PERSONAL PRACTICE

Should the new pneumococcal vaccine be used in high-risk children?

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A new conjugate 7-valent vaccine to prevent pneumococcal infection (Prevenar, Wyeth) has recently received a European licence for use in young healthy children. The vaccine is not currently included in the universal immunisation schedule in the UK or elsewhere in Europe, although it is being used widely in the USA. Its availability for purchase raises the question whether paediatricians should consider using it in high risk children, including those for whom the polysaccharide 23-valent vaccine was previously recommended, until (or unless) it is introduced into general use—indeed the Chief Medical Officer for England and Wales has recently made a recommendation regarding such children aged less than 2 years. We review the evidence concerning use of the vaccine in such children and make suggestions as to how the vaccine may be used while further information is collected.

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Following a positive opinion from the Committee for Proprietary Medicinal Products issued in October 2000, the European Agency for the Evaluation of Medicinal Products (EMEA) announced in February 2001 that a European licence had been granted for Prevenar,[1] a 7-valent conjugate pneumococcal vaccine manufactured by Wyeth Vaccines. The vaccine is licensed for use in healthy children aged 2 months to 2 years, as a course of four doses, to prevent meningitis and septicaemia,[2] and is the first of several new pneumococcal vaccines designed for young children to become available.[3]

This creates a novel situation in the UK. Previous infant vaccines against bacterial meningitis (*Haemophilus influenzae* type b and meningococcus group C) have received national (not European) licensure immediately before being introduced into the universal national schedule in conjunction with a catch up campaign. In the case of this pneumococcal conjugate vaccine, although it is likely that universal introduction will occur in due course, national studies are not complete, the nature and progress of the decision making process remains uncertain, and so there will be a period during which the vaccine is licensed and for sale, but neither recommended nor available as part of a general national programme. On 4 January 2002 the Chief Medical Officer issued a newsletter recommending limited use of the vaccine in children under 2 years old and considered to be at high risk of pneumococcal infection—

suggesting dose regimens similar but not identical to those we will suggest in this paper.[4]

Thus, some paediatricians may be considering whether to use the vaccine to immunise patients at high risk of pneumococcal infection either instead of, or in combination with, the existing licensed 23-valent unconjugated pneumococcal vaccine. Such use lies outside the current licence. However, there is ample precedence in paediatric prescribing of off-licence use of many formulations,[5] and there are encouraging immunogenicity data for pneumococcal conjugate vaccines in children in high risk groups, including those with sickle cell disease (SCD)[6 7] and HIV infection[8–10] which, in general, show better antibody responses following conjugate than polysaccharide vaccines,[8] although further data on this should be available shortly. There is evidence that older children who make poor immune responses to polysaccharide can respond well to immunisation with conjugate vaccine[11 12] as do otitis prone children.[13] It is also possible to extrapolate from the studies in healthy children: the conjugate vaccine is at least as immunogenic as the polysaccharide vaccine in healthy children[14]; unlike polysaccharide vaccine, it induces immunological memory and thus, probably, longer lasting protection against disease[15]; it has a good safety profile in infants and young children; and it is highly protective against invasive disease.[2] Accordingly, we outline here our personal views as to appropriate use of the vaccine in selected patients, pending more information. We believe that, if possible, such clinical use should be centrally audited so that valuable information is not lost. We also suggest that clinicians using the vaccine in this way should consider assessing the immunogenicity of the vaccine by performing pre- and post-vaccination serology for the seven vaccine serotypes. Finally we emphasise that this approach to use of the vaccine can only prevent a tiny proportion of the overall disease burden of pneumococcal infection in children—nevertheless, its use in this way may be of substantial individual benefit to the children concerned.

INDICATIONS
Children at high risk for pneumococcal disease

The current "Green Book"[16] recommends the pneumococcal vaccine for children aged 2 years or older who fall into the following categories:

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Abbreviations: AAP, American Academy of Paediatrics; CSF, cerebrospinal fluid; SCD, sickle cell disease

(1) Asplenia or severe dysfunction of the spleen, including homozygous SCD and coeliac syndrome

(2) Immunodeficiency or immunosuppression as a result of disease or treatment, including HIV at all stages

(3) Chronic renal disease or nephrotic syndrome

(4) Chronic heart disease

(5) Chronic lung disease

(6) Chronic liver disease including cirrhosis

(7) Diabetes mellitus.

The age limit of 2 years reflects the poor immunogenicity of the pneumococcal polysaccharide vaccine in children <2 years of age. At the time of these recommendations this was the only pneumococcal vaccine available.

The American Academy of Paediatrics (AAP) has recently reviewed its guidelines,[17] and lists several other groups of children deemed to be at high risk of pneumococcal disease:

(8) Cerebrospinal fluid (CSF) leaks (presumed high risk)

(9) All children 24–35 months old (moderate risk)

(10) Children 36–59 months old attending "out of home care" (i.e. nursery) (moderate risk)

(11) Children 36–59 months old who are native American or of African American descent (moderate risk).

It should be noted that the AAP guidelines recommend immunisation of all children 23 months of age or younger. Aside from a brief synopsis of evidence relating to nursery attendance, this recommendation and those for otherwise healthy children (numbers 9–11) will not be discussed further in this article as more UK specific data are required (and should be available) before UK recommendations for healthy children are made.

Sickle cell disease, surgical and functional splenectomy, and congenital asplenia (group1)

In children with SCD high rates of invasive pneumococcal disease were observed in the era before prophylactic antibiotics and vaccines,[18] and in certain subgroups even after these interventions.[19 20] Those with combination sickle haemoglobinopathies and thalassaemias have a lower incidence than those with SCD but a higher incidence than the general population. Functional hyposplenia is an important predisposing factor in these children.

HIV infected children (group 2)

Children with HIV have increased rates of infection with encapsulated bacteria, especially *Streptococcus pneumoniae*. The incidence is estimated to be 3–41 fold higher than that in children who are not infected with HIV.[21–23] Children with AIDS and those with high concentrations of IgG or IgM are at greatest risk.[24] Although there is polyclonal B cell activation in HIV infection, there is poor specific antibody production.

Children receiving immunosuppressive or radiation therapy and solid organ transplantation (group 2)

These children are presumed to be at high risk of pneumococcal disease, but attack rates are not known. Defective antibody production and neutropenia are likely to be responsible.

Children with congenital immunodeficiencies (group 2)

Children with primary antibody deficiency, for example, X linked agammaglobulinaemia, common variable hypogammaglobulinaemia, and IgG subclass deficiency, and those with congenital neutropenias are at greatest risk, but many other children with more minor or suspected opsonic defects may merit the best available protection from pneumococcal infections.[13] Of the many possible complement defects only those relevant to the formation of C3b are likely to be relevant (that is, C1–4).

Systemic diseases (groups 3–7)

Those with chronic cardiac, pulmonary (including asthmatics on high dose steroids), renal (including nephrotic syndrome), or liver disease, and children with diabetes mellitus are presumed to be at moderate to high risk of pneumococcal disease. There are insufficient data from which to calculate attack rates of pneumococcal disease in these groups. In some groups this reflects a general predisposition to pneumonia of whatever cause, for example, bronchial obstruction in chronic pulmonary disease. In others, defects more specific for bacterial infection such as *S pneumoniae* may also be relevant, for example, defective phagocyte function in diabetes, and hypogammaglobulinaemia in nephrotic syndrome. It is also in consideration of the consequences of serious infections in children who already have significant organ compromise, that these groups are recognised.

Cerebrospinal fluid leaks (group 8)

Recurrent pneumococcal meningitis may be seen in children with CSF leaks associated with congenital or acquired cranial defects or dermal sinuses.

Children in "out of home care" (nursery) (group 10)

"Out of home care" (nursery attendance) is associated with an increased risk of invasive pneumococcal disease in studies from Finland and the USA.[25 26] In the USA, using a definition of at least four hours/week outside the home, rates of pneumococcal infection were increased by approximately 2–3 fold; in Finland there was an odds ratio of 36 for day care attendance and 4.4 for family day care. This is likely to reflect the greater exposure to pneumococci in this setting, as shown by the higher rates of nasopharyngeal carriage. Studies assessing the risk associated with day care in the UK have not yet been published.

Prevention of pneumococcal disease in high risk groups

It could be inferred that, as the conjugate vaccines appear to be more immunogenic than polysaccharide vaccines in children with HIV[8] and SCD,[6] this will equate with better efficacy to prevent disease. However, this is not certain. Currently there are no generally accepted serological correlates of protection, and studies using available blood tests in such children have shown reasonable but not perfect correlation between available methods[27]; thus it is uncertain how to interpret antibody concentrations. Furthermore, in certain groups, especially those with HIV, their immunodeficiency involves more than just antibody production. Also of concern, and the subject of further study, are data from a study conducted in Uganda of pneumococcal polysaccharide vaccine in HIV infected adults, which showed a higher rate of pneumococcal disease in vaccine recipients.[28] It is unwise to extrapolate from this to HIV infected children in the UK, but this emphasises the importance of further studies and data collection. Finally, although the currently available conjugate vaccine incorporates the seven most common serotypes causing disease in UK children,[29 30] the large number of serotypes which exist (many of which may cause disease—approximately 90), together with the possibility that less common serotypes may to some extent replace the seven vaccine serotypes after introduction of general vaccination,[31 32] means that the additional serotype cover (23 serotypes) provided by the polysaccharide vaccine is still valuable.

Although not the subject of this commentary, antibiotic prophylaxis is clearly indicated for many children in these high risk groups, especially those in group 1.[33] It must also be emphasised that, for any child who falls into these groups, vigilance is still required for pneumococcal disease despite vaccination and/or antibiotic prophylaxis, as complete protection cannot be guaranteed.

Table 1 Suggested dose regimens for pneumococcal immunisation of vaccine naïve high risk children

	Conjugate vaccine (7-valent)	Followed by: Polysaccharide vaccine (23-valent)
Groups 1 and 2, <2 years old	3 doses	1 dose after 2nd birthday
Groups 1 and 2, >2 years old	2 doses	1 dose
Groups 3–8, <1 year old	3 doses (2 doses probably adequate if 10–12 months old)	1 dose after 2nd birthday
Groups 3–8, >1 year old	1 dose	1 dose after 2nd birthday

See text for definitions of groups. Dose intervals: 1–2 months unless delayed to second birthday.

The appropriate schedule for use of the conjugate vaccine in these groups is not known and is the subject of ongoing studies. Indeed, apart from groups 1 and 2 above, the role of vaccination is not at all clear and emphasis should be placed on the need for evaluation of vaccination. Where vaccination is clearly indicated and in those with a relatively normal immune system who are expected to make an antibody response equivalent to that of healthy children, we suggest three doses of conjugate vaccine, 1–2 months apart, may be given if aged <10 months, two doses if aged 10–12 months, and one dose if aged >12 months (see table 1). This would apply to children with CSF leaks and, potentially, those with chronic diseases such as diabetes, liver, renal, cardiac, and respiratory disease—that is, groups 3–8. A further dose of polysaccharide vaccine after 24 months of age may be advisable, both to boost the antibody concentrations of serotypes present in both conjugate and polysaccharide vaccines, as well as to broaden the serotype coverage as responses to the other 16 serotypes are more likely to be adequate after 2 years of age.

For those children whose risk is greatest (groups 1 and 2), additional doses are likely to prove necessary. Antibody measurement following vaccination may be a useful guide (see below). There are data from HIV infected adults showing enhanced immunogenicity to polysaccharide pneumococcal vaccine when conjugate vaccine has been given previously.[34] In those children <24 months of age, three doses of conjugate vaccine are recommended, followed by a dose of polysaccharide vaccine at age 2. For those >24 months of age, two doses of conjugate vaccine are probably sufficient, followed by a dose of polysaccharide vaccine. A period of one to two months between doses of vaccines would be advisable.

Many of these children will continue to be at risk of pneumococcal disease long term. Exceptions include those recovering from chronic or malignant disease, or solid organ or bone marrow transplantation. For those at continuing risk, a further dose of polysaccharide vaccine may be considered 3–5 years after the first dose of polysaccharide.

Generally, it is sensible to commence vaccination in high risk groups as soon as possible. In children with HIV infection, antibody responses to vaccination may be better in younger infants who have a relatively preserved immune system than in children with established AIDS.[9] However, children with established significant immune dysfunction at the time of diagnosis may respond better to immunisation after a period of treatment with effective antiretroviral therapy. Similarly, where possible, vaccination before splenectomy and before the commencement of immunosuppressive therapy is logical. Although immunisation of donors with conjugate Hib vaccine prior to allogeneic bone marrow transplantation has been shown to enhance vaccine responses post transplant in recipients,[35] no data regarding this approach to pneumococcal immunisation have been published.

There are no data on which to base recommendations for high risk children who have previously received the polysaccharide vaccine. There is the potential for an increased incidence of adverse reactions (especially if polysaccharide doses are given close together). Induction of immune hyporesponsiveness has been reported with repeated doses of certain polysaccharide vaccine antigens,[36 37] and so this is a theo-

retical possibility too. By definition, these children will normally be >24 months of age, and either one or two doses of conjugate vaccine (depending on the risk group—see table 1) may be most appropriate. Monitoring of serological responses will often be helpful in this group.

FUTURE RESEARCH
Further studies of the use of pneumococcal conjugate vaccines in at-risk groups, addressing their safety, immunogenicity, and efficacy and identifying the optimal schedules for vaccination are urgently required. Colleagues are encouraged to visit www.pneumo.org.uk—a website where anonymous registration of vaccine use in high risk children is being established for audit purposes, and where further information on ongoing and completed research in this area will be made available.

Ultimately, the introduction of routine infant vaccination with conjugate vaccines may result in the reduction in circulation of some serotypes of *S pneumoniae* in the childhood population, and thereby indirectly protect those who are at higher risk from disease (that is, through herd immunity). This could allow further changes to policies for preventative measures in these at-risk groups.

SEROLOGY
The measurement of pneumococcal antibody in clinical immunology laboratories is often done by immunoassay, measuring the combined antibody titre to all 23 antigens in the conventional 23-valent polysaccharide vaccine. Such assays give little interpretable information as it is unclear against which, and how many, serotypes such antibody titres are directed. Assays which measure IgG antibody to each vaccine serotype are potentially more useful, particularly if serum samples are obtained both before and after immunisation. Such results indicate whether the patient has made an immunological response to the vaccine, which serotypic components have been immunogenic, and give some limited information as to whether the patient is likely to have achieved protection against invasive disease (although definitive serological surrogates of protection have not yet been established). Pneumococcal serotype specific serology is now available in clinical immunology laboratories in several regional centres (for example, Manchester Public Health Laboratory, Withington Hospital, Manchester M20 2LR; tel 0161 291 3539).

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