Immunisation with a polyvalent pneumococcal vaccine

Effect on respiratory mortality in children living in the New Guinea highlands

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SUMMARY In Tari, in the southern highlands of Papua New Guinea, each child experienced, on average, two acute lower respiratory tract infections (ALRTI) between birth and age 5 years. The yearly mortality rate from ALRTI was 30 per 1000 in infants, and 4 per 1000 in children aged between 1 and 4 years. A double-blind controlled trial of a 14-valent pneumococcal polysaccharide vaccine was carried out on 871 children from this community who were aged between 6 months and 5 years. Morbidity from ALRTI was lower (by 37%) in children given the vaccine provided they were at least 17 months of age at the time of immunisation. There were 8 deaths from ALRTI in the placebo group, but only 1 death in the vaccine group.

In 1970, about 10 000 people living in Tari in the southern highlands of Papua New Guinea were placed under household surveillance in order to study morbidity and mortality rates from acute lower respiratory tract infection (ALTRI). In 1973, a trial of a 14-valent pneumococcal polysaccharide vaccine in persons aged at least 10 years showed fewer confirmed pneumococcal infections in the vaccine group; the vaccine was also effective in preventing death from pneumonia.¹

ALRTI constitutes an even greater health problem in children in Papua New Guinea than it does in adults. This paper reports details of morbidity and mortality in children under age 10 living in Tari during 1972 and 1973, as well as the results of a trial, in children under age 5, of the same 14-valent pneumococcal vaccine earlier tested in adults. The trial started in May 1974.

Materials and methods

Study area and population. The Tari basin is an isolated region in the western third of the Southern Highlands Province and lies at an altitude of between 5000 and 6000 feet. The inhabitants, the Huli people, are mainly subsistence farmers whose staple crop is the sweet potato. In mid-1973, 10 260 people were under surveillance for ALRTI, and of these,

3023 were children under age 10. The yearly infant mortality rate was 72 per 1000; mortality in children aged between 1 and 4 years was 16 per 1000; and in children aged between 5 and 9 years it was 3 per 1000. ALRTI was the main cause of death in children, followed by enteritis necroticans, gastroenteritis, and dysentery. Health services in the study area were adequate: oxygen and a range of antibiotics could be obtained from the hospital and the two health-centres, and procaine penicillin could be obtained from the three aid-posts. These health services were well used and 61% of infants under age 1 year, and 70% of children aged between 1 and 4 years had had treatment in the course of terminal illnesses.

Minor degrees of malnutrition are not uncommon in Tari. Median weight for age declines from 96% of the Harvard standard² in the first 6 months of life to 85% in the second 6 months, and then more slowly to 79% in children in their fifth year. Weight for height is less severely affected, and then mainly in children in their second year when the median value is 93% of the Harvard standard.³

Surveillance methods and diagnosis. Households were visited once every 2 weeks by Huli reporters—young men with a primary school education. Children were selected for further examination if they were 'sick with a cough'. They were considered to be suffering

from ALRTI if they suffered from cough or breathlessness, and had some other sign of lower respiratory involvement—such as intercostal indrawing. Each child was placed in one of two groups (severe or moderate ALRTI) according to his respiratory rate.

Severe ALRTI. This was defined as a respiratory rate of 50 per minute or more in an infant under age 1 years, or with a rate of 40 per minute or more in a child aged at least 1 year.

Moderate ALRTI. This was ALRTI which did not meet the above criteria of severity.

If a child died at home before he could be examined, a diagnosis of ALRTI was made if he suffered from cough, and either fever or breathlessness.

Surveillance of all children in the morbidity study area was maintained from January 1972 to June 1974. Thereafter, surveillance was maintained only of participants in the children's vaccine trial. Morbidity surveillance ended in September 1976, and mortality surveillance in mid-1977.

Vaccine. The vaccine (lot 464/c-A260) had been prepared by Merck Sharp and Dohme Research Laboratories, West Point, Pennsylvania for the trial in adults. It was a 14-valent preparation of purified pneumococcal capsular polysaccharide containing the following serotypes: 1, 2, 3, 4, 5, 6, 7, 8, 12, 14, 18, 23, 25, and 46 (Danish nomenclature). The vaccine was supplied in 6.0 ml phials, and the vaccine dose was 0.5 ml. Each 1.0 ml of vaccine contained 93 µg of capsular polysaccharide per pneumococcal type. A saline placebo had been prepared by Merck Sharp and Dohme.

Vaccination procedures. Children entered the trial, which was double-blind, during May and June 1974. Procedures followed closely those of the previously reported trial in adults. At intervals of three days, 3, then 10, then 30 children were vaccinated with known vaccine and any side effect was noted. For the double-blind trial identification labels were removed from phials of vaccine and placebo which had been randomly assigned consecutive numbers. Ten sequentially numbered phials were chosen and successive children were each in turn injected from each phial. (Ten was the maximum number; if only 40 children were to be included from a census point, then only 4 phials were chosen.) A standard form of consent and explanation of the nature of the trial was read out in the local government council and in the churches before the trial, and again when families had assembled for immunisation. The parent's consent was signified by thumb print. The children in the trial

were chosen because they lived in an area that was close to health care. Investigators did not know the vaccine and placebo code numbers until the end of the study in 1978.

These procedures were approved by the Medical Research Advisory Committee of Papua New Guinea.

Investigations. Fewer resources were available to support this trial than had been available to support the trial in adults. It was only possible to give x-ray examinations in 31 % of cases, and it was not possible to carry out microbiological investigations. Serum stored for antibody studies has not yet been analysed.

Statistics. Analysis of vaccine effectiveness has been done using the methods of the poliomyelitis field trial evaluation.⁴ This method assumed an underlying Poisson distribution of cases in schools, and is appropriate in cases where a child could suffer more than a single attack of ALRTI.

Results

Morbidity and mortality from acute lower respiratory tract infections. Table 1 lists the number of attacks in children by year of birth, by age, and by severity, during 1972 and 1973. Each year group is treated as a separate cohort for the period under study. A child could expect to suffer two attacks of ALRTI by age 5, and 1.4 of these would be classified as severe. Half of the attacks would occur in the first year of life. The attack rate was about equal in the first and second 6 months of life; it then fell sharply. During 1972 and 1973, the yearly mortality rate from ALRTI was 30 per 1000 in infants, and 4 per 1000 in toddlers.

During the same period of time the x-ray films of 417 children admitted to hospital with severe ALRTI were examined. There was evidence of pneumonia in 147 (35%), evidence of hyperinflation in 37 (9%), and no abnormality in the remaining 233.

Table 1 *Number of attacks of acute lower respiratory tract infection in children during 1972 and 1973 according to year of birth, age, and severity*

Year of birth	Age (years)	At risk	Acute lower respiratory tract infection			
			Severe and moderate		Severe	
			No	Rate per 1000	No	Rate per 1000
1972	<1	366	393	1074	268	732
1971	1	274	140	511	106	387
1970	2	308	72	234	52	169
1969	3	383	32	84	19	50
1968	4	264	19	72	13	49
1967	5	289	8		4	
1966	6	346	11		2	
1965	7	312	10	25	5	10
1964	8	298	3		1	
1963	9	213	5		2	

Effects of immunisation. No side effects were reported in the 43 children injected with known vaccine, and whose mothers were directly questioned about side effects. Later, the mothers of children who participated in the double-blind trial were asked to report side effects. None did so.

Altogether 871 children, aged between 6 and 59 months at the time of vaccination, were studied. Their distribution by year of birth is shown in Table 2.

The total number of attacks of ALRTI, distributed by year of birth of the children, is also shown in Table 2. The vaccine seems to have been effective in preventing ALRTI in children born before 1973, but not in children born in 1973 or 1974. Among the former (who were at least 17 months of age at the time of vaccination) there were 74 cases in the placebo group, and 39 in the vaccine group; the vaccine was 37% effective ($P = 0.010$, 95% confidence for lower limit of effectiveness = 12%).

Table 3 shows the age in months at the time of immunisation of the affected children. It seems that children <16 months when immunised were not protected. Table 4 shows some characteristics of ALRTI in children born before 1973. The effect of the vaccine was greatest between 1 and 12 months after immunisation. If severity is assessed by respiratory rate the effect of the vaccine was greater on severe than on moderate ALRTI. There may have

been an effect on ALTRI both with and without consolidation.

There were 18 deaths in the placebo group and 10 in the vaccine group (Table 5). Nine deaths were associated with respiratory disease: 8 in the placebo

Table 4 *Characteristics of acute lower respiratory tract infections in children born before 1973*

Characteristic	Vaccine	Placebo
Length of time since vaccination		
> 2 weeks	2	1
> 1 month	8	24
> 6 months	7	17
> 1 year	21	30
> 2 years	1	2
Respiratory rate		
< 39	12	13
40-59	13	32
> 60	12	21
Not known	2	8
Radiology		
Pneumonia	2	6
Not pneumonia	6	12
No x-ray film taken	31	56

Table 5 *Causes of death in trial participants*

Cause	Vaccine (n = 401)	Placebo (n = 470)
Respiratory associated		
Pneumonia	1	6
? Pneumonia	0	1
Gastroenteritis and pneumonia	0	1
Other		
Enteritis necroticans*	4	8
Septicaemia or pyrexia of unknown origin	3	0
Accidental trauma	1	0
Gastroenteritis	0	1
Unknown	1	1

*Malnutrition cited as an associated but not directly contributory factor in 2 cases.

Table 2 *Distribution according to year of birth of children who entered the trial in May and June 1974 and the number of children who had attacks of acute lower respiratory tract infections*

Year of birth	At risk population		Acute lower respiratory tract infections	
	Vaccine (n = 401)	Placebo (n = 470)	Vaccine	Placebo
1973-4	84	96	65	64
1972	97	95	26	46
1971	51	70	7	21
1968-70	169	209	6	7

Table 3 *Distribution by age in months at time of entry to the trial of children who suffered acute lower respiratory tract infections*

Age (months)	No of children who had attacks	
	Vaccine	Placebo
< 9	17	21
10-11	10	9
12-13	7	5
14-15	7	6
16-17	3	5
18-19	4	6
20-21	1	5
22-23	3	3
> 24	21	32

Table 6 *Details of 9 'respiratory associated' deaths*

Characteristics	Vaccine	Placebo
Date of birth		
1974	0	1
1973	0	3
1972	1	2
1971	0	1
1970	0	1
Age at time of death (years)		
< 1	0	2
> 1	0	1
> 2	0	2
> 3	0	0
> 4	1	0
> 5	0	2
> 6	0	1
Length of time since vaccination		
> 2 weeks	0	1
> 1 month	0	2
> 6 months	0	0
> 1 year	0	3
> 2 years	0	1
> 3 years	1	1
Place of death		
Tari hospital	1	2
Home	0	6

group and 1 in the vaccine group. This difference is statistically significant ($P = 0.033$, Fisher's exact test). No respiratory deaths were recorded in the vaccine group in the first 3 years after immunisation; and no relationship was observed between age at the time of immunisation and vaccine effectiveness in preventing death (Table 6). Most respiratory deaths took place in the home.

Discussion

ALRTI is a main cause of mortality among infants and young children in developing countries,⁵ but is often ignored as a health problem by governments.⁶ In Africa, for example, World Health Organisation statistics indicate a yearly mortality rate from ALRTI of 14.5 deaths per 1000 in infancy, and a rate of 4.7 per 1000 in children between 1 and 4 years; there is probably considerable under-reporting of deaths however.⁵

There have been few studies of incidence in open communities anywhere in the world, and ALRTI in Tari can be compared directly with that in only two other communities. In Newcastle upon Tyne between 1947 and 1952, children suffered, on average, 0.8 attacks of bronchitis and pneumonia by age 5.⁷ (In Tari, children suffered two attacks of ALRTI by age 5). On the Colorado plateau, Navajo Indian children had an annual incidence of radiologically-diagnosed pneumonia of 252 cases per 1000 in infancy, and 50 cases per 1000 in children aged between 1 and 4 years.⁸ (There are no directly comparable results from Tari. However if we assume that 35% of severe cases had consolidation the rate in infants would have been 256 cases per 1000, and in children aged 1 to 4 years it would have been 54 cases per 1000 per annum. The rate in Tari is thus at the very least equal to the rate on the Colorado plateau, as many cases of so-called mild ALRTI would also have had consolidation.)

Over age 2 years, children have good antibody responses to immunisation with pneumococcal polysaccharide. Between 3 months and 2 years of age responses are not so good and vary with capsular serotypes.^{9,10} The effect of the vaccine upon morbidity in Tari was consistent with these findings. However, the vaccine may have protected children of all ages from death from ALRTI. If this were so, it is possible that the effect in children was similar to that in adults in the earlier trial in Tari when the vaccine had a greater effect on the severity than on the incidence of disease.

Deaths occurred in Tari despite the widespread availability of antibiotics, and the limited availability of oxygen. Although curative health services in Papua New Guinea have undoubtedly had a striking effect upon mortality in the years since the second world war,¹¹ the results from this trial suggest that further reduction in mortality from ALRTI will be best achieved by the use of vaccines, rather than by improvements in curative services.

A trial of larger scale, with continuous entry of children and with good laboratory support, is clearly needed.

The study was supported by the Department of Health, Papua New Guinea.

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Received 9 January 1980