

Immunization – dramatic new evidence

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SUMMARY

The current EPI (Expanded Programme on Immunization) vaccines do not specifically target the organisms that lead to the two main causes of death in children – pneumonia and diarrhoea. This implies that the EPI vaccines will have only a modest effect on total child mortality. However, recent evidence suggests that measles and BCG vaccines dramatically reduce child mortality through nonspecific effects – that is, they reduce mortality from many causes, not just measles and tuberculosis. The combination of BCG at birth and measles vaccine at 6 months probably reduces total mortality to about one-third of its previous level. This means that immunization must now have the very highest priority. If we could improve immunization in Papua New Guinea so that all children received BCG, measles, diphtheria-pertussis-tetanus and polio vaccines, we would reduce child mortality from 120 to approximately 52 per 1000 livebirths – a truly spectacular reduction. The old polysaccharide pneumococcal vaccine is safe and effective and bulk purchases are likely to cost US\$1 a dose or less. Further studies are needed of the effects of pneumococcal vaccine. Immunization of mothers and babies might reduce child mortality by 20%, at a cost of only US\$83 per life saved. The available evidence suggests that one dose of pneumococcal vaccine given to every Papua New Guinean over 5 years of age every 5 years would save approximately 6600 lives a year and the vaccine would cost only US\$121 per life saved. It will not be easy to achieve high immunization rates throughout Papua New Guinea. Vaccines will have to be given the highest possible priority, with curative medical services secondary to immunization. Health workers, government, the general population and overseas donors will have to be convinced of the very great benefits that will come from effective immunization. A sustained education campaign will be needed in addition to the establishment of an effective delivery system. The time has come for a radical shift in emphasis in Papua New Guinea: from hospitalization to immunization.

Introduction

Papua New Guinea (PNG) has a population of 4.7 million people, life expectancy at birth is 55 years, 146,000 babies are born each year and 17,200 children die before their fifth birthday – so the under-5-year mortality rate is 118 per 1000 livebirths (1). The World Health Organization (WHO) estimate of 118 per 1000 under-5 deaths is higher than the official government estimate, but it is probably less than the actual number. Public expenditure on health is US\$130 million a year (with a further \$38 million in out-of-pocket expenditure) (1); most of the money is spent on curative health

services and very little is spent on immunization. I suggest that much more should be spent on immunization, even if this means that there is less money to spend on curative health services.

Much of Papua New Guinea's predominantly rural population has minimal access to the urban hospitals. In 1984, less than 10% of all deaths in Papua New Guinea were reported to have occurred in hospitals and health centres (and there has been little or no improvement in life expectancy since 1984, so this estimate is probably still valid) (2). Two conclusions follow from this. First, we cannot

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use data from hospitals to determine the causes of death in Papua New Guinea. Second, hospitals and health centres have little impact on total mortality in Papua New Guinea.

Bacterial infections, such as pneumonia, meningitis and septicaemia, are still major causes of death in children in Papua New Guinea despite the fact that antibiotic treatment has been available for many years. There are two reasons for this. First, it is very difficult to arrange for an appropriate antibiotic to be given promptly to children with sepsis in isolated rural areas, where most of the deaths occur (and prompt administration is essential because young children often die very quickly from bacterial sepsis). Second, increasing antibiotic resistance means that inexpensive antibiotics such as penicillin and cotrimoxazole are becoming less effective.

Vaccines have the very great advantage that, unlike antibiotics, they do not have to be available to all children at all times. Vaccines can be given at a time of our choosing; they do not have to be given at a time dictated by the onset of sepsis. However, antibiotics are more popular than vaccines. If a patient with pneumonia gets better after an injection of penicillin, the injection gets the credit (even if the patient would have got better anyway). On the other hand, the people whose lives are saved by immunization never know that their life has been saved. In addition, vaccines are usually given to people who are well and the vaccine is blamed for any symptoms that occur in the next week or so (even if the vaccine was not the real cause of the symptoms).

Nonspecific effect of vaccines

Recent evidence suggests that vaccines may have profound effects on total mortality through nonspecific effects on mortality from diseases other than those targeted by the vaccines (3-5). We therefore need studies of each vaccine's effect on total mortality, not just its effect on mortality from its target disease, morbidity from its target disease or, least important of all, merely its effect on antibody levels (5).

In high mortality areas, both measles vaccine and the antituberculosis BCG (bacille Calmette-Guérin) vaccine appear to reduce

total mortality by about 50% (3-4). This spectacular effect is because measles and BCG vaccines do not act on measles and tuberculosis alone – they reduce mortality from a wide range of diseases, probably by improving cell-mediated immunity (3-5). Even greater nonspecific benefits might be obtained by giving an extra dose of BCG vaccine at 3 months of age (as well as soon after birth) (4), and an extra dose of measles vaccine at 18 months of age (as well as at 6 and 9 months) (3).

On the other hand, a recent prospective cohort study in Guinea-Bissau suggests that diphtheria-pertussis-tetanus (DPT) and polio vaccines may not reduce mortality by as much as we would expect: the large number of children saved from dying from diphtheria, pertussis, tetanus and polio may be partly offset by increased mortality from other causes (4,5).

Streptococcus pneumoniae

Pneumococcal infection is a major cause of death in children and adults in Papua New Guinea (6). There have been very few large randomized trials in any country to test the effect of vaccines on all-causes mortality. However, one study has been done in adults and another in children of the effect of the old polysaccharide pneumococcal vaccine on all-causes mortality – and both studies were performed in Papua New Guinea (7,8).

The trial in adults found that polysaccharide pneumococcal vaccine achieved a 22% reduction in overall mortality – a truly spectacular result from a single dose of an inexpensive vaccine (7). There are about 4 million people in Papua New Guinea aged 5 years or more, with 30,000 deaths every year. With bulk purchase, pneumococcal vaccine is likely to cost US\$1 per dose or less. If it does reduce mortality by 22%, giving one dose every 5 years to every person in Papua New Guinea aged 5 years or more would save 6600 lives a year at a cost of only US\$121 per life saved. Further studies are needed of the effect of giving pneumococcal vaccine to adults in Papua New Guinea.

Immunization of mothers with polysaccharide pneumococcal vaccine will

TABLE 1**MORTALITY CAUSED BY *H. INFLUENZAE* (HI) TYPE B**

Total mortality < 5 years of age:	120/1000 under 5 years
40% of deaths from pneumonia:	$120/1000 \times 0.4 = 48/1000$
50% of pneumonia deaths from Hi:	$48/1000 \times 0.5 = 24/1000$
20% of Hi pneumonia type b:	$24/1000 \times 0.2 = 5/1000$
10% of deaths from meningitis:	12/1000
50% of meningitis deaths Hi type b:	$12/1000 \times 0.5 = 6/1000$
Total Hi type b deaths:	$5/1000 + 6/1000 = 11/1000$
11/1000 (Hib mortality) is 9% of 120/1000 (total mortality)	
60% of deaths < 5 years occur after 4 months of age:	$11/1000 \times 0.6 = 7/1000$

benefit the mother and it may also benefit her children. Ian Riley found a 17% reduction in morbidity from acute lower respiratory infection (ALRI) in the period between 1 and 6 months after immunization of mothers (9).

In controlled trials of polysaccharide pneumococcal vaccine in Papua New Guinean children less than 2 years of age, total mortality was reduced by 25% (8). However, the 95% confidence interval for this estimate was wide: from -6% to 47%. While some people feel that this is strong enough evidence to give polysaccharide pneumococcal vaccine routinely to children at 8-9 months of age in Papua New Guinea, others, myself included, feel that further controlled trials are needed (10). The new conjugate pneumococcal vaccines elicit a better antibody response in young infants than the polysaccharide vaccine, but they cover fewer serotypes than the polysaccharide vaccine and a course of 4 doses of the first of the conjugate vaccines costs US\$177 in America.

Haemophilus influenzae

H. influenzae is a major cause of pneumonia and meningitis in children in Papua New Guinea (6). Although most cases of haemophilus meningitis are caused by *H. influenzae* type b (Hib), in lung aspirates from children with pneumonia in Papua New Guinea only about 20% of *H. influenzae* strains are

type b (11). We cannot be sure about how much the non-type-b strains contribute to mortality, but it is likely that they play a substantial role (12). Table 1 estimates the effect of *H. influenzae* type b on total mortality in children under 5 years of age in Papua New Guinea. Tables 1-3 assume 150,000 births a year, an under-5-year mortality rate of 120 per 1000 livebirths, 40% of under-5 mortality by 6 months of age and 50% of under-5 mortality by 6 months of age (13).

Overall effect of immunization

Table 2 estimates the cost of each life saved by four childhood vaccines in Papua New Guinea. The costs listed in Table 2 include only the price of the vaccines (14) and do not include the cost of administration. Because it ignores labour costs, Table 2 substantially underestimates the true cost of immunization (15). Of course, once a universal immunization program is established, labour costs do not change very much, and the addition of a new vaccine adds little to total labour costs.

Table 3 estimates the effect of immunization on under 5 mortality in Papua New Guinea. Hepatitis B vaccine is omitted because its main benefits occur later in life, and pigbel vaccine is omitted because its use is regional. There is strong evidence for the estimate of the effect of measles vaccine on total mortality in Tables 2

TABLE 2

COST IN US\$ PER LIFE SAVED FOR FOUR VACCINES IN PAPUA NEW GUINEA

	Reduction in mortality	Lives saved	Doses x cost/dose	Cost per life saved
BCG	50% (birth - 4 years)	9000	1 x \$0.08	\$ 1.30
Measles	50% (6 months - 4 years)	4500	2 x \$0.25	\$ 16.00
<i>S. pneumoniae</i>	20% (birth - 4 years)	3600	2 x \$1.00	\$ 83.00
<i>H. influenzae</i>	9% (4 months - 4 years)	970	2 x \$2.50	\$770.00

and 3 (3), moderate evidence for the effect of BCG vaccine, and only indirect evidence about *H. influenzae* type b (Table 1) and DPT-polio vaccines (16-18). Table 3 is for illustrative purposes only: it assumes ideal conditions with 100% immunization rates at the correct ages, which can never be achieved in practice. The calculations assume that the vaccines have independent effects on mortality so that it is valid to multiply the effects of the individual vaccines – it is shameful that we do not have more reliable information about the effect of individual vaccines, and combinations of vaccines, on total mortality (5).

Table 3 suggests that universal immunization with BCG, measles and DPT-polio vaccines would reduce under-5-year mortality from 120 per 1000 livebirths to just 52 per 1000, for a total vaccine cost of only US\$180,000. This is a spectacular reduction in mortality at very modest cost. Two doses of polysaccharide pneumococcal vaccine (to the mother in late pregnancy and to the baby at 8-9 months of age) might achieve a further 20% reduction in mortality, to 42 per 1000 at a cost of another \$300,000. However, *H. influenzae* type b vaccine has only a modest additional effect at considerable cost.

TABLE 3

CUMULATIVE EFFECT ON MORTALITY OF ACHIEVING 100% IMMUNIZATION RATES WITH FIRST BCG, THEN MEASLES, DPT-POLIO, *S. PNEUMONIAE* AND FINALLY *H. INFLUENZAE* VACCINES (ASSUMING 150,000 BIRTHS/YEAR AND 33% CURRENTLY FULLY IMMUNIZED WITH BCG, MEASLES AND DPT-POLIO)

	<5 year mortality per 1000 livebirths			
	Currently not fully immunized	Cost (US\$)	Unimmunized (reference)	Already immunized Total
Current situation			154*	52* 120
BCG	100,000 (67%)	12,000	154 x 0.5 = 77 (4)	52 69
Measles	100,000 (67%)	75,000	77 x 0.75 = 58 (3)†	52 56
DPT-polio	100,000 (67%)	91,500	58 x 0.9 = 52 (16-18)	52 52
<i>S. pneumoniae</i>	150,000 (100%)	300,000	52 x 0.8 = 42 (9)	- 42
<i>H. influenzae</i>	150,000 (100%)	750,000	42 x 0.95 = 40‡	- 40

* The current mortality rates (154 for 100,000 unimmunized, 52 for 50,000 immunized) are calculated so the overall initial rate is 120 and so both rates are the same after adjusting the unimmunized rate for BCG, measles and DPT-polio immunization (154 x 0.5 x 0.75 x 0.9 = 52)

† First measles immunization at 6 months; 50% deaths by 6 months

‡ From Table 1; second dose haemophilus vaccine at 4 months; 40% deaths by 4 months

Delivery of vaccines

It will not be easy to achieve high immunization rates in the isolated rural areas of Papua New Guinea, but with sufficient commitment, it could be done. Occasional special 'immunization days' are certainly not the answer. The conventional wisdom is that we should strengthen hospitals and health centres so that they will then be able to support immunization effectively. Perhaps this should be turned around, so that immunization has the highest priority – and if a strong immunization service leads to improvements in curative services, then that would be helpful.

Health workers, government, the general population and overseas donors will have to be convinced of the very great benefits of effective immunization in Papua New Guinea. A sustained education campaign will be needed in addition to the establishment of an effective system of immunization. There will need to be guaranteed supplies of consumables, an effective cold chain and an efficient delivery system. Where immunization services already exist they will need to be strengthened, but special immunization patrols will need to be established in many remote areas. In isolated regions, there is a strong case for using pulse immunization – in addition to routine immunization, all children in a particular age group are immunized once or twice a year regardless of their immunization history (15,19,20).

The immunization patrols will need to visit remote areas at least every 3 months; this will be a difficult task and expert support and supervision will be critically important. Perhaps appropriate financial inducement should be offered to encourage regular and effective patrols, subject to random independent checks of the proportion of children who have seroconverted. However, the success of immunization must be measured by reduction in disease, not by immunization rates or seroconversion (21).

Conclusion

The current EPI (Expanded Programme on Immunization) vaccines do not prevent the two main causes of death in children – pneumonia and diarrhoea. Until now, it has

been important to prevent pertussis, measles and tetanus by immunization, but this has had to be balanced against the need to provide curative services for pneumonia and diarrhoea. However, the recent evidence that measles and BCG vaccines dramatically reduce child mortality through nonspecific effects means that immunization must now have the very highest priority.

Although we do not know enough about the effect of immunization on total mortality in children or adults, the available data suggest that there would be spectacular reductions in child mortality if there were universal immunization with BCG, measles and DTP-polio vaccines. In addition, we should study the effects of immunizing mothers, infants and adults with polysaccharide pneumococcal vaccine. A radical shift in emphasis from hospitalization to immunization would dramatically improve the health of adults and children in Papua New Guinea.

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