 50% lower than those in the first region. All three estimates were higher than the incidence rate measured by routine surveillance (12.7/100 000 children under age five). The estimates calculated during this assessment were also higher than Hib meningitis rates reported from other countries in the region which range from 13–22/100 000 children under age five.

The team also did a simple cost-effectiveness analysis. They estimated that treatment of Hib disease in Oman cost between 300 000 and 530 000 rials per year. This compares favourably with the estimated 200 000 rials per year needed to implement Hib vaccination using pentavalent vaccine.

Summary of discussion following Dr Nelson's presentation:

Dr Klugman asked if there were reasons to believe that the higher rate found in one region was the best estimate.

Dr Nelson replied that some cases in the first region might have been treated in the capital city but another important consideration is that laboratory procedures were of a higher standard in the second region while other factors such as access to care, antibiotic use upon referral, and use of lumbar puncture to collect CSF seemed to be similar.

Dr Feikin noted that Oman is the only place where the under-five mortality rate has given a lower estimate than the meningitis incidence rate. Also, the differences between the two regions highlight the importance of doing the assessment in more than one place.

Dr Gessner suggested that the regional estimates, while different, could be accurate if access to antibiotics and socioeconomic status were different in the two regions.

The group also discussed the value of the tool in evaluating routine surveillance systems which often underestimate the true burden of disease.

Uganda (Dr Nelson)

Uganda is a relatively poor country in East Africa with a low life expectancy (45 years) and high infant mortality rate (97/1000 live births). Routine surveillance for meningitis is limited. The team decided to focus on sites with laboratories that had the capacity to isolate Hib. Two sites were identified. One was a mission hospital in a rural area with a well defined catchment population. The other was a mission hospital near the capital city with a poorly defined catchment population. The main teaching hospital in the capital Kampala was also visited. In both mission hospitals, laboratory services were not provided at all hours. The rural hospital routinely isolates Hib and had better laboratory capacity than the hospital near Kampala. Outpatient use of antibiotics was low in both areas.

The meningitis incidence method found an incidence rate of approximately 44/100 000 children under age five. This is similar to rates reported from other countries in the region. This translates to about 15 200 cases of Hib meningitis and pneumonia and 1400 deaths due to Hib each year. The under-five mortality rate method yielded an estimate of 16 800 cases of Hib disease and 3500 deaths due to Hib each year.

On the basis of this assessment, the Ministry of Health will gather additional information about Hib disease burden and the need for vaccination. This assessment has raised awareness of Hib disease in Uganda. The country needs time to consider how Hib relates to other pressing health priorities.

Summary of discussion following Dr Nelson's presentation:

Dr Wenger noted that the under-five mortality rate method provides an opportunity to use local data on mortality and causes of death.

Egypt (Dr Watt)

Egypt is a large country with a complex health care system. Communicable diseases such as meningitis are mainly treated at fever hospitals which are located throughout the country. However, other health care structures sometimes care for children with meningitis. During the visit it was found that university hospitals, which are outside the jurisdiction of the Ministry of Health and Population, often see cases. The complexity of the health care system made it difficult to gain access to some hospitals and to identify all possible sites that might see cases of paediatric meningitis.

Egypt has established a sentinel surveillance system for bacterial meningitis in several fever hospitals. These hospitals have the laboratory capacity to routinely isolate common bacteria that cause meningitis, including Hib. They also collect standardized clinical data on each case. Microbiology capacity outside of these sentinel hospitals is limited, and techniques are not used for the isolation of *H. influenzae*. Also, clinical information about cases seen outside the sentinel surveillance hospitals is limited because many hospitals do not store medical records that can be easily retrieved.

The team tried to base the selection of sites on the guidelines shown in Annex B of the tool. However, there were other important issues to consider. First, it was important to choose an area where the fever hospital participated in the sentinel surveillance system and had the capacity to identify Hib in CSF. Second, access to other hospitals which might see children with meningitis would be needed. The team chose Alexandria, a large city on the Mediterranean coast, as one site because a relationship had already been established with several hospitals in the area. The team suspected that cases of meningitis from the surrounding rural areas might come into the city for treatment. Data on the residence of meningitis cases would be important for this assessment.

The second choice was Mahala, a district of about a million persons in the Nile delta region. There are two large cities within 50 km of Mahala and cases from Mahala might seek care outside the district. The team felt that it would be possible to visit the major hospitals in the area to determine if this was a problem. Unfortunately, there were more hospitals in the nearby cities than initially realized, and gaining access to those hospitals was very difficult. Thus, the assessment in Mahala could not be completed.

In Alexandria there are two major hospitals that treat childhood meningitis, the fever hospital and a large university hospital. The team visited other hospitals which reported that they routinely referred meningitis cases out. However, it was not possible to visit all the hospitals in Alexandria, and cases of meningitis could have been missed. The large number of health care facilities was one limitation of doing the assessment in an urban centre. The fever hospital, as one of the sentinel sites, routinely isolated Hib. The university hospital did not use laboratory techniques to isolate Hib. Consequently, the definition of purulent CSF was very important for this assessment.

Using the data from Alexandria, the meningitis incidence method yielded an estimate of 15.8/100 000 for the incidence of Hib meningitis in children under age five. This is similar to other countries in the EMR region.

Summary of the discussion following Dr Watt's presentation:

Dr Wenger suggested that the under-five mortality method might be more useful for calculating Hib pneumonia burden than Hib meningitis burden. The under-five mortality method is important because it makes use of local data that countries are familiar with, such as the under-five mortality rate.

Dr Mulholland observed that the meningitis incidence method uses data from the health care system. This might be appropriate for countries like Oman where the health infrastructure is good. On the other hand, the under-five mortality method uses broader national data which might be more appropriate for a country like Uganda where many children may not present to the health care system.

Dr Feikin pointed out that the two methods rely on many assumptions to estimate the burden of Hib pneumonia. This is unavoidable because Hib pneumonia is so difficult to diagnose. It may be appropriate to have a range of estimates for Hib pneumonia burden. On the other hand, Hib meningitis is easier to diagnose. Relying more on the estimate of Hib meningitis disease burden derived from the meningitis incidence method may be appropriate.

Dr Klugman asked why the under-five mortality method gives consistently higher estimates of Hib meningitis burden.

Dr Levine replied that the assumptions used in step 1 of worksheet #3 are the main differences in the methods.

The group agreed that the under-five mortality method should mainly be used to provide a second estimate of the Hib pneumonia disease burden.

Dr Levine pointed out that there may still be a large difference in the two estimates.

Dr Nelson noted that both methods could be used, and that the persons doing the assessment would have to evaluate the potential errors in deciding how to interpret the data.

Several members of the group noted that in some areas, particularly those with better health care systems, the meningitis incidence method might be more reliable, while in other areas the under-five mortality method might be more reliable. Also, in some countries with limited local data, the under-five mortality method may be the only method possible.

Dr Levine pointed out that the quantitative estimates of disease burden are only part of the reason for conducting rapid assessments using the tool. The process of being in the country and looking for Hib disease is also important to increase awareness of Hib disease and assess current laboratory capacity to isolate Hib.

Dr Otten agreed. He noted that several studies have shown high rates of Hib meningitis in Africa, yet few countries have asked for Hib vaccine funding from the Global Fund for Children's Vaccines. There is a need to increase awareness of Hib disease in many countries. The process of the assessment may be more important than the numerical estimates, especially since regional data already exist showing a high disease burden.

Dr Mansoor observed that the purpose of the tool is to help countries make a decision about Hib vaccine. He observed that because the tool requires local knowledge of health service utilization patterns and laboratory practices the assessment activity should be undertaken together with experienced regional consultants and MOH personnel.

Dr Cherian added that the process of using the tool could help countries evaluate their surveillance systems. In Asia, these systems often show low rates of Hib meningitis even though Hib is found to be a leading cause of meningitis in hospital series.

Dr Measham noted that the tool is designed to give a rapid and rough estimate. It is most important as a way of increasing awareness of Hib disease and advocacy for vaccination. As such, some imprecision of the results is acceptable.

Dr Mulholland expressed the concern that countries using the tool may not be able to interpret the estimates from the tool appropriately. They could forget that the results are rough. It is important to emphasize the limitations of the tool.

Dr Wenger replied that it is possible to present the tool such that people interpret the results appropriately. This tool is valuable because it gives countries the opportunity to begin looking at Hib disease in a rapid, low cost way.

Dr Lau agreed that the tool is important and that the process of using it can sensitize public health officials to the importance of Hib.

Several other participants voiced agreement with Drs Lau and Wenger.

Presentations from meeting participants

Laboratory issues (Dr Mary Slack)

Dr Slack noted that the tool can also be used to help assess laboratory capacity in countries where it is used. This will be important for monitoring vaccine effectiveness if the vaccine is introduced. An annex on appropriate laboratory technique should be included in the tool. It should include the following points:

- Ideally, CSF should be examined immediately.
- CSF should be rapidly transported to the laboratory under suitable conditions. It should be kept at body temperature.
- CSF should be plated immediately onto a suitable solid medium. Transport medium can be used if immediate plating is not possible.
- Chocolate agar made with human blood is not a suitable medium. Horse or sheep blood will give much better results. Ideally the chocolate agar should be supplemented with V Factor (NAD).
- Quality control checks of the media used should be routinely performed to confirm the ability of the batch to support the growth of *H. influenzae*.
- Control strain of *H. influenzae* should be available in the laboratory.
- The culture plates should be incubated at 35–37°C in 5% CO2 (this can be a candle jar).
- Any colonies resembling *H. influenzae* should be confirmed by Gram stain and by demonstrating growth around an XV Factor disc (but not X Factor or V Factor alone) placed on the surface of a nutritionally deficient medium (Tryptic soy agar, Columbia agar).
- Any *H. influenzae* isolates should be serotyped to confirm that they are Hib.
- Latex kits will detect Hib but they will not identify other capsular serotypes or non-capsulated strains (none of which are vaccine-preventable).
- Any strains of *H. influenzae* should be stored. For the short term chocolate agar slants can be used. For the long term they can be stored at –70°C of by lyophilisation.
- If there is a reference laboratory in the country the strains could be sent there for confirmation.
- Proficiency tests of the laboratory's ability to isolate and identify Hib is an ideal to aim for in the future.

Summary of the discussion following Dr Slack's presentation:

Dr Steinhoff noted that two important questions in assessing laboratory capacity are whether the lab has a reference strain and whether they have ever isolated Hib.

Dr Adegbola noted that the team would need to include someone comfortable with laboratory procedures to do a full assessment of the laboratory techniques.

Hib Disease in Dhaka, Bangladesh (Dr Saha)

Dr Saha briefly presented data on Hib disease in Bangladesh. He has found that children frequently use antibiotics prior to presentation at the hospital. Only 4.5% of Hib meningitis cases had a CSF WBC count less than 100. In Dhaka, the Hib meningitis CFR was 23% and 34% of cases had sequelae.

A Proposal to train local health officials to use the Rapid Assessment Tool (Dr Otten)

Dr Otten expressed surprise that so few countries have requested funding for Hib vaccine from the Global Fund for Children's Vaccines. There is a need to quickly increase the awareness of Hib vaccine in countries that are eligible for funding. He proposed a plan to quickly reach a large number of countries and train regional consultants. EPI staff in the AFRO region could be trained during the subregional WHO EPI staff meetings and during the national EPI managers meetings. The training should include a didactic explanation of the tool as well as a field exercise in a local hospital and laboratory. Regional consultants could then be identified and receive further training during national assessments. After some time, a regional debriefing could be held to review results.

Efforts are already under way to develop a regional network of bacterial meningitis laboratories. Training is planned for the second quarter of 2001 so that each country will have a laboratory capable of isolating Hib.

Summary of the discussion following Dr Otten's presentation:

Dr Levine noted that EPI managers are key participants in these rapid assessments. Other important people include those involved in special studies in the country, meningitis control personnel, and academic physicians. Dr Levine also noted that sometimes it is valuable to have a consultant present because the presence of a short-term consultant requires local counterparts to focus on the issues in a way that does not happen otherwise.

Can cost-effectiveness be estimated from a rapid assessment?

Ms Ulla Kou began by noting that cost-effectiveness is very important to countries considering Hib vaccination. She presented the data needed for a cost effectiveness analysis. These include:

- The number of cases of disease due to Hib
- The number of deaths due to Hib
- The costs of introducing the vaccine
- The cost of treating adverse events due to vaccination
- The treatment costs for disease due to Hib
- The treatment costs of sequelae of Hib infection

The annual cost of vaccination can be calculated using the following equation:

Cost = V x B x D x (1/(1-W)) x (1/(1–R)) where:

V = coverage rate

B = birth cohort

D = no. of doses per child

W = wastage rate (in per cent)

R = reserve stock (in per cent)

There may also be initial costs for training, updating materials and social marketing. If a monovalent vaccine is being produced capital improvements to expand transport systems, cold chain equipment and storage areas may be necessary. There may also be increased recurrent costs for syringes, waste disposal, additional personnel, surveillance systems, training and maintenance.

The cost of hospitalization includes the overhead cost (the cost per bed-day) plus costs specific to Hib disease such as laboratory testing, X-ray, medications, and intensive care. Outpatient costs include overhead plus medication costs. Treatment costs of Hib disease can be difficult to estimate rapidly. The cost of sequellae would be very difficult to estimate rapidly, and methods used in developed countries would not be appropriate for developing countries.

Ms Kou felt that treatment costs for Hib disease would be difficult to estimate rapidly. On the other hand, the cost of introducing the vaccine could be estimated during a rapid assessment visit.

Summary of the discussion following Ms Kou's presentation:

Dr Levine commented that a rapid assessment visit might not be well suited for gathering cost-effectiveness data. The agenda for the visit is full even without discussing costs. More generic data on the cost-effectiveness of vaccines, including Hib vaccine, are available and may be sufficient for many countries.

Dr Feikin observed that when treatment costs for Hib disease are high the vaccine may be cost saving. In settings where health care costs are lower, the vaccine may appear to be costly when looking at direct medical costs alone. However, focusing only on direct medical costs will not capture all the benefits of vaccination and may make vaccination appear less valuable than it really is.

Dr Klugman felt that it would be important to deal with cost in some way. Data on the burden of disease would be insufficient on its own.

Dr Measham asked if the cost-effectiveness of Hib vaccination should be compared to the cost-effectiveness of other interventions.

Ms Kou replied that the cost per death averted is a measure which can be used to compare different interventions.

Dr Steinhoff added that some limited data collection about cost may be feasible in the context of a rapid assessment of disease burden.

Recommendations and plan for action

In an open discussion, the participants reviewed some of the topics discussed during the meeting and summarized their recommendations:

- Neonatal cases should be excluded from counts of possible Hib meningitis.
- The definition of purulent CSF should be reviewed. Additional data sets showing the CSF values present in Hib meningitis and bacterial meningitis should be examined to determine the impact of different definitions.
- Whenever possible, local data for Hib meningitis CFR should be used. Table 2 in the tool should be expanded to include additional data on Hib meningitis CFR.
- The tool should include a discussion of the limitations of the available data on the ratio of Hib pneumonia to Hib meningitis cases. Countries with higher rates of ARI may have a higher ratio, while countries with lower ARI rates may have a lower ratio. Acknowledging the limitations, the ratio of 5:1 can be used in the estimation of Hib disease burden.
- Because data are limited, the range of values for Hib pneumonia CFR is appropriate. The Hib pneumonia CFR is likely to vary widely between countries and within countries. Access to care may be a key factor in determining Hib pneumonia CFR.
- The under-five mortality method is useful, but it may give results which are very different from the meningitis incidence method. The results should be interpreted in light of the limitations inherent in this method.
- The mortality rate used in the under-five mortality method should be re-evaluated. Neonatal mortality should be excluded from the calculation of Hib pneumonia deaths. The infant mortality rate, excluding neonatal mortality, should be considered as an alternative.
- Local data on the proportion of childhood deaths due to ARI should be used if available and if consistent with the expected range listed in the tool.
- There is limited data on the proportion of ARI deaths due to Hib. The value listed in the tool (13%) is reasonable.
- Whenever possible, more than one area in a country should be assessed to increase the reliability of the results and address possible regional differences within a country.
- The tool should be validated in an area with population-based surveillance.

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Annex 2: Agenda

Day 1 Thursday 19 October 2000

12:30 – 13:00	Registration
13:00 – 13:15	Opening session • Welcoming comments (Maureen Birmingham, WHO) • Nomination of Chair (Mark Steinhoff, JHU) and Rapporteur (James Watt, CDC)
13:15 – 13:30	Review of meeting objectives and expected outcomes (Chris Nelson, WHO)
13:30 – 15:00	The importance of disease burden data in the process of vaccine introduction and sustaining vaccine programmes • The process of new vaccine adoption: Problems, solutions, and politics (Jay Wenger, WHO) • The importance of local data in the process of arriving at disease burden estimates (Ezzedine Mohsnie, EMRO) • World Bank perspective on the need for disease burden estimates (Tony Measham, World Bank) • How various efforts to estimate disease burden can complement each other (Orin Levine, NIH)
15:00 – 15:30	*Coffee break*
15:30 – 15:50	Introduction to the Rapid Assessment Tool (Chris Nelson, WHO)
15:50 – 17:30	Technical bases for estimating Hib disease burden (Danny Feikin, CDC).
17:30	Close

Day 2 Friday 20 October 2000

09:00 – 10:30	Technical bases for estimating HIB disease burden (continued, Danny Feikin, CDC).
10:30 – 11:00	*Coffee break*
11:00 – 12:00	Performance in the field: experience with the tool in:
	• Tunisia (Ezzadine Mohsni, EMRO)
	• Oman (Chris Nelson, WHO)
	• Uganda (Chris Nelson, WHO)
	• Egypt (James Watt, CDC)
11:30 – 12:45	Discussion
12:45 – 13:45	*Lunch break*
13:34 – 15:00	Laboratory Issues
	• Lab methods for culturing HI (Mary Slack, PHLS Haemophilus Reference Unit)
	• Report from Dhaka Shishu Hospital (Samir Saha, Bangladesh Institute of Child Health)
14:00 – 15:00	Building a regional Hib surveillance system (Mac Otten, AFRO)
14:00 – 15:00	Assessing the cost-effectiveness of a Hib vaccine programme (Ulla Kou, WHO)
15:30 – 16:00	*Coffee break*
16:00 – 17:00	Plan for action – recommendations and future directions
17:00	Close