

## ***Haemophilus influenzae* type b meningitis: how much better is prevention than cure?**

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### SUMMARY

*Haemophilus influenzae* type b (Hib) is a major cause of meningitis and pneumonia in children. In Papua New Guinea (PNG) more than 20% of Hib are now resistant to chloramphenicol, and resistant Hib meningitis treated with chloramphenicol results in certain death or severe brain injury. Third-generation cephalosporins are a therapeutic option but are very expensive, while the *Haemophilus influenzae* type b conjugate vaccine would provide effective prevention. In a province of 380,000 people, using ceftriaxone as standard treatment for meningitis in all health facilities would only save an estimated 8 more lives per year than using chloramphenicol, and cost US\$1514 per additional life saved. Introduction of Hib vaccine would save, each year, 61 more lives than using chloramphenicol and 53 more lives than using ceftriaxone for meningitis treatment. The cost of a vaccination strategy for Hib meningitis would be US\$1216 for each of the 61 additional lives saved. Hib vaccine would be by far the most effective intervention to reduce mortality and severe neurological disability from Hib meningitis in PNG. Nationwide introduction of Hib vaccine is urgently needed, as antibiotics are now less effective in this disease than ever before.

### Introduction

Almost the entire world's disease burden from *Haemophilus influenzae* type b (Hib) meningitis is now with children in developing countries like Papua New Guinea (PNG). Most wealthy countries, where the number of cases of Hib meningitis was already orders of magnitude less than in developing countries, now have virtually eliminated the disease by using conjugate Hib vaccines. The reason for this inequity is largely cost; it has been said that Hib vaccine is too costly for developing countries. But too costly compared to what? Compared to effective treatment for Hib meningitis? In Port Moresby and Goroka more than 20% of Hib isolates from cerebrospinal fluid (CSF) are now resistant to chloramphenicol (1). The World Health Organization suggests using third-generation cephalosporins, either ceftriaxone or cefotaxime, for the treatment of meningitis where chloramphenicol resistance (among pneumococcal isolates, and presumably also

for Hib) is 'high' (2,3). Ceftriaxone or cefotaxime costs at least five times more than chloramphenicol.

In the paper I have estimated the effectiveness and the cost per life saved of Hib vaccine for the prevention of meningitis, and compared it to three antibiotic strategies for treating meningitis in one province with a population of 380,000, where data are available on meningitis incidence, precision of clinical signs to make the diagnosis, case fatality rate and health service utilization (4-7). These, and other data are used to estimate the relative costs and effectiveness of the approaches.

### Methods

#### Antibiotic strategies

The three antibiotic strategies that have been compared to Hib vaccine are:

1. Chloramphenicol as the only treatment for

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meningitis in all health facilities (current PNG standard treatment) (8).

2. Ceftriaxone in the provincial base hospital and chloramphenicol in primary health centres.
3. Ceftriaxone in all health facilities.

### Cost and antibiotic susceptibility data

The treatment cost of Hib meningitis depends heavily on the antibiotics used. Chloramphenicol costs US\$0.60 for a 1 g vial. Ceftriaxone costs US\$4.30 for a 1 g vial. To treat the average 7 kg child for meningitis for 14 days using chloramphenicol costs US\$5.88, compared with US\$30.10 for a 10-day course of ceftriaxone. Hib causes 30% of all cases of meningitis, and at least 20% of Hib isolates from CSF are resistant to chloramphenicol (1). A strategy of using ceftriaxone for *all* children with clinical signs of meningitis AND cloudy cerebrospinal fluid would lead to just over 16 children being treated to save one extra child who has resistant Hib disease ( $1/[0.3 \times 0.2]$ ).

### Diagnostic specificity and antibiotic use

In PNG, CSF culture facilities do not exist in most settings where children present with meningitis, few provincial hospitals reliably isolate pathogens from CSF and only two major hospitals (Goroka Base and Port Moresby General Hospital) have reliable antibiotic susceptibility testing. Therefore treatment based on antibiotic susceptibility patterns (which would save drug costs and limit unnecessary antibiotic use) is not currently feasible in most cases. In primary and district health centres the problems are even greater. Few rural health staff have maintained their skills in doing lumbar puncture, and most children who present to health centres with clinical signs of meningitis are treated empirically with chloramphenicol, if it is available. In a study of 697 children suspected by health workers to have meningitis, 172 (25%) had CSF evidence confirming or suggestive of bacterial meningitis (5). Thus it is likely the strategy of using ceftriaxone for 'clinical' or 'suspected' meningitis in all health facilities would mean that three-quarters of the ceftriaxone prescribed would be for diseases other than meningitis,

even in the unlikely event that the antibiotic was used strictly for 'clinical' or 'suspected' meningitis cases only.

### Outcome of meningitis with chloramphenicol and ceftriaxone

Regardless of the antibiotic used, some children with Hib meningitis die or have severe brain injury. In 150 cases of meningitis at Goroka Base Hospital and Port Moresby General Hospital treated initially with chloramphenicol between 1997 and 1998 there were 45 patients with Hib disease (culture positive or latex agglutination antigen positive), of whom 4 died and 8 had severe sequelae (total poor outcome for Hib 26.7%). Of the 36 children with culture-positive Hib 7 were chloramphenicol resistant (19%), of whom 5 (71%) had an adverse outcome (3 died and 2 survived with severe neurological sequelae).

In a subsequent 196 cases between 1999 and 2000 treated initially with ceftriaxone, there were 65 patients with Hib disease (culture positive or latex agglutination antigen-positive). Of the 65 children with Hib 12 had severe adverse outcomes: 5 deaths and 7 survivors with severe brain injury (18.5%). Of the 54 culture-positive Hib cases, 11 were chloramphenicol resistant (20%). Of these 11 children 1 died (9%) and 10 had a good outcome (T. Duke et al., in press).

Although there was a 31% reduction in adverse outcome (26.7% down to 18.5%) from Hib meningitis treated using ceftriaxone compared to chloramphenicol, this was not statistically significant (Fisher's exact test  $p=0.35$ ). This is likely to be partly because of the small sample size and partly because of the small effect size in the overall cohort. However, in the cases of documented chloramphenicol resistance there was a significantly lower risk of severe adverse outcome in those treated with ceftriaxone (71% vs 9%, relative risk 0.13; 95% CI 0.02-0.87, Fisher's exact test  $p=0.013$ ). This confirms that in chloramphenicol-resistant disease there is an important benefit of ceftriaxone, but we found no evidence that in chloramphenicol-susceptible disease ceftriaxone is substantially better than chloramphenicol.

In primary health centres case fatality and severe sequelae rates from Hib meningitis will be much higher than in a base hospital.

### Summary of the basis of the model

The model used in this estimation therefore assumes:

- There are approximately 10,000 births, and 1000 infant and child deaths in the province annually (9).
- Around 35% of infant deaths occur in the first month of life (before the first Hib vaccine) (7).
- Meningitis causes about 13% of all child deaths (7).
- 30% of cases of meningitis are due to Hib.
- There are 400 cases of meningitis in children each year in the province. Of these about 100 children (25%) are treated in a provincial hospital; 100 (25%) receive treatment at a health centre (4); and 200 (50%) receive no curative treatment.
- Only about 25% of children receiving antibiotics for a diagnosis of meningitis based on clinical findings without CSF confirmation will have meningitis (5).
- The percentage of children who die or have severe sequelae from Hib meningitis in a provincial hospital is 27% when treated with chloramphenicol and 19% when treated with ceftriaxone.
- The percentage of children who die or have severe sequelae from Hib meningitis in health centres is 60% when treated with chloramphenicol and 42% when treated with ceftriaxone.
- If Hib meningitis is untreated 100% of children die or have severe sequelae.
- 60% of children who survive the neonatal period will receive 3 doses of Hib vaccine.
- Hib vaccine results in a 95% reduced risk of Hib meningitis (10).

### Results

Table 1 shows estimates of severe outcomes from Hib meningitis (case fatality or severe brain injury) and the cost of treatment, for three antibiotic strategies and Hib vaccine in the Eastern Highlands Province.

Using alternative strategies of introducing ceftriaxone only in the base hospital (where lumbar punctures can confirm meningitis) or using ceftriaxone in all primary health facilities (based on empirical clinical indications) will only save respectively 2 and 8 lives per year more than using chloramphenicol as standard treatment in all health facilities, and cost US\$1211 and US\$1514 per additional life saved. Using Hib vaccine would save 61 more lives each year than using chloramphenicol only and 53 more lives than the widespread use of ceftriaxone. The maximal cost of a strategy using Hib vaccine would be US\$1216 for each of the 61 additional lives saved from meningitis, compared to the current drug cost of using chloramphenicol as standard treatment in all health facilities.

### Conclusions

From these estimates it can be concluded that conjugate Hib vaccine would be by far the most effective intervention to reduce mortality and severe brain injury from Hib meningitis in Papua New Guinea. On a cost-per-life-saved basis Hib vaccination compares favourably with curative strategies, although the total cost is greater than any antibiotic strategy.

This model does not include the vaccine prevention of deaths from Hib pneumonia that occur because many children cannot access treatment (a large number), the saving of antibiotics that are currently used for Hib pneumonia in children who do access curative treatment (a large amount), or the fact that the Hib vaccine would reduce the number of children who currently die from Hib pneumonia despite receiving treatment (a number that may rise with increasing chloramphenicol and amoxicillin resistance if the vaccine is not introduced). Therefore the number of lives saved by Hib vaccine will be substantially greater and the overall cost per extra life saved will be substantially less than is predicted here. The model does not consider

**TABLE 1**

ESTIMATED COST OF DIFFERENT STRATEGIES FOR TREATMENT OR PREVENTION OF HIB MENINGITIS AND THE EFFECT OF STRATEGIES ON ADVERSE OUTCOMES

| Strategy   | Number of children in the province diagnosed with meningitis each year                          | Treatment (or vaccine) cost in US\$   | Number of children with Hib meningitis dying or severely brain injured | Extra lives saved compared with only using chloramphenicol | Cost per extra life saved    |
|--|---|---------------------------------------|--|--|------------------------------|
| <b>Antibiotic strategies</b>   |   |                                       |  |  |                              |
| Chloramphenicol for cloudy CSF in hospital and suspected meningitis in health centres                      | 100 treated in hospital<br>400 treated in health centres*                                       | 100 x 5.88=588<br>400 x 5.88=2352     | 100 x 0.3 x 0.27=8.1<br>100 x 0.3 x 0.6=18                             | -  | -                            |
| 200 do not have access to curative treatment   | 200   | 0                                     | 200 x 0.3=60   |  |                              |
| <b>Total</b>   |   | 2940                                  | 86   | 86-84=2  | (5362-2940) / 2<br>US\$1211  |
| Ceftriaxone in base hospital for cloudy CSF and chloramphenicol in health centres for suspected meningitis | 100 treated with ceftriaxone in hospital<br>400 treated with chloramphenicol in health centres* | 100 x 30.10=3010<br>400 x 5.88=2352   | 100 x 0.3 x 0.19=5.7<br>100 x 0.3 x 0.6=18                             |  |                              |
| 200 do not have access to curative treatment   | 200   | 0                                     | 200 x 0.3=60   |  |                              |
| <b>Total</b>   |   | 5362                                  | 84   | 86-78=8  | (15050-2940) / 8<br>US\$1514 |
| Ceftriaxone in all health facilities for suspected or proven meningitis                                    | 100 treated in hospital<br>400 treated in health centres*                                       | 100 x 30.10=3010<br>400 x 30.10=12040 | 100 x 0.3 x 0.19=5.7<br>100 x 0.3 x 0.42=12.6                          |  |                              |
| 200 do not have access to curative treatment   | 200   | 0                                     | 200 x 0.3=60   |  |                              |
| <b>Total</b>   |   | 15050                                 | 78   |  |                              |

**Hib vaccine with 60% 3-dose coverage and chloramphenicol for all other meningitis**

|  |   |   |                                  |          |                             |
|--|---|---|----------------------------------|----------|-----------------------------|
| 60% of children immunized (of the live births who survive young infancy) | 1 case of Hib meningitis in 5790 immunized children (risk reduction 95% in vaccinated children) | Vaccine cost=75,000   | 1 death from Hib                 | 86-25=61 | (77093-2940)/61<br>US\$1216 |
| 5790 receive 3 doses of Hib vaccine                                      |   | Cost of chloramphenicol for all other children with suspected meningitis: 200 x 5.88=1176                     |                                  |          |                             |
| 4210 not immunized   | 45 meningitis cases among deaths (350 x 0.13=45)  | 50% access to curative health, therefore 23 cases (and 69 others) receive chloramphenicol: cost 92 x 5.88=541 | 14 deaths from Hib (45 x 0.3=14) |          |                             |
| 3860 survive young infancy but don't receive 3 doses of Hib vaccine      | 3860 x 0.065 x 0.13=33 meningitis cases (deaths)  | 50% access to curative health, therefore 16 cases (and 48 others) receive chloramphenicol: cost 64 x 5.88=376 | 10 deaths from Hib (33 x 0.3=10) |          |                             |
| <b>Total</b>   |   | 77093   | 25                               |          |                             |

CSF = cerebrospinal fluid  
 \*Of the 400 children treated empirically for clinical meningitis in health centres, about 100 will have the disease

the indirect costs of treating Hib meningitis (hospitalization costs, other drugs, oxygen) that would be saved after Hib vaccine were introduced, nor does it include the long-term cost saving to the community of avoiding neurological disability in Hib meningitis survivors. The latter costs to the community are considerable and will become much greater as more rehabilitation and social services are established. On the other hand the model does not include the indirect cost of vaccination (syringes, needles and vaccine patrols); however, many of these costs are already being incurred by the health services. If a Hib vaccine preparation that is pre-mixed with diphtheria-tetanus-pertussis (triple-antigen) vaccine were used, there would be *no* additional consumable costs; apart from initial training there would be no additional work for health workers in the field; and importantly there would be no additional injections for the children. The model assumes rather poor vaccine services, with 100% of required vaccines purchased but only 60% effectively given. The model was designed in this way to reflect the unfortunate current situation in many rural provinces in PNG, and the realities of immunization programs in remote areas. Here again the model underestimates the true beneficial effect of Hib vaccine, as there is a partial protective effect against invasive Hib disease in children who have received only one or two doses (10), and this will apply to a proportion of the 40% of children who are not fully immunized. However, the balance of effect of the four possible strategies for control of drug-resistant Hib meningitis would be even more in favour of Hib vaccine if the quality of immunization services improves.

If Hib vaccine were introduced chloramphenicol would again be effective empirical treatment for meningitis, as resistance to chloramphenicol among CSF isolates of *Streptococcus pneumoniae* is rare (only 2 cases in the 346 described above). This will substantially limit the proliferation of dangerous resistance to third-generation cephalosporins, and allow these expensive antibiotics to be reserved for future life-saving use.

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