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SESSION II

An Epidemiologic Approach to Pneumococcal Disease

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In many countries of the developing world, pneumonia remains a leading cause of morbidity and premature mortality. In their quest for effective control measures not dependent on the socioeconomic changes in Western societies that have paralleled a reduction in mortality from pneumonia, these poorer countries are looking towards modern antibiotic therapy and pneumococcal vaccines as short-term approaches to the problem. This paper summarizes information about the response of human populations to *Streptococcus pneumoniae* with particular reference to the authors' experience in Papua New Guinea, where penicillin resistance is an increasing problem and where pneumococcal vaccines have been shown in field trials to reduce mortality from respiratory disease among both adults and children. In each developing country, basic epidemiologic data are needed to assist in choosing the best available combination of strategies for control of disease due to *S. pneumoniae*. Our current understanding of the determinants of pneumococcal carriage and pneumococcal disease is still inadequate, however, and there is need for studies of the interaction of the pneumococcus and its host at the mucosal surface to better understand the differences in the behavior observed for the various serotypes.

Our interest in disease caused by *Streptococcus pneumoniae* originally was stimulated by the fact that in Papua New Guinea (P.N.G.), pneumonia is the principal cause of admission to hospital and of death in hospital [1]. Our experience with pneumococcal disease in P.N.G. contrasted with that of clinicians in many Western countries, where the occurrence of lobar pneumonia, at least in young adults, is now comparatively infrequent.

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The problem of pneumonia, such as that faced by P.N.G., is shared by many countries in the developing world that cannot, in the near future, hope for the major socioeconomic development that was associated in Western countries with the decline in the early part of this century of mortality due to pneumonia [2]. The developing countries have benefited appreciably from immunization programs against whooping cough, measles, diphtheria, and poliomyelitis and from modern programs directed towards the eradication of smallpox and the control of malaria. The availability of pneumococcal vaccine [3] thus could represent an important new public health strategy. A necessary prerequisite to the widespread application of this vaccine is an understanding of pneumococcal ecology and epidemiology.

The Carrier State

Central to the epidemiology of pneumococcal disease is the carriage of this organism in the upper respiratory tract by significant numbers of healthy individuals. Rates of disease in adults, at least,

seem to depend on the frequency with which invasive serotypes are carried in the nasopharynx of healthy members of the population [4, 5].

The likelihood of transmission of pneumococci from a carrier to another individual is thought to be directly proportional to the frequency and intimacy of their contact. Carrier rates among adults are highest in barracks and in open dormitories [4], and spread of pneumococci within families has been well documented [6]. This spread often occurs in conjunction with viral infection of the upper respiratory tract [7, 8]. Carriage rates are highest in children of preschool age and tend to decrease with increasing age [6, 9]. Colonization of the upper airways with pneumococci may take place in some infants within hours of birth; in one early study [10], the carrier rate was 59% by the twelfth postnatal day—a rate approaching that for the infants' mothers.

It is difficult to compare carriage rates for pneumococci in different populations because culture techniques vary, and the use of different techniques has been shown to affect isolation rates [5, 11]. Blood agar (without mouse inoculation) was used as the culture medium for all of the P.N.G. studies. Despite their use of more sensitive culture techniques, Hendley et al. [6] found substantially lower rates of carriage among American families in 1973 than we have found in P.N.G. They also documented rates of carriage in adults that were higher for the pharynx than for the nose, whereas we have found the reverse. Although the limited data suggest that in Western communities the carriage rates may be lower now than they were in the mid-1930s [6, 7, 12–20], among young children from P.N.G., the rates of nasal carriage, which currently are 55%–69% [21–25], are comparable with those observed in the United States and Britain in the early part of this century.

We have observed higher rates of nasal carriage among highland dwellers than among residents of coastal P.N.G. Highland houses are without chimneys, are full of smoke, and usually have only a single room. Frequently these houses are very crowded. Coastal houses, on the other hand, usually are designed to keep the inhabitants cool and to allow a breeze to flow through the house.

We suggest that one factor that might contribute to persistence of nasal carriage among children in P.N.G. is the high prevalence of chronic nasal discharge [26, 27].

Pneumococcal Serotypes in Carriers of *S. pneumoniae* and in Diseased Individuals in Papua New Guinea

Pneumococcal types 1, 7, and 46 played an important role in cases of bacteremia among adults, but these types were isolated from carriers only infrequently. It would seem that carriage of these types is particularly likely to result in disease. Types 6, 15, 16, and 17 were carried frequently but seldom caused disease in adults. Types 6 and 19 often were associated with disease in children. In longitudinal studies we have noted that some pneumococcal serotypes (e.g., type 17) are particularly likely to persist in healthy carriers for long periods.

Presumably some immune event takes place at the mucosal surface to terminate the carriage of serotypes that are carried only briefly, and perhaps such mechanisms are relatively inefficient for those types that are carried for long periods.

Epidemiologic Aspects of Serum Antibody to Capsular Polysaccharide

In the past particular attention has been focused on the evidence that active specific immunity to the pneumococcus depends on the availability of humoral antibody directed against the capsular polysaccharide [25]. Whilst not denying the importance of antibody in serum, it is important to emphasize that it comes late in the sequence of host defenses and that we are relatively ignorant of the immune events at the mucosal surface of the upper and lower respiratory tract.

Figure 1 summarizes the antibody response to capsular polysaccharide in serum of 50 adult American patients with pneumococcal bacteremia due to various pneumococcal serotypes. In some instances convalescent-phase sera were monitored by radioimmunoassay [28] for up to 80 days. Bacteremia had occurred in some cases in spite of high levels of preformed specific antibody to capsular polysachcharides early after the apparent onset of illness. These patients were not investigated for evidence of dysfunction of phagocytes or complement. Levels of specific antibody usually rose but sometimes fell or remained unchanged in the convalescent-phase sera of patients with bacteremic infection. In some patients a decrease in specific antibody in convalescent-phase sera was associ-

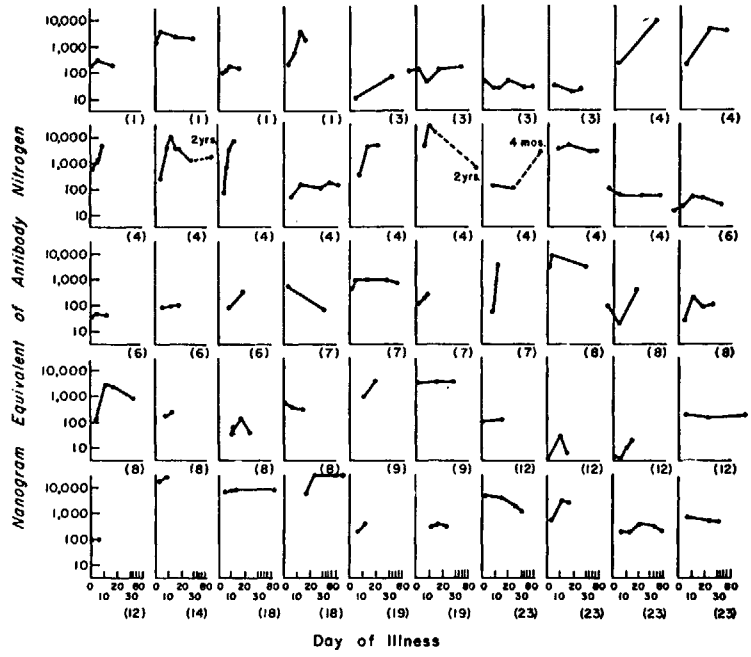

Figure 1. Homotypic antibody responses in 50 American patients with pneumococcal bacteremia who were followed for various periods after onset of illness. Pneumococcal serotypes are shown in parentheses under data for each patient. Antibody levels were measured by radioimmunoassay and expressed as ng equivalents of antibody N/ml of serum. (Studies were done in collaboration with Drs. G. Schiffman, M. Bonner, and R. Austrian.)

ated with demonstrable antigen-antibody complexes [29]. The failure of other patients to show any change in the level of specific antibody during the convalescent period from the low baseline values was found to be associated with detectable free capsular polysaccharide in the serum. Patients whose baseline levels of antibody in serum were already significantly high often did not show any appreciable change in levels during the convalescent phase.

Figure 2 compares levels of serum antibody to type 3 polysaccharide before illness with those in early and late convalescent-phase sera of 29 adult patients who had experienced an episode of seropositive pneumococcal pneumonia. Also shown are the levels of antibody to type 3 polysaccharide before vaccination and soon after vaccination in the group of elderly recipients of a vaccine containing type 3 polysaccharide. The majority of the subjects shown here possessed measurable levels of specific antibody to type 3 polysaccharide before immune stimulation, although the median level was <0.1 μg of antibody N/ml of serum. For some individuals levels as high as 0.75 μg of antibody N/ml were observed shortly before or shortly after the onset of illness. These and the observations given in figure 1 do not negate the importance of serum antibody, but they do emphasize the need to consider defense mechanisms other than serum antibody. Figure 2 also underlines the observation made earlier by Heidelberger that the absolute levels of serum antibody to capsular polysaccharides that can be stimulated by infection and polysaccharide vaccines are comparable [30].

Figures 3 and 4 show the binding profiles determined by radioimmunoassy of sera collected before and after immunization from two young adult human recipients of a dodecavalent vaccine that included type 7 polysaccharide. The sera were layered onto a Sephadex G200 (Pharmacia, Uppsala, Sweden) column, and the resultant fractions were assayed for antibody to type 7 polysaccharide with use of the radioimmunoassay system. For both of these individuals, as well as for 16 others whose antibody responses to six of the vaccine serotypes we have studied [22], the proportion of each immunoglobulin class in the antibody elicited by vaccination apparently was similar to that in the prevaccine sera.

Such findings suggest that the primary immunizing experience of an individual somehow determines the relative proportion of IgM-, IgG-, and IgA-producing cells that will be committed to that antigen. Our experience further indicates that this proportion may differ for different polysaccha-

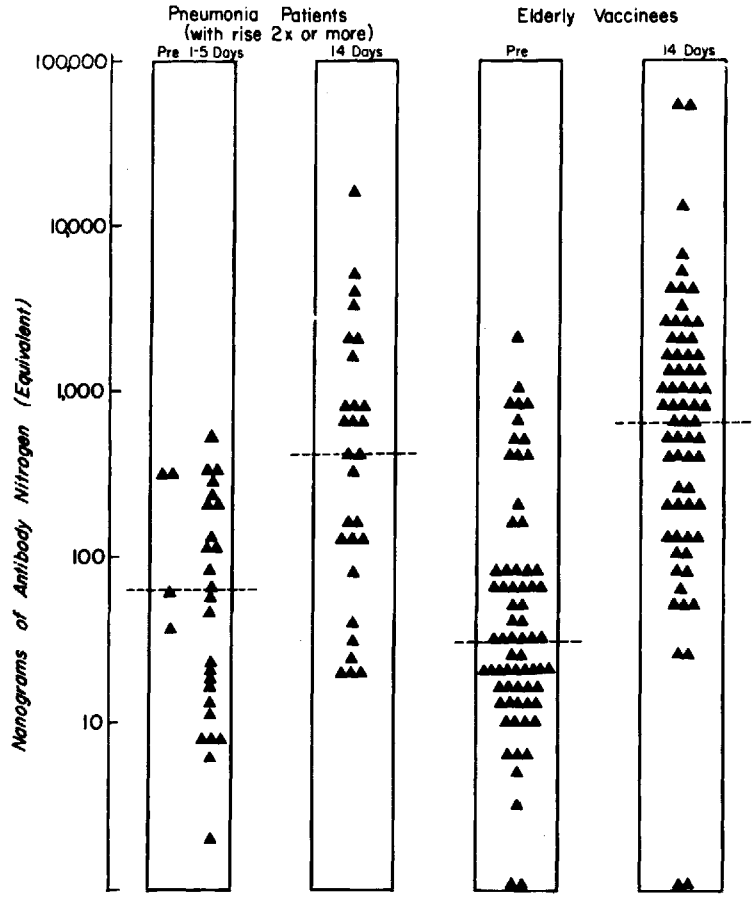

Figure 2. Comparison of levels of antibody to type 3 pneumococcal polysaccharide of 29 patients with seropositive pneumococcal pneumonia, who had an increase in antibody of twofold or greater over values before illness, with those of 67 elderly volunteer recipients of type 3 pneumococcal vaccine. Antibody levels were measured by radioimmunoassay and expressed as ng equivalents of antibody N/ml of serum. The mean value for each group is indicated by a broken line. (Studies were done in collaboration with Drs. G. Schiffman, M. Bonner, A. Ammann, and R. Austrian.)

rides in the same individual and from individual to individual for the same polysaccharide.

Presumably primary humoral immunity to capsular antigens develops in many individuals as a result of direct exposure either to the organism or to cross-reacting antigens presented to the host in some form [31]. Whereas ~50% of children develop an increase in homotypic antibody after nasopharyngeal acquisition of pneumococci, adults (who already usually have detectable levels of specific antibody to many serotypes) do not exhibit such an increase as a response to nasopharyngeal carriage [8].

The relevance of levels of antibody before vaccination to the serologic response to vaccination is emphasized in a comparison made between the response to tetradecavalent pneumococcal polysaccharide vaccine of a group of 22 P.N.G. adults and that of a group of 10 Australians of similar age residing temporarily in P.N.G. For 12 of the 13 pneumococcal serotypes for which antibody assays were carried out [24], prevaccination levels of antibody were significantly lower in the Australians than in the Papua New Guineans. Apparently as a consequence of this difference, the fold increase in antibody to capsular antigens after vaccination was significantly greater for the Australians. Multiple regression analysis for which fold increase was used as the dependent variable showed that 60% of the variance in the individual fold increase in antibody was accounted for by the prevaccination level of antibody. Differences in age and sex accounted for only 0.4% of the variance and differences in race, for only 0.001%. Nine of the serotypes accounted for only 1.4% of the variance. The relationship between fold increase and "ante" (the reciprocal of the prevaccination level of antibody) was expressed by the equation

$$\text{Fold increase} = 1.18 \times (\text{ante} + 2.65)$$

[28]. This equation is shown graphically in figure

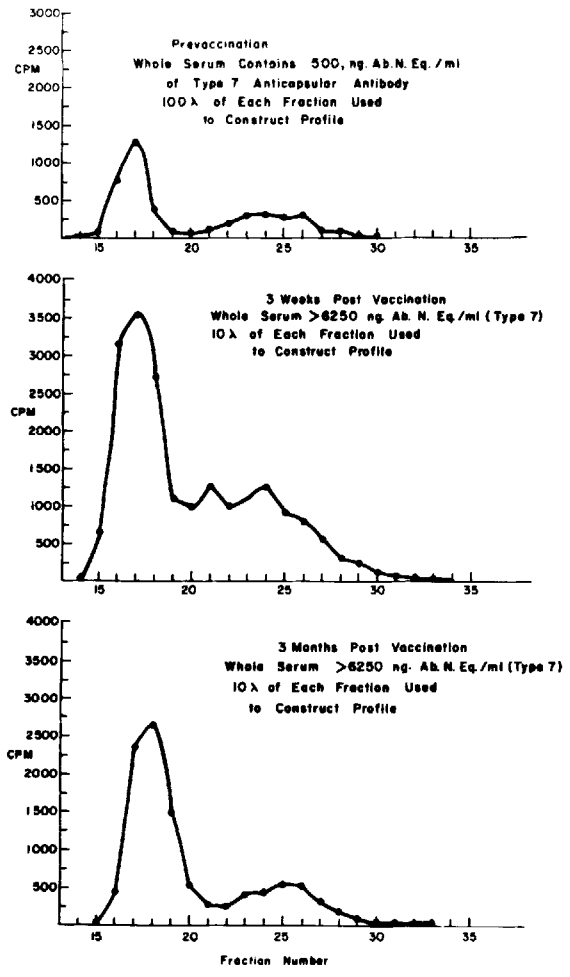

Figure 3. Pre- and postimmunization binding profiles of antibody in serum of a recipient of a dodecavalent pneumococcal vaccine that included type 7 polysaccharide. Whole serum (1 ml) was layered onto a Sephadex G200 column and the resulting fractions were assayed by radioimmunoassay with type 7 polysaccharide. Results are expressed as cpm of bound, labeled polysaccharide.

5. The shape of this graph indicates that where prevaccination levels of specific antibody N are <0.75 μg/ml, small variations in baseline values are associated with changes in fold increase that are quite large.

Why would the pneumonia-prone P.N.G. adults, as a group, have higher baseline levels of serum antibody than do their Australian counterparts who apparently are less prone to the disease? The answer could lie in the differences in the range and extent of childhood exposure of these two groups to invasive pneumococci, or perhaps, to their different exposure to cross-reacting antigens.

As reported by Heidelberger [30], the decrease in the level of serum antibody to pneumococcal polysaccharide vaccine usually occurs very slowly in young adult volunteers (see figure 6).

The Relationship Between Pneumococcal Carriage and Pneumococcal Disease

Elsewhere [32] we have reviewed published evidence relating to chilling, splenic dysfunction, alcohol consumption, viral infections of the upper respiratory tract, advanced age, and concomitant systemic disease as factors that can lower a carrier's defenses against an invasive pneumococcus. Here we will concentrate on epidemiologic aspects of the organism itself.

Hodges and McLeod [5] concluded that for each pneumococcal serotype the occurrence of pneumococcal pneumonia in a population of military recruits could be expressed with reasonable accuracy by the formula

$$\text{pneumonia rate} = \text{pneumococcus carrier rate} \times \text{nonbacterial respiratory disease rate} \times K$$

where K varied with the infectivity of the serotype of pneumococcus involved, the type-specific resistance to pneumococcal infection of individuals in the population, and, perhaps, to the nature of the nonbacterial respiratory disease involved. In the experience of Hodges and McLeod, the infectivity factor for type 1 pneumococcus was 20 times greater than that for type 9.

The above formula would lead us to expect epidemics of pneumococcal pneumonia in communities where rates of carriage of invasive serotypes are high and where a stream of susceptible recruits continuously enters the population. These circumstances apply in the South African goldmines [33], and a similar combination of circumstances probably underlies the high incidence of pneumococcal pneumonia among young adults living in the squatter settlements of the rapidly growing cities in developing countries. A continuous stream of immigrants from the remote rural areas ensures a constant pool of susceptible new recruits who may not have previously encountered or developed immunity to the invasive serotypes prevailing in the cities.

Studies of the South African gold miners have revealed that after six months in the community,

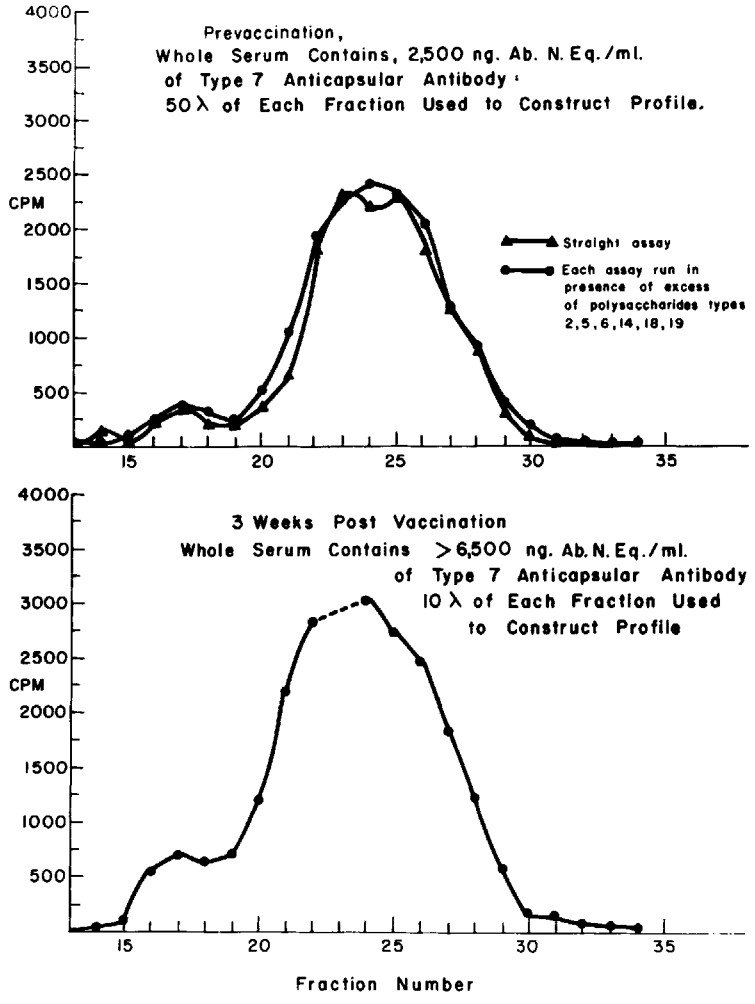

Figure 4. Pre- and postimmunization binding profiles of antibody in serum of a recipient of a dodecavalent pneumococcal vaccine that included type 7 polysaccharide. See legend of figure 3 for method of assay.

the risk to a new recruit of developing pneumonia falls dramatically [33]. It seems most likely that temporary carriage of an invasive serotype by susceptible individuals induces immunity at the level of the serum, the mucosa, or both. Although there is evidence that carriage of pneumococci can induce humoral immunity in susceptible individuals [8, 34], the relationship between immunity at the serum level and at the mucosal level has not been clarified. The possibility that the two levels of immunity may not depend on the same factors is suggested by the observation that parenteral immunization with capsular material is more effective for preventing serious disease than for inhibiting colonization of the respiratory tract by vaccine-type organisms [35, 36].

Our experience concerning the importance of a few highly invasive serotypes in P.N.G. simply supports the observation made previously by many other investigators [5, 9, 37–39] that some pneumococcal serotypes are more invasive to humans than are others. The use of pneumococcal vaccines is predicated on this observation. However, the question of whether this invasive behavior is more a reflection of the biology of the organism than of the epidemiologic inexperience or immunologic incapacity of the population remains a matter of some conjecture. It is worth considering type 6 in this context. This type is commonly carried for long periods in childhood [19, 22] and often is the cause of disease among members of that age group [38]. It has been particularly difficult to stimulate serum antibody to type 6 polysaccharide in early childhood [40] although the same capsular polysaccharide is a good immunogen in adults [41]. Type 6 does not seem to behave as invasively

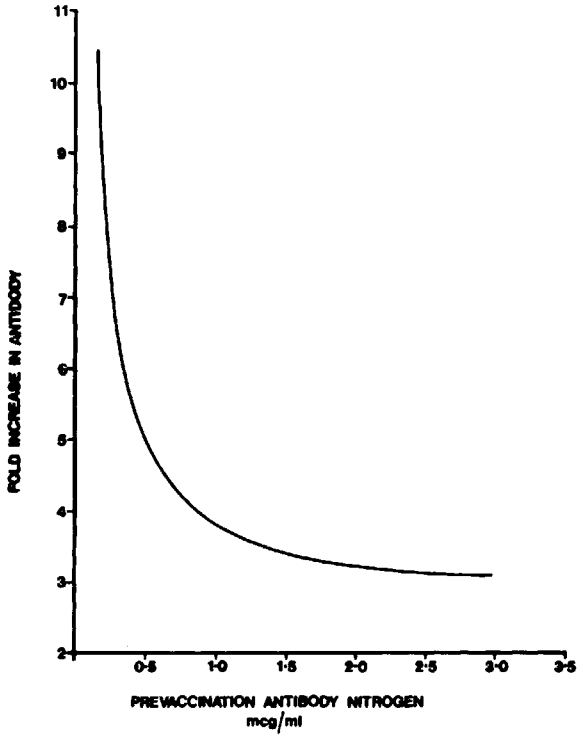

Figure 5. The equation of best fit representing the relation between fold increase and prevaccination level of antibody for the 406 antibody responses of 32 adults immunized with tetradecavalent pneumococcal vaccine. Levels of antibody were determined by radioimmunoassay. Fold increase = 1.18 × ("ante" + 2.65), where "ante" = the reciprocal of the prevaccination level of antibody.

in adults as in children, and it is carried much less frequently in the former group. The precipitation of disease in a healthy carrier of an invasive serotype might thus occur because either a precipitating factor such as viral infection or body chilling takes place before the host's immune response to the carried organism has become effective or, alternatively, because the individual is relatively incapable of mounting an adequate protective response to that pneumococcal serotype.

Antibiotics and Penicillin Resistance

The population of P.N.G. is largely rural, and since the early 1950s, its health services have been built around the rural aid post orderly, who has a limited supply of potent drugs, including procaine penicillin, at his disposal. As a consequence a great deal of procaine penicillin has been used throughout the country, and the decline in mortality from pneumonia among the rural population has been attributed to the use of this drug [42].

The undesirable consequence of making procaine penicillin readily available to all has been the widespread emergence of strains of pneumococci with increased resistance to penicillin. The earliest reports of insensitivity to penicillin [43] came from an area where systematic prophylaxis with penicillin had been tested as an approach to the control of pneumococcal pneumonia [44]. The evidence suggests that the effect of the trial was to increase transmission in the study population of penicillin-resistant strains that were present in the population before the trial began. Since that time penicillin-resistant strains have been shown to be of a great many serotypes, to be widespread throughout P.N.G. [24, 45], to occur in other countries [46, 47] and to cause pneumonia and meningitis [48, 49]. These facts notwithstanding, penicillin remains the agent of first choice in the management of pneumonia in P.N.G. and continues to be

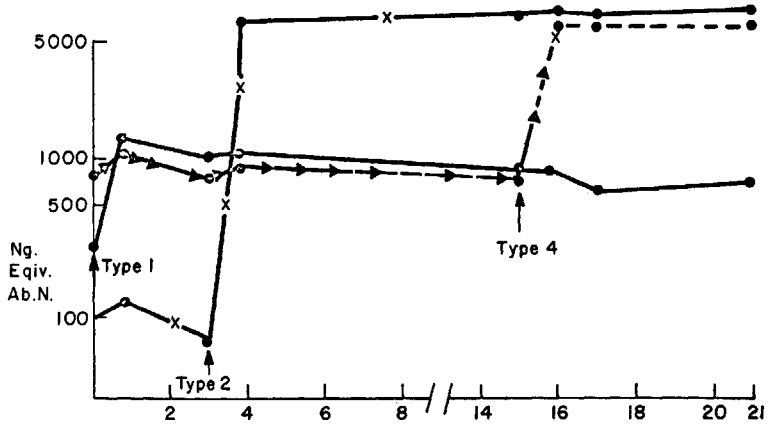

Figure 6. The persistence of antibody in a recipient of three different monovalent pneumococcal polysaccharide vaccines administered during a 15-month period. Type 1 vaccine was administered first; types 2 and 4 were administered during months 3 and 15, respectively. Antibody was measured by radioimmunoassay for up to 21 months after immunization (abscissa). Results are expressed as ng equivalents of antibody N/ml of serum. (Studies were done in collaboration with Drs. G. Schiffman, M. Bonner, and R. Austrian.)

effective in the vast majority of cases. Social and economic considerations make it likely that penicillin will continue to be the antibiotic of first choice in many developing countries until such time as the level of resistance substantially diminishes its efficacy. It is estimated that during the 10-year period from 1961 to 1971, the 2.5 million people of P.N.G. received 10,700,000 five-day courses of penicillin. The antibiotic used next most frequently during that period was chloramphenicol, for which 232,000 five-day courses were prescribed [24].

Unquestionably the availability of effective antibiotic therapy has changed the outlook for pneumococcal disease in countries where antibiotics are readily available and where primary health care services are sufficiently accessible to ensure early therapy. Yet even when services are sophisticated and accessible, pneumococcal infections with some pneumococcal serotypes reap a high mortality. It seems that in some infected individuals, antibiotics are incapable of reversing the disease process [37]. In terms of the standards for developing countries, the primary care services in P.N.G. are well developed, easily accessible, and well stocked with antibiotics, yet mortality from pneumococcal disease is high. This situation may be related in part to irreversible changes that have taken place in host physiology by the time of presentation to health services, but it also is related to the fact that health services are not used at all by some patients with pneumococcal disease.

In view of the increasing insensitivity of the pneumococcus to a variety of antibiotics and of the irreducible mortality that persists despite available antibiotic therapy, we conclude that countries like P.N.G. could benefit from an immunologic approach to the control of pneumococcal disease.

Pneumococcal Vaccines in Papua New Guinea

A randomized, double-blind, controlled trial of a tetradecavalent polysaccharide vaccine was undertaken in 1973 among 12,000 adults living in a remote rural area; the control group was given 0.9% NaCl [36]. In the three years following immunization, mortality from pneumonia was 44% less in the immunized group than in the control group, and the protective effect was still evident during an influenza epidemic three years after immunization, when vaccinees experienced a 40% lower mortality from pneumonia than did the controls. Studies of morbidity were confined to a smaller segment of the population and the period of follow-up was shorter. There were 29% fewer cases of pneumonia in the immunized population than in the control population, and the number of cases of proven pneumococcal infection (i.e., bacteremia and cases in which the lung aspirate was positive) was 85% lower. The total reduction in pneumococcal pneumonia was less impressive than was the reduction in serious cases of lobar pneumonia, bacteremic pneumonia, and death.

The limited studies of pneumococcal carriage did not suggest a reduction in carriage of vaccine serotypes in the immunized population, and we concluded that, in a population whose serum antibody levels are elevated already, enhancement of serum antibody by use of the vaccine does not decrease colonization of the pharynx or alveoli by pneumococci.

The impact of the vaccine on mortality was greatest among young individuals and among those with pneumonia that was not associated with chronic lung disease.

Data were collected also on the incidence of acute infection of the lower respiratory tract among children of mothers who had received vaccine or placebo. These data are tabulated according to the age of the child at the time the mother received vaccine (table 1). During the first one to five months after immunization, the vaccine was 32% effective ($P = 0.003$) in reducing the incidence of pneumonia among children 17 months of age or younger at the time of their mothers' entry into the trial; the efficacy diminished after that period. Children older than 17 months at the time of maternal immunization did not appear to be protected. We presume that this protective effect of maternal immunization relates either to diminished carriage of pneumococci by the mother (not demonstrated) or to the existence of antibodies in maternal milk [50].

Because of difficulties in establishing the existence of pregnancy at the time of immunization, 187 pregnant women received vaccine and 167 received placebo in a trial of vaccine in an adult population (table 2). In the three-year follow-up period, 73 (44%) of the children who had been in utero when their mothers received placebo and 57

Table 1. Effects of immunization in 1973 of mothers in Tari, Papua New Guinea, on the incidence of acute lower respiratory tract infection (ALRI) in their children.

Year of birth of children	No. of cases of ALRI in children under surveillance/no. of their mothers immunized with: Pneumococcal vaccine	Placebo
1974	17/101	9/145
1973	108/142	139/155
1972	110/144	145/155
1971	44/96	46/106
1970	22/109	21/108
1969	17/140	10/150
1968	6/107	10/97
1967	2/106	2/91
1966	4/127	4/135
1965	5/113	2/107
1964	0/101	1/114
1963	2/68	0/50
Total	337/1,354*	389/1,407
In utero in 1973	57/84	73/93

* The efficacy of the vaccine was 10% ($P = 0.08$) for the entire group of children under surveillance. For children 17 months of age or younger at the time of their mothers' immunization, the efficacy of the vaccine was 17% ($P = 0.02$) for the period of surveillance and 32% ($P = 0.003$) for the first five months after immunization.

(30%) of those whose mothers received vaccine suffered acute infection of the lower respiratory tract. The protective effect of vaccine for this group of children was of the same order of magnitude as for children younger than 17 months at the time of maternal immunization. In the three years after commencement of the trial of vaccine in adults, there were 13 deaths from all causes among children immunized in utero and 11 deaths of children whose mothers had received placebo (table 2).

There are significant difficulties in establishing the role of pneumococci in infection of the lower respiratory tract in children. The high carriage rate for pneumococcus in healthy children largely invalidates the use of nasopharyngeal swabs in diagnosis. In 1974 after analysis of the preliminary results of the trial in adults was completed, 871 children from the same population, who were between six months and five years of age, were included in a pilot, double-blind, randomized, controlled trial of the same vaccine. The morbidity

Table 2. Outcome for offspring of women immunized during pregnancy.

Outcome	Incidence for children of women given: Pneumococcal vaccine (187)	Placebo (167)
Abortions	2	0
Congenital defects	1	2
Stillborn	6	4
Died during first week of life	2	1
Died during infancy or childhood	13	11

and mortality (but not the bacteriology) of these children were carefully monitored during the ensuing three and one-half years, and the results are shown in table 3. There were 18 deaths in the placebo group and 10 in the vaccine group. The difference in the number of deaths associated with respiratory infection in the two groups was statistically significant. No deaths due to respiratory infection were recorded for the vaccine group during the first three years after immunization, and no relation was observed between the age of children at the time of immunization and the effectiveness of the vaccine in preventing death. In fact, among placebo recipients four deaths associated with respiratory infection occurred both in the group of children younger than 17 months when immunized and among those older than 17 months when immunized. There were 73 cases of acute infection of the lower respiratory tract in the placebo group and 39 in the vaccine group, i.e., the vaccine was 38% effective ($P = 0.01$). However, children who were 16 months of age or younger at the time of immunization were not protected against infection of the lower respiratory tract. These findings are consistent with the evidence that children younger than two years exhibit a variable antibody response to immunization with pneumococcal vaccine and that immunologic responsiveness may mature later to some serotypes than to others [40].

As with the trial in adults, the impact of the vaccine on the prevention of death in children was more impressive than its demonstrated effect in reducing episodes of disease. These results have been the stimulus for a more substantive evaluation of pneumococcal vaccine in childhood that commenced in P.N.G. in 1980.

Table 3. Results of a pilot trial of pneumococcal vaccine (serotypes 1, 2, 3, 6, 8, 9, 12, 14, 18, 23, 25, and 46; Danish nomenclature) in 871 children six months to five years of age in Tari, Papua New Guinea: incidence of acute lower respiratory tract infection (ALRI) and of death due to ALRI in the three and one-half year follow-up period.

Group, year of birth	Vaccine	Placebo
ALRI		
1973–1974	65/84*	64/96
1972	26/97	45/95
1971	7/51	21/70
1968–1970	6/169	7/209
Total	104/401†	137/470
Death due to ALRI		
1974	0/0‡	1/1
1973	0/3	3/6
1972	1/5§	2/6
1971	0/1	1/2
1970	0/0	1/1
1969	0/1	0/2
Total	1/10‖	8/18

NOTE. The trial was double-blind, randomized, and controlled; 0.9% NaCl was used as the placebo.

* No. of cases of ALRI/total no. of children in age group.

† For children older than 18 months at time of immunization, the efficacy of the vaccine in reducing the ALRI was 38% (P = 0.01).

‡ No. of deaths due to ALRI/no. of deaths due to all causes.

§ The only death associated with respiratory infection in a vaccine recipient occurred more than three years after immunization.

‖ For all children the efficacy of the vaccine in reducing mortality due to ALRI was 88% (P = 0.033).

The Community Control of Pneumococcal Disease

It is manifestly impossible to eradicate the pneumococcus. Nor are therapeutic services—even if they could be optimally developed in poorer countries—an adequate answer to the problem of pneumococcal disease. Polyvalent pneumococcal polysaccharide vaccines offer some promise of enhancing host resistance to systemic invasion by the highly invasive serotypes, but these vaccines have some important defects. The first is the inability of the vaccines to stimulate humoral immunity in the very young, and the second is the occasional transience of the humoral antibody response to vaccine among the elderly. What applies to young adult volunteers may not always be true for the elderly. For some of the elderly American volunteers immunized with types 3 and 8 monovalent polysaccharide vaccines, antibody decay over a 12-month period was quite marked. For others, antibody levels remained virtually unchanged after 12 months. For the group as a whole, one year after immunization the geometric mean level of antibody to type 8 was about half that achieved one month after immunization and to type 3 was just over one-third that achieved at one month [22]. It is these two groups, the very young and the elderly, who are particularly vulnerable to pneumococcal infection. In addition to the logistic difficulties encountered in the delivery of vaccine to susceptible populations, there is the added problem of ensuring the appropriateness of the vaccine formulation. Presently, as well, the cost of production of the vaccine puts its use well out of budgetary reach for most developing countries.

The declining importance of pneumococcal infection as a cause of premature death in Western society appears to have coincided with a decline in the rate of carriage of pneumococci and with a change in social arrangements, housing patterns, nutrition, and levels of crowding. Widespread community use of antibiotic therapy for treatment of viral infections of the upper respiratory tract also may have contributed to lower rates of pneumococcal carriage and transmission. These kinds of changes cannot be replicated in the developing world in the short term.

Computerized epidemiologic models [51] have been advocated to assist in the planning of national programs for the control of infectious disease. An adequately comprehensive model has not yet been developed for pneumococcal disease, and there are difficulties in applying such techniques to an organism that has many serotypes and that interacts with other respiratory pathogens in various ways. Construction of simulation models may help focus attention on the current epidemiologic ignorance surrounding pneumococcal disease.

Throughout an individual's lifetime, his or her relationship with each pneumococcal serotype may pass through a number of distinct stages. At any one time an individual may be in one, or sometimes more, of the following states or have one or more of the listed manifestations of infection: (*1*) newborn, nonimmune; (*2*) passively immune due to maternal antibody; (*3*) temporary carrier; (*4*) partially immune; (*5*) chronic carrier; (*6*) vaccinated; (*7*) permanently and naturally immune;

(*8*) otitis media; (*9*) sinusitis; (*10*) pneumonia; (*11*) meningitis; (*12*) bacteremia; or (*13*) dead.

The total incidence of pneumococcal infection in a community will be a reflection of the probability, for each serotype, of individuals in that community passing from a given state to any of the others. We presently are unable to assign probabilities or vague estimates to these transfer events for even a handful of serotypes, even for communities in which extensive studies of pneumococcus have taken place; however, a carefully focused effort might enable us to make such estimates. Once it is possible to simulate the known behavior of pneumococcal disease by means of computer models, it will become feasible to explore the ramifications of different control strategies.

The Financial Benefits of Immunization

At present two approaches to control, chemotherapy and immunization, are available to public health administrators, and these officials need to weigh the relative costs and benefits of each approach. The cost of treating pneumonia varies widely in P.N.G. A report on the P.N.G. National Health Plan for 1974–1978 [52] gives the following estimates of the costs of treating an episode of pneumonia at various levels of health care: rural aid post, K0.5; health center, K4.5; district hospital, K37.5; and base hospital, K100.[1] If we can assume that pneumococcal vaccine provides immunity for four years, that the incidence of pneumonia in adults is 20 per 1,000 per annum, and that the vaccine is 30% effective in preventing pneumonia, then the vaccine would prevent 2,400 cases of pneumonia in a population of 100,000 people over a four-year period. (The estimates given here are based on our best estimates of these rates in P.N.G.) The following sums of money might then be saved at various levels of the health care system: rural aid post, K1,200; rural health center, K10,800; district hospital, K90,000; and base hospital, K240,000.

If vaccine could be produced for K2 per dose, and if delivery of vaccine were to cost K0.5 per dose, the cost of vaccinating 100,000 people would be K250,000. It is clear then that only at the level of the base hospital is there any approximate equivalence of the cost of vaccination and the cost of therapy. For these computations we have ignored indirect financial benefits that result from lives saved and work loss prevented by a program of vaccination. Such benefits are immensely difficult to compute for developing countries.

The possibility of financial benefit from vaccination is greater for children than for adults because of the higher rates of disease in the former group. Let us assume again that the vaccine acts for four years, that the incidence of infection of the lower respiratory tract in children between the ages of six months and five years is 150 cases of pneumonia per 1,000 per annum, and, in view of the immaturity of the children's response to vaccine, that the vaccine is only 13% effective for lowering this incidence of pneumonia in this age group. Over a four-year period, in a population of 100,000 vaccinated individuals, the vaccine would prevent 7,800 cases of pneumonia, the treatment of which would cost K780,000 at base hospitals and K292,500 at district hospitals. The cost of vaccination would have been the same as in the previous example: K250,000. Under these circumstances, in purely financial terms, a case could be made for the immunization of children near base and district hospitals but not of children near aid posts or health centers.

It is these kinds of considerations, when coupled with information about prevention of mortality, that are likely to determine the feasibility of using pneumococcal vaccine in the developing world, where resources for health care are pitifully limited.

Looking Ahead at the Control of Pneumococcal Disease

Despite 100 years of effort, our understanding of the epidemiology of the pneumococcus still is fragmentary; this organism continues to pose a major threat to vast numbers of the world's inhabitants. As the second century of research on the pneumococcus begins, the entry of the World Health Organization [53] into the field of acute respiratory infections, the massive death rates from pneumonia in many developing countries, the growing levels of antibiotic resistance among

[1] The P.N.G. Kina (K) currently trades for about U.S. $1.50.

pneumococci, and the licensure of pneumococcal vaccines pose important challenges to epidemiologists, immunologists, microbiologists, health care administrators, and clinicians throughout the world.

Antibiotics and pneumococcal vaccines can be applied optimally only in the light of extensive epidemiologic information about prevailing rates of disease, distribution of serotypes, and sensitivity of microbes to antibiotics. Conventional bacteriologic and serologic techniques are too costly and cumbersome for use in the wide range of studies that are needed to make the two existing control measures more effective, and new methods of diagnosis are needed. New approaches to the control of pneumococcal infections may well evolve from improved understanding of the human ecology of this organism and from much needed studies of the interaction of the pneumococcus and its host at the mucosal surface. We still do not understand the basis of the injury done to the human host by the pneumococcus, knowledge of which would provide the real foundation for an understanding of the apparent differences in invasiveness of the various serotypes.

Our experience in P.N.G. leads us to suggest that much could be gained by focusing detailed epidemiologic research on a limited number of serotypes. We would suggest that, in P.N.G. at least, serotypes 1, 6, 15, and 46 deserve special attention: types 1 and 46, because of their highly invasive behavior in adults, type 6 because of its apparent importance in disease in children and the difficulty that young children have in making antibody to it, and type 15 because of its frequent presence in carriers but rare role as the cause of serious disease. The application of modern microbiologic and immunologic techniques to trace, from birth, the epidemiology of such serotypes could well provide information essential to the evolution of new methods of control.

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