Haemophilus influenzae Type B Infection in Children in Pacific Countries

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Abstract: *The Haemophilus influenzae type b (Hib) disease burden among children under five years in four Pacific island countries (PIC was estimated. The incidence of confirmed Hib meningitis was calculated using numbers of culture confirmed isolates. In addition, the WHO Hib Rapid Assessment Tool (RAT) was used to estimate the true Hib meningitis incidence and the number of Hib meningitis and pneumonia cases and deaths. The Hib meningitis annual incidence in three PICs was 70 to 84 per 100,000 children under five years. The high Hib disease burden and the relative cost-effectiveness of Hib vaccine, make the introduction of Hib vaccine a good investment for PICs costing US$ 1,000-10,000 for each death prevented — ignoring treatment cost savings. (PHD 2004 Vol 11 No 1 Pages 79 - 83)*

Introduction

Haemophilus influenzae type b (Hib) was the most common cause of life threatening bacterial infection in children in industrialized countries, until universal immunization virtually eliminated the disease. Equally dramatic effects have been seen in developing countries that have introduced Hib vaccine. The World Health Organization (WHO) recommends the addition of Hib vaccine to immunization programmes, according to national capacities and priorities. However, uptake in developing countries has remained slow. This is due partly to the cost of Hib vaccine, and partly to uncertainty about the true disease burden.

Measuring Hib disease burden is not straightforward. To assist less developed countries in measuring their burden of Hib disease, WHO has developed a Rapid Assessment Tool (RAT) that uses existing data to estimate the number of cases and deaths due to Hib meningitis and pneumonia. The Hib RAT provides two methods for estimating Hib disease burden: the meningitis incidence rate method (based on cases of culture-confirmed meninqitis) and the under-5 mortality rate method (based on overall mortality rate in children).

Nine of 20 Pacific island countries (PICs) have not yet added Hib vaccine to their immunization programmes. These nine islands cover the three ethnic groups in the Region: Polynesia (the Cook Islands, Nauru, Samoa, Tokelau, Tonga, Tuvalu), Melanesia (Solomon Islands, Vanuatu), and Micronesia (Kiribati). To assist them in deciding about the value of Rib vaccine introduction, Hib disease burden was estimated in a subset of countries to provide a regional estimate. The complete report of our findings has been published separately. We here present a brief summary of the findings for the information of readers in Pacific island nations.

Methods

To estimate the burden of Hib in PICs, existing reports and publications were requested from each P a Medline literature search was performed, and four site visits were undertaken. The PICs visited were selected based on having a population over 80,000, the availability of hospital and laboratory data, and with the aim of having at least one estimate from each of the three ethnic groups: Kiribati (in Micronesia), the Solomon Islands (in Melanesia), and Samoa and the Kingdom of Tonga (in Polynesia).

Hospital laboratory registers were reviewed for purulent and culture confirmed cases. The paediatric discharge books were reviewed for all possible cases of meningitis of the defined time frame. The medical records of a possible case were reviewed to confirm the number of clinical cases of meningitis.

To calculate the annual Hi or Hib disease incidence in children aged less than five years, the proveri Hi or Hib meningitis incidence was calculated based on positive Hib cultures from cerebro-spinal fluid (CSF) or blood in cases of clinical meningitis. The incidence of proven invasive Hi disease (positive culture in blood or CSF with any clinical presentation) was also calculated, where possible.

Hib disease burden estimates were calculated using the two methods outlined in the Hib RAT. The meningitis incidence method starts with the number of Hib meningitis cases for a known population over a defined period. Various assumptions are applied to this figure (the proportion of suspected meningitis cases that do not undergo LP, the proportion of purulent meningitis cases that are culture negative, the ratio of Hib meningitis : Hib pneumonia cases, and case fatality rates) to estimate the total number of cases and deaths due to Hib. The under-5 mortality rate method uses a number of similar and other assumptions to estimate cases and deaths due to Rib disease, starting with the overall mortality rate in children. This method could not be used for Kiribati, as no under-5 or neonatal mortality rate data were available.

Results

Hib disease burden

Culture confirmed Hi meningitis incidence rates per 100,000 under-Ss per year were 52, 33, and 25 in Tonga, the Solomon Islands, and in Samoa respectively (Table 1). Kiribati had a single Rib isolate giving an annual rate of 11 per 100,000 under- In Tonga the 13 Hi isolates comprised seven culture positive CSFs, six cases with Hi positive blood cultures, four of whom had no LP taken (but clinical meningitis) and two of whom had sterile and purulent CSF. In addition, another five cases of invasive Hi disease were identified from blood culture isolates, including four cases of pneumonia. Including these cases, the annual incidence of all culture confirmed invasive Hi disease in Tonga was 71 per 100,000 children aged less than five years (95% confidence interval [11-15].

Laboratory methods used were not optimal. All laboratories used expired human blood to make chocolate blood agar for CSF culture and subculture of positive blood cultures. LP rates were 50%, 90%, 69%, and 81% for Kiribati, the Solomon Islands, Samoa, and Tonga respectively. The Rib RAT adjusts for these potential missed cases, that is, those cases that either did not have an LP performed or for which the laboratory methods were suboptimal for isolating Hib. This gave estimates of 70 to 84 per 100,000 children aged less than five years in three PICs (Table 2). The estimate for Kiribati was also consistent with the other three PICs, although this was based on only a single isolate.

The estimates for Tonga, the Solomon Islands and Samoa were lower using the under-S mortality rate method than those obtained by the meningitis incidence rate method (Table 3). In Tonga, the estimated Hib meningitis incidence using the under-S mortality rate method was even lower than the proven Hi culture based incidence (Table 1).

Other estimates of Hib disease burden

Estimates of the burden of Hib disease for PICs are summarized in Table 4. The quality of data, ability of the laboratory to isolate Hib, and LP rate from French Polynesia are unknown, so this rate may be a substantial underestimate of the true Rib burden. Data from Melanesian and Polynesian countries are of good quality and reasonably consistent, with estimates of the incidence of Rib meningitis ranging from 54 to 94 per 100,000 children aged less than five years. However, the data are insufficient to provide a regional estimate for Micronesia.

Cost of Immunization

Based on a cost of US$7.50 for three doses of Hib vaccine per child (the current United Nations Children's Fund [price), approximate annual costs to immunize each country's birth cohort are shown in Table 5. These costs exclude vaccine wastage, extra vaccine delivery costs, and any catch-up programme that might take place.

Discussion

The Hib meningitis incidence rates estimated in all four PICs using the Hib RAT were similar. These estimates are consistent with other data and suggest that the annual Rib meningitis incidence in all PICs is between 70 and 100 per 100 000 children less than five years. This is higher than the weighted worldwide incidence of Rib meningitis of 60 per 100 000 in children aged less than five years in developing higher than rates reported from sub-Saharan Africa' and much higher than rates reported from Asia.

In each country visited, Hi was the most common organism isolated from the CSF of children with meningitis. All PICs visited used expired human blood for preparation of culture media, which is not recommended' so these rates may be an underestimate The Hib RAT provides a quick, simple, and relatively reliable method to estimate the true burden of Hib disease in developing countries, where existing surveillance and laboratory data are of reasonable quality. The meningitis incidence rate method is likely to be more accurate than the under-S mortality rate method, given that the former is based on local data with fewer major assumptions.

Table 1. Annual incidence of culture-proven Haemophilus influenzae (Hi) meningitis in children aged less than five years in four Pacific Island countries

	Kiribati	Solomon Islands	Samoa	Tonga
Incidence of culture-proven Hi meningitis* (95% confidence interval)	I1# (0,60)	33(19,53)	25(13,42)	52(27,88)
Number of Hi isolates	1	17	13	13±
Lumbar puncture rates**	50%	90%	69%	81%
At-risk population	11,798	63,632	24,413	14,436
% of population covered in assessment	50%	45%	70%	70%
Period of analysis	16 months	24 months	36 months	31 months

** Annual incidence, per 100,000 children aged less than five years.*

** * Lumbar puncture rates were estimated by the number of clinical cases of meningitis that had lumbar punctures performed, as documented in either the laboratory records or medical records over the designated time frame.*

 # The laboratory in Kiribati was able to type Hi therefore the incidence shown is the annual incidence of Hib meningitis rather than Hi meningitis.

** These 13 isolates comprise 7 culture positive cerebrospina (CSF5), 2 cases with sterile but purulent CSFs and Hi positive blood cultures, and 4 cases who had clinical meningitis (no LP taken) and Hi positive blood culture.*

Table 2. Estimating the annual incidence of Haemophilus influenzae type b (Hib) meningitis in children aged <5 years using the Rapid Assessment Tool (RAT) meningitis incidence rate method

	Kiribati	Solomon Islands	Samoa	Tonga
Time period of surveillance (months)	16	24	36	31
Number of purulent Cerebrospinal fluid (CSF) specimens in children < 5 years	3	63	79	21
Number from which Hi was identified	1	17*	13	9#
Number from which no bacterial pathogen was identified, but which were likely due to Hi t	2	24	19.1	4.5
Hi isolated from non-purulent CSF	0	1	0	0
Percentage of children with clinical meningitis estimated to get lumbar puncture	50%	90%	69%	81%
Calculate annual number of Hi meningitis cases per year, from above data 4'	4.6	21.6	14.7	6.8
Population of children <5 years of age in. region of surveillance	6,955	25,703	17,578	9,716
Estimated annual incidence rate of Hib meningitis per 100 000 children <5 years of age	66	84	84	70

** 14 purulent cerebrospinal fluid spinal ((SF4 were I culture positive, 3 purulent (SF were Gram stain positive for Grain negative bacilli hut were culture negative. All infants were> 3 months old.*

 # 7purulent CSFs were Hi culture positive and 2 had purulent hut sterile (SF and [positive blood cultures.

I Assumes that the proportion of culture-negative purulent (which were likely due to I is the same as that from culture-positive purulent (SE

.f Lumbar puncture rates were estimated by the number of clinical cases of meningitis who had lumba punctures performed and documented in either the laboratory records or medical records over the designated time frame. 4' Based on annual number qf Hi tneningitis from those with an LP peiformed, divided by the proportion of meningitis cases estimated to get a lumbar puncture. Assumes 95% of Hi isolates are tub (except in Kirihali, where the only Hi isolate was typed as Hub).

a 7 of 9 of proven Hi meningitis had positive blood cultures. Therefore, if Y represents the number of ill meningitis cases in children who had clinical meningitis and no LI then Yx 7/9 = 4. V = 5.1. Therefore the annual number of cases of Hi tneningitis is 5.1/2.6= 2. Note this is not the standard step in the Hib RAT which instead assumes that the rate ofneoingitis in the 19% who did not get LI' ic the same as in the 81% who did.

Table 3: Estimating the burden of 1-lib disease in 3 Pacific island countries using the Hub RAT under-S mortality rate method*

	Solomon Islands	Samoa	Tonga
Annual number of live births in country	13,513	4,602	2,581
Under mortality rate (excluding neonates) **	43#	25#	9.7
Percentage of childhood deaths from acute lower respiratory infection (ALRJ)	20%	20%	15%
Annual number of ALRI deaths in children <5	116	23	3.8
Annual number of F pneumonia deaths t	15	3	0.5
Annual number of Hib pneumonia cases"	150	59	10
Annual number of HE meningitis cases ^	30	12	2
Annual number of Hib meningitis deaths	3	12	0.2
Annual incidence of Hib meningitis per 100,000 children <5 years in the region	47	49	14

** The under-S maitali rate method could not he used for ICirihaii. as no under five or neonatal mortality 'ate data were available.*

*** The number of deaths in children aged under 5 years ('excluding neonates) per 1.000 live births.*

 # No neonatal mortalite tate was available. It Was estimated to be ha If the infant mortality rate of 66 and 25 per 1000 live births in the Solomon Islands and Samoa respectively.

This is nor based on local data and re/leers' the under-S mortality rate. This is estimatedfrorn the ptvpon'ion of deaths due to ALRJ (lit

fit is assumed chat /3% of all ALR1 deaths in child,'en less the five yea old were due to Rib. This is not based on local data bitt based on a review oft/ic lite,'atu,'e by the developers c/the RAT (/1).

A The H/b pneumonia case fatality i-ate is ,iot based on local data and reflects the under-S mortality tat This is estimated jèvrn the proportion of deaths due to acute respiratory in/eetions and the proportion c/these deaths which 'itay be due to Rib (H). This is estimated to be 5%/or Samoa and Tonga. and 10% for Solomon islands.

The Rib ,neuin gills case fatality of 10%/or the Solomon islands and Tonga, and /4%/or Samoa was calculated from Ministry of Health and paediatric discharge tlaia,

Universal Hib immunization is likely to be very effective in reducing Hib disease in those PICs not currently using Hib vaccine. The introduction of universal childhood Hib immunization would reduce the number of Hib meningitis and pneumonia cases substantially. The cost per case or death prevented here is relatively small. Factoring in treatment costs, including the large social cost of long-term care for the neurological damage suffered as a complication in up to 30% of meningitis cases, universal immunization in each country would be very cost-effective, even using these conservative assumptions, at between US$ 1000 and US$10,000 per death prevented. Data from the present study suggest that Hib vaccination would be a good public health investment for PICs and regional donor nations to support.

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References

1. Peltola H. Worldwide Haemophilus infiuenzae type b disease at the beginning of the 21st century: global analysis of the disease burden 25 years after the use of the polysaccharide vaccine and a decade after the advent of conjugates. *Cli Microbiol Rev 2000*; 13:302-17.

2. Peltola H, Kilpi T, Anttila M. Rapid disappearance of Haeunophi infiuenzae type b meningitis after routine childhood immunisation with conjugate vaccines. *Lancet 1992*;340:592-4.

3. Vadheim CM, Greenberg DP, Eriksen E, et al. Eradication of Haemophilus influenzae type b disease in southern California. Kaiser-UCLA Vaccine Study Group. Arch Pedia Med 1994;148:51-6.

4. McIntyre PB, Chey T, Smith WT. The impact of vaccination against invasive Haemophilus unJluenzae type b disease in the Sydney region. Med J Aust 1995;162:24

5. Wilson N, Mansoor 0, Wenger J, et al. Estimating the Haeinophilus unfluenzae type b (Hib) Disease Burden and the Impact of Hib Vaccine in Fiji. Vaccine 2003; 21:1907-12.

6. WHO position paper. Haemophilus influenzae type b (Hib) vaccines. Weekly Epideniiological Record 1998;73 :64-8.

7. World Health Organization. Estimating the local burden of Haetnophilus influenzae type b (Hib) disease preventable by vaccination. A rapid assessment tool, 2001 (WHO/V&B/01.27), Geneva: WHO, 2001.

8. Russell FM, Carapetis JR, Mansoor 0, et al. High incidence of Haemophilus influenzae type b infection in children in Pacific island countries. Clii hnfDis 2003 (accepted for publication).

9. Anglaret X, Buissonniere RF, Duval P et al. Invasive Haemophilus infiuenzae disease of Melanesian and Caucasian children in New Caledonia. Pediatr Infect Dis J 1993;12:888-9.

10. Carroll K, Carroll C. The epidemiology of bacterial meningitis occurring in a Pacific Island population. *P N G MedJ 1993*;36:234-42.

11. World Health Organization. Haemophilus unfluenzae type b (Hib) meningitis in the pre vaccine era: a global review of incidence, age distributions, and case-fatality rates. *(WHO/V&B/02. 18)*. Geneva: WHO, 2002.

12. Voss LM, Lennon D, Gilles M. Haemophilus influenzae type b disease in Auckland children 1981-87. *NZMedJ 1989*;l02:149-51.

13. Lennon D, Voss L, Gilles M, Heffernan H. Epidemiology of invasive Haemophilus influenzae type b disease in New Zealand (1978-1987). *Pediatr Res 1989*;25:183A.

14. Wilson N, Wenger J, Mansoor 0, et a!. The beneficial impact of Hib vaccine on disease rates in New Zealand children. *NZMedJ2002;1* 15: 122.

15. Adegbola RA, Mu BK, Falade AG, et al. Haeunophilus influenzae type b disease in the western region of The Gambia: background surveillance for a vaccine efficacy trial. Ann *Tropical Paediatr 1996;*16: 103-11.

16. Pe H. Spectrum and burden of severe Haemophilus unfluenzae type b diseases in Asia. *Bull World Health Organ 1999*;77:878-87.

17. Lau YL. Haemophilus unfiuenzae type b diseases in Asia. *Bull World Health Organ 1999*;77:867-8.

18. World Health Organization. Laboratory methods for the diagnosis of meningitis, *(WHO/CDS/CSR!EDC/99.7)*. Geneva: WHO, 1999.

There are no shortcuts to any place worth going
(Beverly Sills 1924)