

Pneumonia vaccine trials at Tari

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SUMMARY

Pneumonia is the commonest cause of death of children in Papua New Guinea (PNG). At Tari pneumonia is most commonly caused by *Streptococcus pneumoniae* and *Haemophilus influenzae*, which set up rapid severe infections in the lungs that require urgent treatment. In rural PNG, however, treatment is often delayed. Penicillin-resistant forms of these bacteria are on the increase. It is therefore important to have another means of protection against this serious disease. This paper describes three field trials of a vaccine against the commonest serotypes of *S. pneumoniae* found in PNG. The trials show that a pneumococcal vaccine can prevent deaths from uncomplicated acute lower respiratory tract infection in small children and adults. It is likely that the vaccine does this by limiting the replication of bacteria in the lungs and thus limiting their spread to other parts of the body.

Introduction

Pneumonia in Papua New Guinea

A community health surveillance program was begun at Tari Hospital in 1970 to study acute lower respiratory tract infections, commonly known as pneumonia. By 1972 results from the program were showing that every year at least 10% of all children under five years old were suffering episodes of pneumonia and of every 1000 children under five years, 5 died each year as a result of pneumonia. 20 persons in every 1000 aged between 20 and 49 years suffered from pneumonia each year and 2 in every 1000 died as a result. Persons between 5 and 19 years were far less likely to suffer from pneumonia than those older or younger (1). Subsequent continued surveillance showed even higher mortality from pneumonia in children: of the children aged under 5 years dying in the Tari area, 36% died as a result of pneumonia (2) and they numbered more than 10 per 1000 per year. A similar surveillance program in the Asaro Valley near Goroka produced a rate of 32% of all child deaths caused by pneumonia

(3). Elsewhere in Papua New Guinea (PNG) the death rate from pneumonia in children is similar to these rates; although these country-wide figures are based only on deaths which occur in hospitals, pneumonia has been well established as the commonest cause of death in children in Papua New Guinea (4).

Pneumonia

Pneumonia is a general term used to describe inflammation of the lungs, in which fluid fills the alveoli, or air sacs, severely restricting breathing. Pneumonia can be caused in a number of ways, but the most common cause in PNG is through an acute infection of the lungs by certain species of bacteria.

The symptoms of acute lower respiratory tract infection appear fairly suddenly and include a fever, localized pain in the chest, rapid, shallow and wheezy breathing with grunting and flared nostrils, the drawing in of the body below the chest and a cough which often produces a yellow-green mucus. Babies with severe pneumonia may be cyanosed (that

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is, have blue lips and fingers), often cannot feed and will probably have an enlarged liver. X-ray pictures of the chest of a pneumonia sufferer will reveal a build-up of fluid in part of the lungs.

These symptoms are the result of the body's reaction to an invasion of the lungs by one or more of a number of bacteria. At Tari it was found that strains of the bacteria *Streptococcus pneumoniae* and *Haemophilus influenzae* were the major cause of severe pneumonia in children and this has since been found to be the case elsewhere in PNG (4). These bacteria can be found in the noses and throats of up to 40% of all humans, where they cause few problems. In the highlands of PNG, however, they occur in larger numbers than usual, being found in the noses and throats of over 95% of infants and children (5). They may be the cause of the chronic running noses that many highlands children exhibit. Crowded, smoky and poorly ventilated houses may be responsible for the larger than usual numbers of bacteria carried by highlands children.

It is likely that these bacteria quickly invade the lungs from the nose and throat when children are affected by another infection, particularly one of the many viral infections such as colds, influenza or measles, which causes lowered resistance to bacterial infection, rapid breathing and increased mucus production from the nose, some of which finds its way into the lungs. If the bacteria become established in the lungs they cause inflammation in the alveoli. The alveoli fill with fluid and leukocytes (white blood cells, which are phagocytes (cells which attempt to destroy the bacteria); this causes pain and difficulty in breathing. The bacteria may escape from the lungs to the pleura (the membrane which lines the lungs), which increases the pain and difficulty in breathing. They may also spread into the bloodstream and be carried to other parts of the body, where they can cause heart failure and secondary infections such as meningitis.

Because these bacteria can set up a severe infection in the lungs quickly and because the death rate from a lower respiratory infection is high, especially in children, it is important that treatment is given quickly. Treatment usually

involves the use of the penicillin group of antibiotics, with chloramphenicol being reserved for severe cases. In rural PNG, however, treatment is often delayed until the sick person is severely ill. More serious is the increasing prevalence of partially penicillin-insensitive *S. pneumoniae* bacteria in PNG, almost certainly the outcome of the widespread overuse of procaine penicillin. It is likely that resistant strains of *H. influenzae* will also become more common (4). It is therefore important to have another means of protecting people from this serious disease.

Vaccines against pneumonia

It has long been known that humans who have recovered from infectious diseases are often resistant or completely immune to a subsequent infection by the same agent. When bacteria enter the human body, they carry with them, or produce on their surfaces, molecules called antigens. Antigens induce an immune response from the human body which results in the production of antibodies. Antibodies are most commonly found in the blood serum, the liquid part of the blood. Antibodies bind to the antigens on the surface of the bacteria, allowing the phagocytes to envelop the bacteria more effectively and so reduce the effects of the infection on the body.

The numbers of antibodies in the blood increase only slowly following the first invasion of the body by a bacterium. So the first time a person suffers from an infectious disease the illness may be severe. Although the number of antibodies in the blood falls away after the illness, if the body is again invaded by the same bacterium, antibodies to that bacterium are produced rapidly. The person either suffers no illness, or only a mild one.

Vaccines are materials which when injected into a person's body induce it to produce antibodies against a particular infection, without the person suffering the illness. Vaccines may be made from dead or living bacteria which have been inactivated in some way so that they cannot cause a serious illness. Many bacteria that cause pneumonia have a smooth capsular exterior made from polysaccharide molecules and pneumonia

vaccines have been made from this material. They are therefore called polysaccharide vaccines.

In order to increase knowledge about the efficacy of vaccines against pneumonia in PNG, research has been carried out at Tari since 1974 to test a number of vaccines. The rest of this paper describes that research and its findings.

Methodology of the trials

Three trials of pneumonia vaccines have been conducted at Tari. The first, on persons over 10 years of age, began in 1973, the second on children under 5 years in 1974 and the third on children between 6 months and 5 years in 1981. The third trial was conducted in conjunction with a similar trial in the Asaro Valley of the Eastern Highlands.

The vaccines trialed

The bacteria which cause pneumonia, although they may be classified as a single species like *S. pneumoniae*, are not identical in form. One internationally recognized method of classifying the different forms of a bacterium is known as serotyping. Different serotypes of a bacterial species induce different antibodies in the human body. To be successful, a pneumonia vaccine must be able to get the body to produce antibodies to all the major serotypes found to be causing pneumonia in an area.

In Port Moresby by 1973 it was known that seven serotypes (1, 3, 5, 7, 8, 19 and 46 in the Danish nomenclature) were found in sputum or blood of up to 68% of pneumonia patients. Except for type 46, these serotypes were the common causes of pneumonia elsewhere in the world. In Madang in 1970 and 1971 type 46 caused an epidemic and types 1, 4, 7 and 8 were also commonly found. At Tari, where identification was difficult because of lack of equipment, types 1 and 3 seemed to be most common (1).

The Tari trials all used vaccines prepared by the Merck, Sharp and Dohme Research Laboratories, West Point, Pennsylvania, USA. The first trial, conducted in adults, used a

vaccine of purified pneumococcal capsular polysaccharides which contained 14 serotypes (types 1, 2, 3, 4, 5, 6, 7, 8, 12, 14, 15, 18, 23 and 46). The second trial, conducted in children, used the same vaccine. The third trial, again conducted in children, used two vaccines: the first, Pneumovax, also contained 14 serotypes (1, 2, 3, 4, 6A, 7F, 8, 9N, 12F, 14, 18C, 19F, 23F and 25); the second, which was used when the expiry date of the first ran out before the trial had terminated, was Pneumovax 23 and contained 23 serotypes (1, 2, 3, 4, 5, 6B, 7F, 8F, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F and 33F).

Trial procedures

All the pneumonia trials at Tari were conducted as controlled, randomized, double-blind trials. In a controlled double-blind trial a group of people is selected from a larger population. The vaccine to be trialed is given to approximately half of the selected group, while the other half, the control group, is given a placebo, a harmless and inactive substitute, such as a sterile salt-water solution. The trial is said to be randomized because all the persons in the selected group have an equal chance of receiving either the vaccine or the placebo. During the trial, neither the staff carrying out the trial, nor the people participating in it, know who has received the vaccine and who has received the placebo: it is thus 'double-blind'. Only a monitoring staff, who are not actually involved in carrying out the trial, know which participants have received the vaccine and which ones have received the placebo. The whole group is then monitored for a period of time, to see whether the people who have received the vaccine suffer, as a group, fewer infections, or less severe infections, than the placebo group. Mathematical methods are used to decide whether the differences between the two groups are more likely to be real or the result of chance.

Before each of the trials began, messages of explanation in Huli and tok pisin were read out in churches, and given to local government councillors to pass on to their constituents. When people assembled on request to participate in the trial, they were again asked if

they wanted to participate, or if they wanted their children to participate, and their consent was recorded, with a thumb print if they could not write. Care was taken to minimize the effects of any unknown reactions to the vaccines, but nothing abnormal was observed.

Surveillance and diagnosis

Since the whole purpose of the trials was to assess whether the groups of adults and children who received the vaccine had fewer cases of pneumonia than the groups which did not receive the vaccine, it was important that the people participating in the trials were monitored for illnesses and deaths, and that illnesses which resembled lower respiratory tract infections were properly diagnosed and recorded.

The participating population (that is everyone who received either the vaccine or the placebo) was divided into two groups. One group, the 'morbidity' group, was visited at their homes, or contacted elsewhere, every two weeks by the reporters from the Tari Research Unit. The reporters asked whether any person in the household was suffering from a cough and, if so, whether they were sick. Persons who were found to be sick with a cough were examined by a doctor or a trained male nurse and if the onset of the illness was recent and there was evidence of a lung infection, a diagnosis of acute lower respiratory tract infection was made. Where possible the diagnosis was based on X-ray examination; otherwise it was based on a physical examination only. Bacteriological examination was carried out on lung fluids, on sputum and from nose and throat swabs to determine the strain of the infecting organism.

The second group, the 'mortality' group, were not followed fortnightly, but were censused at 6-monthly intervals and deaths recorded. Most deaths took place outside of a hospital and diagnosis of the cause of death was based on interviews with relatives. A diagnosis of pneumonia was made if the person had three of four symptoms: cough, fever, breathlessness and chest pain. People who had a cough and breathlessness for six months or more before the death were diagnosed as suffering from chronic lung disease.

The first trial

The first trial involved 11,958 persons aged 10 years and over, 5946 of whom received the vaccine and 6012 the placebo. Three small groups of 10, then 30 and then 100 persons were vaccinated first to test for unknown side-effects. Of the total trial population, 5373 were kept under fortnightly surveillance as a 'morbidity' group. Blood serum was collected from 22 persons before they were vaccinated and again 4 weeks afterwards and the levels of antibodies estimated by radioimmunoassay at the Department of Research Medicine, University of Pennsylvania, USA.

The second trial

The second trial used procedures very similar to the first. A small group of 43 children were vaccinated first to guard against side-effects (there were none) and then 401 children aged between 6 and 59 months at the time of the trial were given the vaccine and 470 the placebo. Fewer resources were available to conduct this trial than the first trial; only 31% of cases could be given X-ray examination and microbiological studies were not possible.

The third trial

Although the second trial strongly suggested that a vaccine could prevent child deaths, the numbers of children involved were too small to justify a program of childhood vaccination against pneumonia in PNG. The third trial involved 4862 children at Tari (2417 vaccine and 2445 placebo) and a further 1487 children at Asaro. The Asaro population was randomized by hamlet cluster in order to study the effect of the vaccine on group immunity. This was not done at Tari because the Huli do not live in hamlets. At Tari children aged between 6 and 59 months were given either the vaccine or the placebo in a first round. After that children aged 4 months and over entered the trial continuously through three rounds of vaccination per year.

In a continuous trial such as this, it is necessary to establish conditions which when satisfied will cause the trial to be terminated. The results of the trial were plotted on to sequential analysis charts. On such charts it is possible to establish a barrier or upper limit,

where the number of deaths from pneumonia of children in the placebo group is greater than the number of deaths of children in the vaccine group to an extent greater than would have occurred by chance alone, showing that the vaccine is giving protection to those children who have received it. Separate and combined charts were kept for the Tari children and the Asaro children, and for deaths from pneumonia alone and for pneumonia combined with other causes. The results from the second Tari trial were also combined with this trial.

Results

The first trial

In the three years after the trial began 303 of the almost 12,000 people in the trial died from all causes, 170 from the placebo group and 133 from the vaccine group. This represents a 22% difference in mortality between the groups, or a crude difference of 2 deaths per 1000 per year. The greatest difference between the two groups, however, involved a 42% reduction in mortality from pneumonia uncomplicated by chronic lung disease (41 placebo, 23 vaccine), which was statistically significant ($p < 0.05$ by the χ^2 test). Although persons already suffering from chronic lung disease were given much less protection, all deaths due to respiratory causes were reduced (94 placebo, 64 vaccine) (6). In early 1976, when an influenza epidemic occurred at Tari, there were 25 deaths in the trial population from respiratory causes (16 placebo, 9 vaccine), which suggests that the vaccine was continuing to reduce mortality by around 40%.

This trial also showed that antibody levels were increased following vaccination. The greatest increases occurred in people with already high antibody levels, but the highest rates of increase occurred in those with the lowest initial levels.

Pneumonia was diagnosed in 252 people in the 'morbidity' group (138 placebo, 114 vaccine) and bronchial breathing was found only in the placebo group. X-ray examination of 186 persons (102 placebo and 84 vaccine) showed a reduction in the numbers of people with more than one part of the lung infected, but other radiological differences were not significant. Bacteria cultured from the sputum

of patients showed little difference in either the isolation rates or type of infection between the placebo and the vaccination groups. However, cultures from blood and lung aspirates from 136 patients produced vaccine-specific pneumococci from 14 placebo and 2 vaccinated persons.

The vaccine reduced the multiplication of the bacteria in the lungs and their invasion of the bloodstream, but had little effect on preventing the invasion of the lower respiratory tract. The lower death rates were the result of a reduction in the severity of the pneumonia rather than of the occurrence of fewer cases. The failure of the vaccine to reduce the numbers of bacteria carried in sputum or the noses and throats of trial participants is probably because of the very high levels of exposure to the bacteria which the Huli experience. Other trials in the United States and South Africa in which vaccines did reduce the level of bacterial carriage were conducted in populations which were newly exposed to the bacteria.

The second trial

The results of the second trial were less unambiguous than those of the first trial. The main reason is that the age of the child at vaccination appeared to influence the efficacy of the protection against pneumonia. The vaccine seems to have been efficacious in preventing pneumonia in children aged 16 months and over at the time of vaccination, but not in younger children. In the 16 months and older group, 83 cases of pneumonia were diagnosed, 51 in the placebo group and 32 in the vaccine group. In the lower age groups there were 82 cases, 41 in each group, which suggests that children in the lower age groups were not protected.

There were 28 deaths from all causes (18 placebo, 10 vaccine). There were 9 deaths associated with respiratory disease (8 placebo, 1 vaccine), a significant difference ($p < 0.05$ by χ^2 test) (7). No respiratory deaths were recorded in the vaccine group in the first three years after immunization and age at time of vaccination was not associated with the efficacy of the vaccine in preventing death.

The Tari results in the second trial were

similar to trials elsewhere where children over two years have shown good responses to immunization with pneumococcal polysaccharide. However, children aged between three months and two years have had responses which vary with pneumococcal serotype and are not so good. The vaccine may have reduced the severity of pneumonia cases, as it did in the first trial, but it was not possible to show this conclusively.

The third trial

The third trial began in August 1981. At Tari the upper limit of the sequential analysis chart had been reached for pneumonia combined with other causes in April 1985 (26 deaths, 20 placebo, 6 vaccine). The upper limit for pneumonia alone had been reached earlier (20 deaths, 16 placebo, 4 vaccine). The combined Tari and Asaro limits for pneumonia alone were reached after 23 deaths (18 placebo, 5 vaccine), but the limit for combined Tari and Asaro, pneumonia combined with another cause, was never reached. It was decided on 30 June 1985, on the basis of the results to date, to stop the trial and all children who had been given the placebo were offered the vaccine. The final results differ slightly from the above figures because of deaths which occurred before the trial stopped, but were reported afterwards, or which occurred after the trial had been terminated (3). Monitoring of deaths continued until the end of 1985.

In the final result, acute lower respiratory tract infection was the sole cause of 41 deaths (29 placebo, 12 vaccine), the underlying cause associated with other causes of another 14 deaths (5 placebo, 9 vaccine), and included elsewhere in the list of causes in 23 deaths (11 placebo, 12 vaccine). There were 173 deaths from all causes (95 placebo, 78 vaccine). Thus the vaccine was efficacious in reducing the death rate only when pneumonia was the single cause of death.

The protective efficacy of the 14-valent vaccine at Tari and Asaro was 61% and of the 23-valent vaccine 53%, but the difference is not significant.

Conclusions

These trials have shown that pneumococcal vaccine can prevent death from uncomplicated

acute lower respiratory tract infection in small children and in adults. It is likely to do this by limiting the multiplication of the bacteria in the lungs and by preventing the movement of the bacteria into the blood. In the absence of a vaccine, children admitted to Goroka Hospital with pneumonia caused by bacterial infection are four times more likely to die than children admitted with pneumonia of nonbacterial origin. The death rate for admitted adults is similarly high. At Tari, between 1977 and 1983, 85% of the children in the trial who died of pneumonia had been taken to aid posts or health centres and penicillin was freely available, but 41 deaths due directly to pneumococcal pneumonia still occurred.

The trials confirmed that pneumococcal vaccine does not stimulate antibody production as effectively in young children as it does in adults. Serum antibody levels decline rapidly in children vaccinated at age 3 to 6 months so that by 2 years there is little difference between them and nonvaccinated children. Immunity is acquired steadily over time, rather than suddenly. The trials suggest that vaccination against pneumococci should first take place at six months of age. The necessity for revaccination was not conclusively demonstrated.

The trials also confirmed that if the serotypes contained in the vaccine do not match the invading bacteria in children, the vaccine cannot be effective. Further work has continued to attempt to identify which strains of pneumococcus and *H. influenzae* are most frequently responsible for serious infections.

Finally, special mention must be made of the willing cooperation of Huli parents and adult participants in the trials of pneumonia vaccines at Tari. Without them and without the dedicated work of the Tari Research Unit's Huli staff and reporters, these extremely valuable insights into the behaviour of a disease which kills so many people in PNG and around the world every year, and the means to reduce its toll, would have been impossible.

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