The Effectiveness and Use of the Rapid Assessment Tool to Estimate the Incidence Rate and Disease Burden of *Haemophilus influenzae* Type b (Hib) in Developing Countries; A Review of Available Data

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August 4, 2004

A writing project submitted in partial fulfillment
of the requirements for the degree

Master of Science in Statistics

APPROVAL

of a writing project submitted by

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This writing project has been read by the writing project director and has been found to be satisfactory regarding content, English usage, format, citations, bibliographic style, and consistency, and is ready for submission to the Statistics Faculty.

8/4/04

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INTRODUCTION

In developing countries, the majority of deaths due to bacterial meningitis and bacterial pneumonia can be attributed to *Haemophilus influenzae* type b (Hib). In fact, this organism is the leading cause of bacterial pneumonia deaths in children under the age of 5. In the US, the rates of Hib disease have been reduced >95% because of the introduction of the Hib vaccine. The incidence rate in the US for Hib in the time span from 1980-1990 was 40-100/100,000 children under the age of 5. Following introduction of the first conjugated polysaccharide Hib vaccine in the US, the incidence rate has fallen to 1.3/100,000 children. However, Hib disease is still a problem in developing countries, where Hib remains the leading cause of lower respiratory tract infections in infants and children (3). It is estimated that 350,000 – 700,000 children worldwide die each year of Hib related diseases (2). Some of these deaths could be prevented through the use of the Hib vaccine.

However, introducing the Hib vaccine to developing countries has been problematic. Three major difficulties in introducing the Hib vaccine to developing countries are cost, limited awareness of the impact of *Haemophilus influenzae* disease, and questions regarding the vaccine's efficacy against Hib pneumonia. The Hib vaccine costs approximately $2.50 US per dose, so most developing countries would need outside funding in order to acquire the vaccine (1). Organizations such as GAVI (The Global Alliance for Vaccines and Immunizations) will provide financial resources to developing countries for the purchase of vaccines. UNICEF is also involved in getting affordable vaccination programs established in developing countries. Still, these countries do not apply for aid because they are not aware of the impact Hib disease makes on their

country. In the past, questions were raised about the efficacy of the vaccine against Hib pneumonia. In developed countries, Hib infections were primarily meningitis, while in developing countries the incidence of Hib pneumonia is much higher than it was in developed countries.

Other issues plague developing countries in the fight against Hib disease. It is very difficult to diagnose Hib disease without appropriate lab supplies and necessary procedures. The two most common diseases attributable to Hib are meningitis and pneumonia. Symptoms of these diseases can be caused by other infectious organisms and so misdiagnosis often occurs. To diagnose Hib meningitis a lumbar puncture is required. Cerebral spinal fluid (CSF) obtained from the lumbar puncture must be processed quickly in order to isolate Hib. Culturing Hib requires blood agar and CO_2 chambers, which are not always available in hospitals and laboratories in developing countries. In these conditions, human blood is often used, leading to false results. In addition, lumbar punctures are not always performed on suspected Hib meningitis patients due to fear of the complex procedure.

Without these procedures, misdiagnosis or improper treatment can occur leading to low numbers of reported Hib cases. To definitively diagnose Hib pneumonia, blood is drawn and cultured for Hib. Although the specificity of blood cultures is high for Hib, the sensitivity is low (20%) (1). Specificity is the true positive rate and sensitivity is the true negative rate. Low sensitivity indicates that you may get many false negatives. In some cases antibiotics are given before diagnosis, thus leading to false laboratory results and, again, low numbers of reported Hib cases.

One of the World Health Organization's (WHO) aims is to bring awareness of Hib disease to developing countries (8). Their hope is that if these countries understand the burden Hib disease places on their country, they will introduce the Hib vaccine, thus saving lives. Current data shows the prevalence of Hib in developing countries and, therefore, supports the need for the vaccine. In 1993, a randomized trial of the Hib conjugate vaccine was conducted in The Gambia. This trial did show that the Hib vaccine provided protection not only against Hib meningitis but also against Hib pneumonia. The incidence rate per 100,000 from July 1990 – June 1993 in The Gambia was 215 (95% CI 178-258) and dropped to 21 (95% CI 7-48) from May 1998 – April 1999 following introduction of the Hib vaccine (6).

However, before introducing vaccines, most countries want local data. Vaccination trials are time-consuming and expensive, and many ethical concerns must be considered when conducting a trial. Some of these ethical concerns surfaced during the Gambian trial. The investigators wanted to use control groups, but when a vaccine has already been shown that it is efficacious, to withhold the vaccine from one group is not ethical. The Hib vaccine had already been shown to be efficacious against Hib meningitis in developed countries but not for Hib pneumonia; therefore, it was decided that using control groups would be acceptable. Another consideration concerning the Gambian trial was that the Hib vaccine would always be beyond the financial scope of developing countries so instigating the trial may hold no future benefit on the community. Because the results of this study were positive, The Gambia has introduced the Hib vaccine as part of their immunization program. UNICEF and Pasteur Merieux Connaught have made the Hib vaccine available to The Gambia. In addition, based on

the positive results of this trial, the WHO began to promote the use of the Hib vaccine worldwide, if the disease burden of a country substantiates its use (7). Therefore, in 2001, WHO developed a Hib Rapid Assessment Tool (RAT) to help investigators to estimate the Hib incidence rate and the number of cases and deaths per year attributed to Hib disease (2). Using the incidence rate, the Hib disease burden on the country can be assessed. One benefit of the RAT is it can typically be completed in 7 to 10 days where a vaccination trial may take years.

The purpose of this paper is to evaluate the WHO RAT and review the statistical analyses of two studies, covering different countries in the Pacific Island region. First, the methodology used by the RAT to calculate an estimate of the incidence rate and disease burden will be presented. Then, estimates calculated by Russell, et.al., using the WHO RAT, from four Pacific Island Countries will be reviewed (4). Finally, the RAT methods will be used to calculate estimates of the incidence rate and disease burden from raw data obtained from a study in Fiji (5).

ESTIMATION METHODS (2)

As presented in the WHO publication (2), the RAT uses two methods to calculate an estimate of Hib disease burden on a nation. Method #1 starts with a local estimate of Hib meningitis incidence rate and Method #2 starts with the country's under-5 mortality rate. The under-5 mortality rate is the number of children per 1000 live births who die before their fifth birthday. The WHO developed three Worksheets to be used to estimate the disease burden. The first two Worksheets are used for Method #1 and the third Worksheet is used for Method #2.

Method #1 – The Incidence Rate Method

Method #1 is referred to as the incidence rate method. In Worksheet 1, the Hib meningitis incidence rate is calculated. The incidence rate is used to calculate the national Hib disease burden in Worksheet 2 and also can be used for comparison with other nations. Examples of Worksheets 1 and 2 can be found in Appendix D and Appendix E, respectively.

To estimate the incidence rate, all the new cases of Hib meningitis that occur in children less than 5 years old who live in a certain area during a specific time is divided by the number of children under-5 living in the same area during the same time multiplied by a base of 100,000 individuals. That is,

$$\text{Hib Incidence rate} = \frac{\#\text{ new cases of Hib men. in children <5 yrs. in area during time period}}{\#\text{ children <5 yrs. in area during time period}} \times 100{,}000\,.$$

First the investigator must choose an area to sample. The WHO provides a checklist for "guiding the selection of a region for the accurate assessment of Hib meningitis incidence using local data" (2). Guidelines for a specific population and area, for use in the study, are defined, in addition to specific criteria for selection of a hospital that has laboratory services sufficient to differentially diagnose Hib. As discussed in the introduction, such laboratory facilities are scarce in developing countries. The complete guidelines provided by the WHO can be found in Appendix A. In the WHO publication it states that, "Only patients that meet all criteria should be included in the numerator of the incidence rate." (2).

In estimating the denominator of the Hib incidence rate, it is necessary to determine the population that patronizes the hospital and to determine the number of children under-5 years of age in this population. The residence of each case of Hib at that

hospital needs to be determined. Only patients that live in the defined area surrounding the hospital should be included in the numerator of the estimate. In the WHO publication, Estimating the local burden of *Haemophilus influenzae* type b (Hib) disease preventable by vaccination: A rapid assessment tool, (2) the ideal setting is described as, "An ideal setting would be a relatively isolated region with well-defined borders in which all children with potential meningitis would be brought to a small number (no more than three) of regional hospitals and where few children die at home without first obtaining treatment at a hospital. These hospitals should routinely obtain cerebrospinal fluid from patients with suspected meningitis and have the clinical and laboratory capabilities to determine the major causes of meningitis, including Hib. Because of potential variations in different parts of a country, two such areas should be selected for study, if possible."

After the defined area is chosen, Worksheet 1 is used to help identify the number of cases of meningitis and estimate the incidence rate. Because of limited laboratory supplies and lack of lumbar punctures, adjustments are made in Worksheet 1 to give a better estimate of meningitis incidence.

Worksheet 2 is used to estimate the national burden of Hib disease using the estimate obtained in Worksheet 1. The data needed for these calculations is defined by WHO in, Estimating the local burden of *Haemophilus influenzae* type b (Hib) disease preventable by vaccination: A rapid assessment tool,(2). This list, including referenced Tables, is included as Appendix B.

Method #2 – The Under-5 mortality rate method

Method #2 is referred to as the under-5 mortality rate method. To estimate the national burden of Hib disease from the under-5 mortality rate and the proportion of under-5 deaths attributable to Hib pneumonia, Worksheet 3 is used. The WHO provides a list of definitions for the data inputs for Worksheet 3, included as Appendix C. An example of Worksheet 3 is given as Appendix F.

Problems associated with the RAT.

Using the two methods described above would yield two estimates of the national burden of Hib disease in children under the age of 5. The WHO warns that these estimates may differ making it important to realize that each method has strengths and limitations. The incidence rate method (Method #1) will provide a rather accurate estimate of the Hib meningitis burden if the Hib meningitis incidence rate can be estimated using local data. Using both methods will provide a range of estimates for the true national burden of Hib disease. To ensure the RAT is providing reasonable estimates, local estimates can be compared to those from other countries within the same region with similar health status. The WHO warns that local estimates should not deviate from others in the same region by more than 20% (2).

As with any statistical tool, there are biases associated with data collection that could influence the estimate of disease burden. Undercounting the number of deaths of children in rural areas can lead to a lower under-5 mortality ratio than is accurate for the country. Often lumbar punctures were done on only the sickest patients, causing the Hib meningitis case fatality rate to possibly be overestimated (2).

USING THE TOOL IN THE FIELD

Pacific Island Countries Study (4)

Several groups have used the WHO RAT to estimate the Hib disease burden in developing countries. In 2003, nine of 20 Pacific Island Countries were not including the Hib vaccine in their national immunization program. F.M Russell and colleagues used the WHO RAT to estimate the disease burden in these countries to provide information for making decisions about introduction of the Hib vaccine (4). The investigators chose four sites to visit based on Medline literature searches and reports and publications from each of the 9 Pacific Island Countries.

In this study, the majority of the laboratories in the countries visited could not type *Haemophilus influenzae*, so 95% of Hi isolates were assumed to be type b. The investigators followed the RAT guidelines and used both methods to estimate Hib disease burden. As is the case in many developing countries, microbiological laboratories in these Pacific Island Countries did not use appropriate media and procedures to culture Hib. Expired human blood was used to make plates for culturing CSF samples and for subculturing positive blood cultures. In addition, lumbar punctures were not always done. Rates for lumbar punctures were 50% for patients in Kiribati, 90% for patients in the Solomon Islands, 69% for patients in Samoa, and 81% for patients in Tonga (4). The Hib RAT does adjust for the potentially missed patients by estimating the percent of cases where Hib was positively identified out of all purulent CSF samples.

The following two tables are excerpts from the Russell et.al. publication to provide the estimates calculated by the authors using the RAT (4). They are referred to as Table 2 and Table 3 as indicated in the figure descriptions. Table 2 gives the estimated

annual incidence of Hib meningitis in children under the age of 5 for Pacific Island Countries using Method #1. Overall the annual incidence rate of Hib meningitis per 100,000 is similar for all four Pacific Island Countries. Only one case of Hib was reported for Kiribati during this surveillance period, so estimates may not be accurate for Kiribati. The estimates for the other three Pacific Island Countries vary from 70 - 84 cases per 100,000 children < 5 years old.

Table 2. Estimation of the annual incidence of *Haemophilus influenzae* type b (Hib) meningitis in children aged <5 years in 4 Pacific island countries, using the Hib Rapid Assessment Tool (RAT) meningitis incidence method.

Variable	Kiribati	Solomon Islands	Samoa	Tonga
Period of surveillance, months	15	24	36	31
Purulent CSF specimens obtained from children aged <5 years, no.				
All	3	63[a]	75	21
With Hi identified as bacterial pathogen	1	17[b]	13	9[c]
With Hi considered likely pathogen[d]	2	34	19.1	4.6
LP performed,[e] estimated % of children with clinical meningitis	50	90	69	81
Hi meningitis cases,[f] no. per year	4.6	21.6	14.7	8.5[g]
Population of children aged <5 years in catchment area	6955	26,709	17,578	9716
Estimated annual incidence rate of Hib meningitis, cases per 100,000 children aged <5 years	66	84	84	70

NOTE. Hi, *Haemophilus influenzae*; LP, lumbar puncture.

[a] Hi was isolated from 1 nonpurulent CSF specimen obtained from a child <5 years old in the Solomon Islands.

[b] Fourteen of the purulent CSF samples obtained were Hi culture-positive, and 3 of the purulent CSF samples obtained were gram-stain positive for gram-negative bacilli but were culture-negative. All infants from whom samples were obtained were >3 months old.

[c] Seven of these patients had purulent CSF samples and were culture-positive for Hi, and 2 of these patients had purulent but sterile CSF samples and Hi-positive blood cultures.

[d] Number of samples in which no bacterial pathogen was identified but for which Hi is the likely pathogen. These estimates assume that the proportion of culture-negative, purulent CSF samples in which Hi is the likely pathogen is the same as the proportion of culture-positive, purulent CSF samples in which Hi is the likely pathogen.

[e] Estimated according to the number of patients with clinical cases of meningitis who had LPs performed, as documented in either laboratory records or medical records, over the designated period of surveillance.

[f] Calculated estimate based on the annual number of cases of Hi meningitis for which an LP was performed, divided by the estimated proportion of meningitis cases in which an LP is performed. This number assumes that 95% of Hi isolates are Hib (except in Kiribati, where the only Hi isolate was typed as Hib).

[g] Seven of 9 patients with proven Hi meningitis had positive blood cultures. Therefore, if Y represents the number of Hi meningitis cases in children who had clinical meningitis and no LP, then $Y \times 7/9 = 4$, and $Y = 5.1$. Therefore, the annual number of cases of Hi meningitis is determined as follows: $5.1/2.6 = 2$. Note that this is not the standard step in the Hib RAT, which instead assumes that the rate of meningitis in the 19% of patients who did not receive an LP is the same as in the 81% of patients who did.

Table 3 gives the estimated burden of Hib disease for the Pacific Island Countries using Method #2, excluding Kiribati. The estimates using Method #2 were substantially lower than those derived with Method #1. To investigate why these estimates differed so much, the authors performed a sensitivity analysis using both of the RAT methods but using a ratio of Hib pneumonia to meningitis of 1:1 instead of the ratio estimated by the WHO of 5:1 (4). The 5:1 ratio is based on Hib vaccine trials in The Gambia and Chile. In developed countries, the ratio would be closer to 1:1 or even less than 1:1. Tonga has a lower mortality rate for children <5 years old (15.5 deaths per 1000 births) and this

could account for a lower ratio of Hib pneumonia to meningitis. Because The Solomon Islands and Samoa have higher mortality rates for children <5 years old, a higher Hib pneumonia to Hib meningitis ratio is appropriate. In Tonga when the more conservative ratio of 1:1 was used, the Hib meningitis estimate was 69 cases per 100,000 children less than 5 years old using Method #2. This estimate is much closer to the incidence rate calculated with Method #1 (70 cases per 100,000) (4).

Table 3. Estimation of the burden of Hib disease in 3 Pacific island countries using the *Haemophilus influenzae* type b (Hib) Rapid Assessment Tool (RAT) under-5 mortality rate method.

Variable	Solomon Islands	Samoa	Tonga
Annual live births, no.	13,513	4602	2561
Under-5 mortality rate[a]	43[b]	25[b]	9.7
Deaths due to ALRI,[c] % of childhood deaths	20	20	15
Deaths among children aged <5 years, no. per year			
Due to ALRI	116	23	3.8
Due to Hib pneumonia[d]	15	3	0.5
Hib pneumonia cases among children aged <5 years,[e] no. per year	150	59	10
Hib meningitis case fatality rate[f], % cases	10	14	10
Hib meningitis cases among children aged <5 years,[g] no. per year	30	12	2
Hib meningitis deaths among children aged <5 years, no. per year	3	2	0.2
Annual incidence of Hib meningitis, cases per 100,000 children aged < 5 years	47	49	14

NOTE. The under-5 mortality rate method could not be used for Kiribati because no mortality rate data on children aged <5 years or on neonates were available for that country. ALRI, acute lower respiratory infection.

[a] The number of deaths among children aged <5 years, excluding neonates, per 1000 live births.

[b] No neonatal mortality rate was available. It was estimated to be one-half the infant mortality rate (which was 66 per 1000 live births in the Solomon Islands and 25 per 1000 live births in Samoa).

[c] This is not based on local data and reflects the under-5 mortality rate. This is estimated from the proportion of deaths due to ALRI [11].

[d] It is assumed that 13% of all ALRI deaths in children aged <5 years were due to Hib. This is not based on local data but based on a review of the literature by the developers of the RAT [11].

[e] The Hib pneumonia case fatality rate is not based on local data and reflects the under-5 mortality rate. This is estimated from the proportion of deaths due to ALRI and the proportion of these deaths which may be due to Hib [11]. This is estimated to be 5% for Samoa and Tonga, and 10% for Solomon Islands.

[f] The Hib meningitis case fatality rate of 10% for the Solomon Islands and Tonga and 14% for Samoa was calculated from Ministry of Health and pediatric discharge data.

[g] Calculated using the Hib pneumonia/Hib meningitis ratio of 5:1.

The estimates calculated using the methods from the WHO RAT were consistent with data from other studies in the Pacific Island Countries. The conclusion of the investigators is that, "The Hib RAT provides a quick, simple, and relatively reliable method to estimate the true burden of Hib disease in those developing countries where existing surveillance and laboratory data are of reasonable quality."(4)

Fiji Study (5)

The Fiji study differed from the other Pacific Island Countries study because Fiji had already introduced the Hib vaccine at the time of the study. The main goal of this study was to show that introduction of the vaccine had indeed caused a reduction in the incidence rate, using the WHO RAT. The hope was that other countries in the region could use the results to assist them in making informed decisions regarding the introduction of the Hib vaccine into their national immunization program. Fiji was an ideal place for the study because it had adequate microbiology laboratories, which are necessary for the culturing of Hib, and it also collects hospitalization and mortality data that were used in this study to provide another estimate to compare with those obtained using the RAT.

Data were collected from both pre- and post-vaccine periods. The pre-vaccine years were 1992 and 1993, and the post-vaccine year chosen was 1999. The culture confirmed *Haemophilus influenzae* meningitis incidence for pre-vaccine years was 19 per 100,000 children under-5 years of age (5). The annual incidence rate for pre-vaccine years of Hib meningitis per 100,000 children under 5 years of age from Worksheet 1 using Method #1 was estimated at 84.4309 (assuming 95% of Hi is Hib) based on adjustment for missing cases (Worksheet 1, Appendix D). Using the Hib meningitis incidence rate method, the RAT estimated the local burden of Hib disease as 476 cases and 36 deaths per year (Worksheet 2, Appendix E).

In comparison, using the under-5 mortality rate method, the RAT estimated the local burden of Hib disease as 70 cases and 5.25 deaths per year (Worksheet 3, Appendix F). The estimate for the number of cases from Method #1 is nearly 7 times higher than

that from Method #2. As mentioned above, the 5:1 ratio of cases of pneumonia to meningitis is based on the Gambian study and may not be accurate for all developing countries. If a more conservative estimate of a ratio of 1:1 is used, the estimates from both methods are similar. The incidence rate method estimated the local burden of Hib disease as 159 cases and 12 deaths per year (Worksheet 2, appendix G), and the under-5 mortality rate method estimated the local burden of Hib disease as 116 cases and 9 deaths (Worksheet 3, appendix H). The estimated incidence rate for Fiji (84 per 100,000) is similar to those found by the WHO RAT in the other Pacific Island Countries mentioned above.

The investigators did not use the RAT to calculate estimates for the post-vaccine period. To show that the Hib vaccine was effective, they instead compared the number of hospitalizations due to meningitis and pneumonia attributed to *Haemophilus influenzae* from the pre-vaccine period and the post-vaccine period. They did see a statistically significant decline in hospitalization due to meningitis from 1991 to 1999 but not in hospitalization due to pneumonia. The under-5 incidence rate ratio for pre-vaccine to post-vaccine was 0.68 (95% CI 0.52-0.89) (5).

The investigators used the decline in meningitis hospitalizations to estimate the pre-vaccine Hib burden, assuming that the decline is completely attributable to the Hib vaccine. The incidence rate declined from 131 cases in 1991-1993 to 86 cases in 1999 showing that the burden was 45 cases per year. The investigators showed that the actual pre-vaccine burden was closer to 62 cases per year, because only 76% of children were vaccinated and the efficacy of the vaccine is only 95% (45 x (1/0.76) x (1/0.95) = 62), giving a pre-vaccine incidence rate of 66 per 100,000 children under-5 for Hib meningitis

(5). This estimate was adjusted again to take into account the Hib burden among infants too young to be vaccinated and the herd immunity effect. Vaccination had not been introduced long enough to provide immunity to unimmunized children. Herd immunity occurs when those who have not been immunized are protected because so many others have been immunized that the threat of the disease is diminished. The authors used 90% as the population for which this effect would provide an overall protective efficacy. Then the true pre-vaccine burden would be closer to 50 cases, giving an incidence rate of 54 cases per 100,000 children under the age of 5. They believe that the true incidence rate of Hib disease would fall between 54 and 66 cases per 100,000 children under-5 using this method (5). This method yields a similar incidence rate to that under the RAT method.

CONCLUSION

From developed country data, The Gambia vaccine trial, and the Fiji study it can be concluded that introduction of the Hib vaccine does significantly reduce the burden of Hib related disease. The Gambian vaccination trial results led the WHO to recommend the addition of the Hib vaccine to developing countries' national vaccination programs. However, the cost of the vaccine is still a problem. If an accurate estimate of Hib disease burden can be found for a developing country, it could help the country decide whether or not to apply for funding to introduce the Hib vaccine. The WHO RAT has been shown to be able to give an accurate estimate of the true burden of disease attributable to *Haemophilus influenzae.*

The two studies reviewed here give substantial proof that the WHO RAT is an efficient and accurate method to determine an estimate of the true burden of Hib disease. The incidence rate method appears to be a more accurate representation of the true burden because it does not rely on as many assumptions as the under-5 mortality rate method. The RAT uses data from major local hospitals with adequate laboratories for identifying *Haemophilus influenzae* type b. Therefore, the RAT may underestimate the true burden of disease attributable to Hib. Despite the limitations of the WHO RAT, if the WHO guidelines for the selection of a region are followed, an accurate estimate of the true burden of Hib disease should be calculated.

REFERENCES

1. Felkin D.R, Nelson C.B., Watt J.P., Mohsni E., Wenger J.D., Levine O.S. Rapid Assessment Tool for *Haemophilus influenzae* type b Disease in Developing Countries. Emerging Infectious Disease. July 7 2004;10:1270 - 1276.

2. World Health Organization (WHO). Estimating the local burden of *Haemophilus influenzae* type b (Hib) disease preventable by vaccination: a rapid assessment tool, 2001. WHO document no. WHO/V&B/01.27 Geneva: WHO. 2001

3. CDC: Division of Bacterial and Mycotic Diseases. *Haemophilus influenzae* Serotype b (Hib) Disease. December 2003.

4. Russell F.M, Carapetis J.R., Mansoor O., Darcy A., Fakakovi T., Metai A., Potoi N.T., Wilson N., Mulholland E.K. High Incidence of *Haemophilus influenzae* type b Infection in Children in Pacific Island Countries. Clinical Infectious Diseases. 2003;37:1593-1599.

5. Wilson N., Mansoor O., Wenger J., Martin R., Zanardi L., O'Leary M., Rabukawaqa V. Estimating the *Haemophilus influenzae* type b (Hib) disease burden and impact of Hib vaccine in Fiji. Vaccine. 2003;21:1907-1912.

6. Adegbola R.A., Usen S.O, Weber M., Lloyd-Evans N., Mulholland K., McAdam K.P.W.J., Greenwood B.M., Milligan P.J.M. *Haemophilus influenzae* type b meningitis in The Gambia after introduction of a conjugate vaccine. The Lancet. September 25, 1999;354:1091-1092.

7. Mulholland K., Smith P.G., Broome C.V., Gaye A., Whittle H., Greenwood B.M., A randomized trial of a *Haemophilus influenzae* type b conjugate vaccine in a developing country for the prevention of pneumonia – ethical considerations. Int J Tuberc Lung Dis. 1999;3(9):749-755.

8. World Health Organization (WHO). Vaccines, Immunization and Biologicals: 2002-2005 Strategy. WHO document no. WHO/V&B/02.02 Geneva: WHO.2 2003.

Appendix A: Taken from, Estimating the local burden of *Haemophilus influenzae* type b (Hib) disease preventable by vaccination: a rapid assessment tool, 2001. (2)

Form A: Criteria for guiding the selection of a region for the accurate assessment of Hib meningitis incidence using local data

	Population criteria
1.	More than 250 000 people in the region.
2.	The majority of children in the region (>90%) utilize one (or two) regional hospital(s). (Children with Hib meningitis who do not live in the region but are diagnosed in the regional hospital should not be included in the calculation of the incidence rate. Children who live in the surveillance region and who are hospitalized with Hib meningitis in another region should be included in the incidence rate for the surveillance region.)
3.	Children with meningitis are attended to in the health care system; they do not generally die at home.
4.	There is low use (<10%) of the new Hib vaccine in the private sector in the region.

	Hospital criteria
1.	Paediatric services exist to treat children with bacterial meningitis.
2.	Not more than 40% of children pretreated with antibiotics before arriving at hospital.
3.	All suspected meningitis cases should undergo (be offered) lumbar puncture.
4.	All cerebrospinal fluid (CSF) should be promptly submitted to the laboratory for cell count, biochemistry, direct exam and culture.

	Laboratory criteria
1.	CSF should be transported to lab, examined and plated onto media as soon as possible after being obtained.
2.	Primary cultures of CSF specimen should be done on chocolate agar (supplemented with V factor preferable) or supplemented blood agar (for example, polyvitex or isovitalex). Human blood should not be used.
3.	Incubation should occur at 35-37°C in a 5-10% CO_2 environment (by candle jar or CO_2 incubator).
4.	Suspicious colonies must be subcultured onto a nutritionally deficient agar (for example, tryptic soy agar or Columbia agar) with X, V and XV disks or strips placed. H. influenzae will only grow in presence of both X and V factors.[1,2]
5.	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.

[1] *H. influenzae* isolates should be serotyped to confirm that they are type b (Hib). Latex kits will detect Hib but they will not identify other capsular serotypes.

[2] Short-term storage of Hib isolates should be done on chocolate agar slants. Long-term storage should be done by freezing the isolates at –70°C.

Appendix B – Data Inputs for Worksheet 2 from Estimating the local burden of *Haemophilus influenzae* type b (Hib) disease preventable by vaccination: a rapid assessment tool, 2001. (2)

1) Number of children <5 years old – if this is not available, you may consider multiplying the annual number of surviving infants by five.
2) Incidence rate of Hib meningitis – this is the annual number of cases of Hib meningitis per 100 000 children less than five years of age. This should be obtained from Worksheet 1. However, if a local estimate of Hib meningitis incidence cannot be made, an estimate from a nearby country can be used (see Table 1 for examples).
3) Hib meningitis case-fatality rate (CFR) – this is the proportion of children with Hib meningitis who die from the infection. In selecting a local hospital to obtain this data, most of the hospital and laboratory criteria outlined in Form A should be fulfilled. In particular, the reliability of the calculated CFR may be questioned if any of the following indicators are found:
    - <20% of childhood deaths occur outside of the hospital;
    - lumbar puncture is not done on all suspected meningitis cases;
    - all abnormal CSF is not cultured;
    - <25% culture-confirmed bacterial meningitis cases in children <5 years old are due to Hib. (If local data is not available, an estimate from Table 1 can be used).
4) Ratio of Hib pneumonia to Hib meningitis – this is the number of Hib pneumonia cases that are expected to occur for each Hib meningitis case. Based on data from two clinical trials, we suggest using a ratio of 5 Hib pneumonia cases to each Hib meningitis case. Because this number can only be measured in detailed clinical vaccine trials, local data will not be available.
5) Hib pneumonia CFR – this is the proportion of children with Hib pneumonia who die from the infection. The CFR will vary according to whether children are treated with antibiotics. The U5MR serves as a surrogate marker for access to care (and antibiotics) in a country. Therefore, we have suggested Hib pneumonia CFR's based on a country's U5MR (Table 2).

Table 1: Sources of local data for calculating Hib disease burden, including expected range of values.

Data	Ministry of Health	Literature review	National health statistics	Major urban hospitals	Regional hospitals	Expected range
Under-5 mortality rate method						
Annual number of live births	x		x			Varies
Under-5 mortality rate	x	x	x			20-250
Proportion of under-5 deaths due to acute lower respiratory infection (ALRI)	x	x	x			10-25[2]
Proportion of ALRI mortality due to Hib	Estimates based on intensive, special studies. Generally not available from existing local data.					13
Hib pneumonia case-fatality rate		x[1]		x[1]	x[1]	5-25[3]
Hib meningitis incidence rate method						
Hib meningitis incidence	x	x				15-60[3]
Hib meningitis CFR		x		x	x	10-40
Ratio of Hib pneumonia: meningitis	Estimates based on controlled vaccine trials. Not available using existing local data					5:1

1 Most likely only bacteraemic Hib pneumonia CFR will be available unless studies include other diagnostic techniques, such as lung puncture or antigen testing. See section VI for explanation.
2 See Table 2.
3 Rates may be higher in select subpopulations (i.e. Australian aborigines). Rates may be lower in some Asian countries.

Table 2: Percentage of the under-5 mortality rate (U5MR) due to ARI and the Hib pneumonia case-fatality rate (CFR) based on the U5MR.

U5MR	% U5MR due to ARI[1]	Hib pneumonia CFR (%)[2]
>150	25	20
75-149	25	15
35-74	20	10
10-34	15	5
<10	10	5

1 From Garenne 1992.
2 Based on literature review of CFR in bacteraemic and non-bacteraemic pneumonias in children treated and not treated with antibiotics.

Appendix C – Data Inputs for Worksheet 3 from Estimating the local burden of *Haemophilus influenzae* type b (Hib) disease preventable by vaccination: a rapid assessment tool, 2001. (2)

1) Annual number of live births – this may sometimes be referred to as the "birth cohort".
2) Under-5 mortality rate (U5MR) – the U5MR is the number of children out of every 1000 live births who die before they reach 5 years of age.
3) Neonatal mortality rate – this is the number of deaths per 1000 neonates. Neonatal deaths are considered to be those that occur during the first month of life. The neonatal mortality rate will be subtracted from the under-5 mortality rate because neonatal deaths are unlikely to be due to Hib (WHO Young Infants Study Group 1999).
4) Proportion of childhood deaths due to acute lower respiratory infection (ALRI) – this is the proportion of deaths in children less than 5 years of age attributed to ALRI. This can be estimated based on a country's U5MR (Table 2, Garenne 1992).
5) Proportion of ALRI mortality due to Hib – this is the proportion of all ALRI deaths in children less than 5 years of age attributable to Hib. This number is very difficult to calculate using local data. Based on a review of several different studies, we suggest using 13%.
6) Hib pneumonia CFR – this is the proportion of children with Hib pneumonia who die from the infection. See description under meningitis incidence method section above and Table 2.

Appendix D

Worksheet 1 **Retrospective estimate of Hib meningitis incidence**

enter data in blue cells
calculated data in yellow

Pre-Vaccine period 1992 -1993 Fiji

		Data input
STEP 1:	**Number of Hi meningitis cases diagnosed from CSF**	
1A	Number of purulent* CSF specimens in children < 5 years *If this information is not available, put "0" in cell* *Note that only children residing in defined region of interest should be included. If possible, do not count neonatal cases (newborns 0-1 month of age)* **Purulent defined as the following:* *a. turbid or cloudy OR* *b. ≥ 100 white blood cells OR* *c. 10-99 wbc AND glucose < 40 mg/dl AND protein > 100 mg/dl*	377
1B	Number of purulent meningitis cases from 1A in which a bacterial pathogen was identified *(Bacteria can be identified by positive culture, latex agglutination test or gram stain)*	86
1C	Number of purulent meningitis cases from 1A in which Hi was identified *(Hib can be identified by positive culture, latex agglutination test or gram stain showing gram negative coccobacilli)*	33
1D	Percentage of purulent meningitis cases with a bacterial source identified due to Hi *(1C / 1B)*	0.3882
1E	Number of purulent meningitis cases from 1A in which NO bacterial pathogen was identified *(1A - 1B)*	292
1F	Number of purulent meningitis cases in which no bacterial pathogen was identified which were likely due to Hi *(1D x 1E)*	113.3647
1G	Total number of cases of Hi meningitis with purulent CSF in region in children < 5 years of age during time period of surveillance *(1C + 1F)*	146.3647
1H	Hi isolated from nonpurulent CSF *(cases in which Hi was found but CSF did not meet purulent definition listed above)*	4
1I	Number of months of surveillance used to obtain values in *1A - 1C*	24
1J	Number of years of surveillance	2
1K	Annual number cases of Hi meningitis in region in children < 5 years of age who had a lumbar puncture *(1G + 1H / 1J)*	75.1824
STEP 2:	**Estimating Hi meningitis cases among children who did not get lumbar puncture** *If 100% of children with suspected meningitis get lumbar puncture, put 100 into 2A and proceed to step 4.*	
2A	Percentage of children with clinical meningitis who get lumbar puncture	90
2B	The annual number of cases of Hi meningitis that were missed in children who did not get lumbar puncture *(1K / (2A/100) - 1K)*	8.3536

STEP 3:	**Estimating the number of children < 5 years of age in region of surveillance**	
	If known, the annual population of children < 5 years of age in the region of surveillance can be entered directly into 3A below. If unknown, proceed through steps 3B1 - 3B5 below.	
3A	Annual population of children < 5 years of age in region of surveillance	93993
3B1	Total annual population of country	
3B2	Annual population of children < 5 years of age in country	
3B3	Percentage of national population < 5 years of age *(3B2 / 3B1)*	
3B4	Total annual population in region of surveillance	
3B5	Annual population of children < 5 years of age in region of surveillance *(3B3 x 3B4)*	

STEP 4:		
4A	Total number of Hi meningitis cases in children during period of surveillance *(1K + 2B)*	83.5359
4B	Annual incidence rate of Hi meningitis per 100 000 children < 5 years of age in region of surveillance *(4A/ (3A or 3B5) x 100 000)*	88.8746
4B	Annual incidence rate of Hib meningitis per 100 000 children < 5 years of age in region of surveillance (assuming 95% Hi disease is Hib) (4Bx95%)	84.4309

Appendix E

Worksheet 2 — **Estimating the local burden of Hib disease**
Hib meningitis incidence rate method
(pneumonia to meningitis ratio 5:1)

enter data in blue cells
calculated data in yellow

Pre-Vaccine period 1992 -1993 Fiji

		Local data
STEP 0:	**Population data**	
	Number of children < 5 years old in country	93993
STEP 1:	**Hib meningitis cases**	
1A	Incidence of Hib meningitis *(number of cases per 100 000 children < 5 years old)*	84.4
1B	Annual number of Hib meningitis cases *(1B = 1A / 100 000 x number of children < 5 years old)*	79.3301
STEP 2:	**Hib meningitis deaths**	
2A	Hib meningitis case-fatality rate *(enter as a percent)*	0.078
2B	Annual number of Hib meningitis deaths in children < 5 years old *(1B x 2A)*	6.1877
STEP 3:	**Estimate the number of Hib pneumonia cases**	
3A	Ratio pneumonia:meningitis cases	5
3B	Annual number of Hib pneumonia cases *(1B x 3A)*	396.6505
STEP 4:	**Estimate the number of Hib pneumonia deaths**	
4A	Hib pneumonia case-fatality rate *(enter as a percent)*	0.075
4B	Annual number of Hib pneumonia deaths *(3B x 4A)*	29.7488
STEP 5:	**Summary**	
5A	Hib meningitis and pneumonia cases *(1B + 3B)*	475.9806
5B	deaths *(2B + 4B)*	35.9365

Appendix F

Worksheet 3

Estimating local burden of Hib disease
Under-5 mortality rate method
(pneumonia to meningitis ratio 5:1)

enter data in blue cells
calculated data in yellow

Pre-Vaccine period 1992 -1993 Fiji

		Local data
STEP 0:	**Population data**	
	Annual number of live births in country	18849
STEP 1:	**Hib pneumonia deaths**	
1A	Under-5 mortality rate *(number of deaths per 1 000 live births)*	23
1B	Neonatal mortality rate *(number of deaths per 1 000 live births)*	11
1C	*U5MR - Neonatal mortality rate (1A-1B)*	12
1D	Percentage of childhood deaths from ARI *(enter as a percent)*	0.148
1E	Annual number of deaths from ARI in children < 5 years old (excluding neonates) *(live births x 1C / 1 000 x 1D)*	33.4758
1F	Percentage of ARI deaths due to Hib *(enter as a percent)*	0.13
1G	Annual number of Hib pneumonia deaths *(1E x 1F)*	4.3519
STEP 2:	**Hib pneumonia cases**	
2A	Hib pneumonia case-fatality rate *(enter as a percent)*	0.075
2B	Annual number of Hib pneumonia cases *(1G / 2A)*	58.0248
STEP 3:	**Hib meningitis cases**	
3A	Ratio pneumonia:meningitis cases	5
3B	Annual number of Hib meningitis cases *(2B / 3A)*	11.6050
STEP 4:	**Hib meningitis deaths**	
4A	Hib meningitis case-fatality rate *(enter as a percent)*	0.078
4B	Annual number of Hib meningitis deaths in children < 5 years old *(3B x 4A)*	0.9052
STEP 5:	**Summary**	
	Annual Hib meningitis and pneumonia	
5A	cases *(2B + 3B)*	69.6297
5B	deaths *(1G + 4B)*	5.2570

Appendix G

Worksheet 2	Estimating the local burden of Hib disease Hib meningitis incidence rate method (pneumonia to meningitis ratio 1:1)	enter data in blue cells calculated data in yellow
	Pre-Vaccine period 1992 -1993 Fiji	
STEP 0:	**Population data**	
	Number of children < 5 years old in country	93993
STEP 1:	**Hib meningitis cases**	
1A	Incidence of Hib meningitis *(number of cases per 100 000 children < 5 years old)*	84.4
1B	Annual number of Hib meningitis cases *(1B = 1A / 100 000 x number of children < 5 years old)*	79.3301
STEP 2:	**Hib meningitis deaths**	
2A	Hib meningitis case-fatality rate *(enter as a percent)*	0.078
2B	Annual number of Hib meningitis deaths in children < 5 years old *(1B x 2A)*	6.1877
STEP 3:	**Estimate the number of Hib pneumonia cases**	
3A	Ratio pneumonia:meningitis cases	1
3B	Annual number of Hib pneumonia cases *(1B x 3A)*	79.3301
STEP 4:	**Estimate the number of Hib pneumonia deaths**	
4A	Hib pneumonia case-fatality rate *(enter as a percent)*	0.075
4B	Annual number of Hib pneumonia deaths *(3B x 4A)*	5.9498
STEP 5:	**Summary**	
	Hib meningitis and pneumonia	
5A	cases *(1B + 3B)*	158.6602
5B	deaths *(2B + 4B)*	12.1375

Appendix H
Worksheet 3

Estimating local burden of Hib disease
Under-5 mortality rate method
(pneumonia to meningitis ratio 1:1)

enter data in blue cells
calculated data in yellow

Pre-Vaccine period 1992 -1993 Fiji

		Local data
STEP 0:	**Population data**	
	Annual number of live births in country	18849
STEP 1:	**Hib pneumonia deaths**	
1A	Under-5 mortality rate *(number of deaths per 1 000 live births)*	23
1B	Neonatal mortality rate *(number of deaths per 1 000 live births)*	11
1C	*U5MR - Neonatal mortality rate (1A-1B)*	12
1D	Percentage of childhood deaths from ARI *(enter as a percent)*	0.148
1E	Annual number of deaths from ARI in children < 5 years old (excluding neonates) *(live births x 1C / 1 000 x 1D)*	33.4758
1F	Percentage of ARI deaths due to Hib *(enter as a percent)*	0.13
1G	Annual number of Hib pneumonia deaths *(1E x 1F)*	4.3519
STEP 2:	**Hib pneumonia cases**	
2A	Hib pneumonia case-fatality rate *(enter as a percent)*	0.075
2B	Annual number of Hib pneumonia cases *(1G / 2A)*	58.0248
STEP 3:	**Hib meningitis cases**	
3A	Ratio pneumonia:meningitis cases	1
3B	Annual number of Hib meningitis cases *(2B / 3A)*	58.0248
STEP 4:	**Hib meningitis deaths**	
4A	Hib meningitis case-fatality rate *(enter as a percent)*	0.078
4B	Annual number of Hib meningitis deaths in children < 5 years old *(3B x 4A)*	4.5259
STEP 5:	**Summary**	
5A	Annual Hib meningitis and pneumonia cases *(2B + 3B)*	116.0495
5B	deaths *(1G + 4B)*	8.8778