Controlling invasive pneumococcal disease: is vaccination of at-risk groups sufficient?

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SUMMARY

Risk factors for invasive pneumococcal disease (IPD) include young and old age, comorbidities (such as splenic dysfunction, immunodeficiencies, chronic renal disease, chronic heart or lung disease or cerebral spinal fluid leak), crowded environments or poor socioeconomic conditions. Universal use of the 7-valent pneumococcal conjugate (7vPncCRM) vaccine for infants and young children has led to significant decreases in IPD in the vaccinated population (direct protection), and there has also been a decrease in the incidence of IPD among the nonvaccinated population (indirect immunity; herd protection). While 7vPncCRM vaccine is administered universally to children in USA, many countries of the European Union have chosen to target children with comorbidities. This review aims to highlight individual risk factors for IPD, describe studies that evaluated pneumococcal conjugate vaccines in at-risk groups and estimate the proportion of at-risk children who may have been vaccinated in the European Union since the 7vPncCRM vaccine was introduced, using UK as an example. Although immunisation targeting only children with comorbidities may achieve satisfactory results for a few, many otherwise healthy children at risk simply because of their age will be neglected, and herd protection might not be established.

Keywords: Pneumococcal disease; risk factors; conjugate vaccine; herd protection; immunisation programmes; USA; UK; European Union; epidemiology; infant

INTRODUCTION

Streptococcus pneumoniae (pneumococcus) is a leading cause of bacterial illnesses among children throughout the world, responsible for invasive pneumococcal disease (IPD) (e.g. meningitis, sepsis, bacteraemic pneumonia and bacteraemia) and non-IPD (e.g. pneumonia, acute otitis media and sinusitis). A 20-year (1980–1999) surveillance study conducted in Nottingham, UK, for instance, found that the mean annual incidence of IPD was 47.1 per 100,000 in infants younger than 1 year (1). The expansion in recent years of pneumococcal strains with diminished sensitivity to antibiotics has complicated the treatment of IPD.

The 23-valent pneumococcal polysaccharide (23vPncPS) vaccines, available since the 1980s, are licensed only for at-risk individuals older than 2 years of age. With the advent of the pneumococcal conjugate vaccine, the focus of disease management for children below 2 years of age has shifted to prevention. In spite of this advance in vaccinology, from the polysaccharide to the conjugate vaccine, the concept that pneumococcal vaccination would only be meant for at-risk individuals has persisted in the minds of many public health officials and practitioners.

Children younger than 2 years are one of the highest risk groups for IPD; therefore, a 7-valent pneumococcal conjugate (7vPncCRM) vaccine was developed that protects against the important paediatric serotypes, 4, 6B, 9V, 14, 18C, 19F and 23F. Although young age is a major risk factor for IPD, factors such as crowded living conditions and lower socioeconomic status may further increase the likelihood of developing pneumococcal disease (2) among otherwise healthy children.

Two 7vPncCRM vaccine immunisation approaches have been utilised to date: universal vaccination of all infants and children, or vaccination targeted to certain vulnerable groups. The USA adopted the former approach in August 2000, when
the Advisory Committee on Immunization Practices (Centers for Disease Control and Prevention) recommended vaccination for every infant and child younger than 2 years of age and also recommended catch-up vaccination targeted for all children 2–5 years of age with particular comorbidities (e.g. sickle cell anaemia, splenic dysfunction, human immunodeficiency virus (HIV) infection, chronic disease or an immuno-compromising condition). Furthermore, US authorities underscored that vaccination also should be considered for all other children 2–5 years of age, with priority given to those who are 2–3 years of age, those of African-American, Native American or Alaskan native descent or those who attend out-of-home childcare.

By contrast, the countries in the European Union have, to date, adopted an approach targeted uniquely towards at-risk children. The UK approach, for instance, is based on the January 2002 recommendations of the Joint Committee on Vaccination and Immunisation, which were subsequently broadened in August 2004 to include additional comorbid conditions.

The goal of this article is to compare the two approaches: universal vaccination of all infants and children and targeted vaccination for certain at-risk groups. Specifically, we seek to i) highlight the risk factors for IPD; and ii) describe studies that have evaluated pneumococcal conjugate vaccines in at-risk groups. Using UK as an example, we have tried to estimate the proportion of at-risk infants and young children who may have been vaccinated between the introduction of 7vPncCRM vaccine and the broadening of recommendations in August 2004.

RISK FACTORS FOR IPD

Predisposing factors, such as genetic factors, comorbidities or other pathologies, may place an individual at risk of developing IPD. Multiple genetic factors, for instance, are almost certainly associated with an individual’s risk of IPD, and some recognised phenotypic bases for risk include hypogammaglobulinaemia, impaired opsonophagocytosis activity, complement defects, or poor splenic clearance of intravascular bacteria. Anatomic abnormalities (e.g. skull fracture/ cerebrospinal fluid leak, cochlear implant or congenital heart disease), immunosuppressive therapy, bone marrow and solid organ transplantation, chronic disease (pulmonary, neurological or hepatic), diabetes mellitus and renal conditions (renal insufficiency or nephrotic syndrome) are other pathologies that increase risk (Table 1). The possibility of developing IPD is further complicated by the impact of socioeconomic factors, perinatal factors and age – individuals younger than 2 years or older than 65 years are particularly at risk (Table 1) (3–10).

Nonetheless, most children hospitalised for IPD do not belong to any recognised at-risk group. In a US surveillance study, only 27% of hospitalised children had an underlying condition (11), while Canadian, French, Spanish and Finnish studies found that 23.2% (12), 16.7% (13), 10% (14) and 16% (15) of hospitalised children, respectively, had underlying conditions.

Table 1 Some risk factors for invasive pneumococcal disease (IPD)

| Condition | Incidence/Risk | Reference |
|-----------|----------------|----------|
| <2 years of age | 34.3/100,000 | USA population (3) |
| ≥65 years of age | 41.6/100,000 | Vs. children not in group day care (4) |
| Group day care (defined as spending ≥4 h/week with ≥2 unrelated children under adult supervision) | Two to threefold greater risk | |
| Low birth weight | 2.6-fold greater risk | Vs. normal birth weight (5) |
| Pre-term <38 weeks gestation | 1.6-fold greater risk | Vs. full term (5) |
| HIV-positive/AIDS | 6100 cases/100,000 | HIV-infected children <7 years (6) |
| | 11,300 cases/100,000 | HIV-infected children <3 years (6) |
| Sickle-cell disease | 5500–6500 cases/100,000 | Children with sickle cell disease <5 years (6) |
| Socioeconomic factors | Rate of IPD >threefold greater | Canadian Aboriginals vs. Canadian non-Aboriginals (7,8) |
| Pneumococcal bacteraemia and pneumococcal meningitis rates are >fourfold greater | Alaskan Native children <5 years compared with non-Alaskan Native/non-Native American children (9) |
| IPD rates are 1.6-fold greater | African-American children <2 years compared with white children (10) |
Table 2  Recommendations for 7-valent pneumococcal conjugate vaccine use in individuals by selected countries of Europe (reviewed January 2006)

| Risk-based recommendations | AUT | BEL | DEU* | DNK | ESP | FIN | FRA | GBR† | GRC | IRL | ISL | ITA‡ | LUX | NLD | NOR | PRT | SWE§ |
|-----------------------------|-----|-----|------|-----|-----|-----|-----|------|-----|-----|-----|------|-----|-----|-----|-----|-----|
| Medical comorbidities       |     |     |      |     |     |     |     |      |     |     |     |      |     |     |     |     |     |
| Splenic dysfunction**       | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  |     |     |     |
| Immunodeficiency ††         | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  |     |     |     |
| Chronic disease§            | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  |     |     |     |
| CSF leak                    | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  |     |     |     |
| Diabetes mellitus           | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  |     |     |     |
| Cochlear implant            | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  |     |     |     |
| Previous IPD infection      | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  |     |     |     |
| 'Any other at-risk pathology' |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |

| Predisposing conditions     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Developmental delay         | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  |     |     |     |
| Failure to thrive           | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  |     |     |     |
| Prematurity                 | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  |     |     |     |
| Low birth weight            | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  |     |     |     |

| Other considerations        |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Day care                    | ✔   | ✔   | ✔   | ✔   | ✔   | ✔   | ✔   | ✔   | ✔   | ✔   | ✔   | ✔   | ✔   | ✔   | ✔   | ✔   |     |
| Family with >2 children     | ✔   | ✔   |     | ✔   |     | ✔   | ✔   | ✔   |     | ✔   | ✔   | ✔   | ✔   | ✔   | ✔   |     |     |
| Breast feeding <2 months    | ✔   | ✔   | ✔   | ✔   | ✔   | ✔   | ✔   | ✔   | ✔   | ✔   | ✔   | ✔   | ✔   | ✔   |     |     |     |
| Age-based policy (children <5 years old) – private physicians | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  |     |
| National (regional) immunisation programs | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  | ✔  |     |

AUT, Austria; BEL, Belgium; DEU, Germany; DNK, Denmark; ESP, Spain; FIN, Finland; FRA, France; GBR, United Kingdom; GRC, Greece; IRL, Ireland; ISL, Iceland; ITA, Italy; LUX, Luxembourg; NLD, Netherlands; PRT, Portugal; SWE, Sweden. *The German STIKO extends the risk-based recommendations to children <5 years of age. (July 2005). †Universal recommendations are anticipated in 2006 in Great Britain. ††Three regions have universal recommendations (Liguria, Sicily and Puglia), five have risk-based vaccination programs (Veneto, Lombardia, Lazio, Toscana and Friuli) and one has extended vaccination program (active offer) to day-care subjects (Emilia-Romagna). National Vaccines Committee has approved, in principle, universal recommendations from National Authority, through an offer to all children <24 months of age and a three-dose schedule for newborns. §One region (O¨rebro) has issued risk-based recommendations. **Including causes of splenic dysfunction such as homogamous sickle cell disease, thalassaemia, asplenia or coeliac disease. ††Primary or secondary immunodeficiency (e.g. malignancy such as lymphoma, Hodgkin’s disease or leukemia, immunosuppressive therapy, transplantation or HIV/AIDS. Immunosuppressive therapy is defined in GBR as on or likely to be on systemic steroids for more than a month at a dose equivalent to prednisolone at 20 mg or more per day, any age or for children under 20 kg at a dose of 1 mg or more per kg per day). ‡‡Excluding chronic granulomatous disease. §§Renal disease including nephrotic syndrome, chronic renal failure, renal transplantation, chronic heart disease such as congenital heart disease or heart failure, lung disease, liver disease including cirrhosis, or neurological disease. ‖Excluding asthma, apart from asthma under chronic corticosteroid therapy. [In GBR, ‘chronic lung disease’ includes asthma requiring continuous or repeated use of inhaled or systemic steroids (or with previous exacerbations requiring hospital admission) and includes children who have previously been admitted to hospital for lower respiratory tract infection]. ***Defined as ‘children kept for more than 4 h/week with more than two children not counting siblings’. †††By private physicians, nationwide. †††By private physicians, particular regions of the country.
In most countries, the schedule for paediatric 7vPncCRM vaccine vaccination is a three-dose primary series followed by a booster dose in the second year of life. There are exceptions. In UK, a three-dose primary series only is recommended (i.e. no booster). In the Nordic countries and in Italy, the standard paediatric vaccine regimen consists of a two-dose primary series and a booster dose at about 12 months of age.

EFFICACY OF PNEUMOCOCCAL CONJUGATE VACCINES IN AT-RISK GROUPS

Safety and immunogenicity studies in at-risk groups aim to demonstrate that the immune response to a pneumococcal conjugate vaccine is comparable to that seen in healthy subjects, for which vaccine efficacy may have been demonstrated. Some of the groups studied include children with sickle cell disease, HIV-infected adults and children, adults with Hodgkin’s disease or patients undergoing bone marrow transplantation.

The immunologic response in children with sickle cell disease is at least as substantial as that found in healthy patients (16). Moreover, toddlers first immunised with a 9-valent pneumococcal conjugate vaccine candidate followed by a 23vPncPS vaccine had significantly higher antibody levels for the serotypes tested than those vaccinated with the 23vPncPS vaccine alone (17). In children 2–6 years of age with sickle cell disease who were previously given the 23vPncPS vaccine, higher antibody concentrations were achieved with 7vPncCRM vaccine compared with no subsequent conjugate vaccine dose (18). It has also been shown that one conjugate vaccine dose can prime toddlers for immunologic memory, indicating that 7vPncCRM vaccine may confer protection after one dose in children 2–5 years of age (19).

The immunogenicity of the 7vPncCRM vaccine has also been demonstrated in HIV-infected adults (20) and children (21,22), in adults with Hodgkin’s disease (23) and in patients undergoing bone marrow transplantation (24). In one study of HIV-infected infants, 7vPncCRM vaccine induced geometric mean concentrations of serotype-specific serum antibody to levels >0.15 μg/ml in 95% of HIV-infected infants. Although concentrations declined at 24 months, they remained well above preimmunisation levels (25). In adults with Hodgkin’s disease, priming with a 7vPncOMPC vaccine candidate resulted in a significant increase in antibody concentration values after a subsequent dose of 23vPncPS vaccine compared with nonprimed individuals (23). In patients undergoing bone-marrow transplantation, post-transplantation antibody responses after the first two vaccine doses were greater among patients whose donors had initially received 7vPncCRM vaccine. By the third dose, >60% of patients had antibody concentrations for each vaccine serotype considered by these investigators to indicate protection (i.e. ≥0.5 μg/ml) (24).

The immune response in individuals who are nonresponders to polysaccharide vaccine has also been shown to be comparable to that seen in healthy subjects. In children and adolescents with recurrent infections, two doses of 7vPncCRM vaccine resulted in a successful vaccination (defined in this study as postvaccination titres of >1 μg/ml for ≥5 of 7 serotypes) in 50% of patients; 80% responded to ≥2 serotypes (26). In a separate study, 7vPncCRM vaccine elicited only low responses in the recurrent infections patient group; nevertheless, antibody levels were superior to those observed with the 23vPncPS vaccine (27).

In contrast to these safety and immunogenicity studies, there are a few efficacy studies in at-risk individuals. Studies conducted to date show that 7vPncCRM vaccine is highly efficacious in low birth weight and premature infants and is protective for children of the Navajo Nation in North America (5,28). Furthermore, in USA, where vaccination with 7vPncCRM vaccine is recommended for every infant and child younger than 2 years, and catch-up programmes are targeted towards at-risk children younger than 5 years, the racial disparity in IPD incidence, of children younger than 2 years, between African-Americans and whites has decreased from 3.3-fold to 1.6-fold (8). Protection from IPD has also been reported in children in the Republic of South Africa with HIV infection (29).

ESTIMATED USE OF 7vPncCRM VACCINE IN AT-RISK CHILDREN IN UK

The number of distributed doses was obtained from UK Wyeth sales records. It was assumed that all 7vPncCRM vaccine administered in UK up to the issue of the broadened recommendations in August 2004 had been given to at-risk infants and children younger than 2 years, and that they had only received, on average, two doses. (For an unvaccinated English child aged 6–12 months, only two doses are necessary, while after the first year only one dose is indicated). The estimates of the number of infants and children in UK at risk for IPD January 2002 to August 2004 were obtained by speaking with senior paediatric specialists in each clinical area (gastro, haem, cardio, CF, liver, renal, neonatal, HIV) and from their knowledge of the number of patients in their own clinics and similar clinics throughout UK, estimating numbers for UK. The numbers are likely to be underestimates.

The estimated number of infants and young children in UK who belonged to one of the groups identified to be at increased risk for IPD during the period January 2002 to August 2004 is summarised in Table 3. Excluding patients for whom exact prevalence data were unavailable (i.e. diabetes, bone marrow transplantation, primary immunodeficiency or splenectomy), there were an estimated 4000 infants and young children in UK who were eligible for 7vPncCRM vaccine in the first 2.5 years after its recommendation. Over that period, 14,800 doses
of 7vPncCRM vaccine were sold in UK. Although it is not
certain that all the doses were used for this purpose (e.g. some
doses may have been administered to healthy children or used in
clinical trials), the number of doses distributed suggests that a
large proportion of eligible patients may have been immunised.

IMPACT OF 7vPncCRM VACCINE ON US POPULATION

Clinical evaluation of 7vPncCRM vaccine for prevention of
IPD was obtained in a large-scale trial from October 1995 to
April 1999 involving 37,868 healthy infants in the Northern
California Kaiser Permanente (NCKP) population (30). In this
trial, the vaccine was 97% efficacious in the prevention of IPD
cased by 7vPncCRM vaccine serotypes in children vaccinated
with at least three doses, and 94% efficacious in children receiv-
ing at least one dose of the vaccine. Furthermore, the vaccine
was 89% effective in reducing all IPD, regardless of serotype. A
postlicensure analysis of 7vPncCRM vaccine that included the
entire NCKP population (vaccinated and nonvaccinated)
showed that from April 2002 to March 2003, no cases of
vaccine serotype disease were seen in children younger than 1
year, which compares favourably with a former incidence
ranging from 51.5 to 98.2 cases per 100,000 person-years in
the years before vaccine licensure. Additionally, there was no
evidence of a concomitant increase in IPD caused by nonvaccine
serotypes (31), although close surveillance continues.

Pneumococcal conjugate vaccines reduce pneumococcal naso-
pharyngeal carriage among vaccinated individuals, which can
decrease the likelihood of transmission to unvaccinated persons,
with less risk of infection (referred to as indirect immunity or
herd protection). In a community-randomised, 7vPncCRM vac-
cine trial among Native Americans (28), nasopharyngeal carriage
was studied in family members living in the same household as a
child vaccinated with the 7vPncCRM vaccine (32). Although
adult family members of vaccinated children had the same overall
pneumococcal nasopharyngeal rate as adult family members of
nonvaccinated children, adult family members of vaccinated
children had a significantly lower carriage rate of vaccine-type
pneumococci (p = 0.02). Similarly, nonvaccinated children in the
same household as vaccinated children were less likely to carry
a vaccine-type strain than those living with nonvaccinated chil-
dren (relative risk = 0.8; 95% confidence interval 0.7, 1.0) (32).

Recently, there has been further evidence that universal
immunisation of children younger than 2 years of age may
positively affect nonvaccinated populations. According to
Centers for Disease Control and Prevention’s Active
Bacterial Core Surveillance system, statistically significant
reductions in IPD incidence are observed in adults 20–39
years of age and in elderly adults >65 years of age (31,33).

THE FUTURE

Immunogenicity trials in individuals with HIV, sickle cell disease
or Hodgkin’s disease, as well as in haematopoietic cell transplant
recipients, show that the 7vPncCRM vaccine is both safe and
appropriately immunogenic; however, further research may be
needed in these and other high-risk groups to establish the
optimum schedule for the 7vPncCRM vaccine. Moreover,
several specific actions can be taken, both at the level of the
individual and in the general paediatric population, to
improve protection for at-risk groups. At the individual level, systemic
and mucosal immune responses to pneumococci might be enhanced
using an adjuvant, such as interleukin-12 (34) or LT-K63 (35),
or administering the vaccine by the mucosal route. In addition,
practical considerations should be implemented for children at
elevated individual risk of infection (i.e. anatomic defects, immu-
nosuppressive conditions or comorbidities), such as increasing
the number of outpatient visits for preventive care or improving
the provision of prophylactic antibiotics (36).

The diversity of recommendations for administration of
7vPncCRM vaccine to at-risk groups in countries of the
European Union is detailed in Table 2, and the lack of con-
sistency seems to reflect uncertainty among national authorities
as to who exactly is at risk. Clearly, the paediatric group at
highest risk for IPD includes all children younger than 2 years
of age; however, most of these children are not classified as at-
risk and therefore currently remain unprotected. As the identi-
fication of at-risk groups remains problematic, measures imple-
mented in the general paediatric population can benefit both
identified and unidentified at-risk groups.

An effective means of protecting at-risk individuals is to
reduce the chance of transmission by decreasing pneumococcal
nasopharyngeal carriage in the general paediatric population.
Thus, universal vaccination of children younger than 2 years
protects immunised children and, by means of herd protection,
CONTROLLING IPD

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The identification of high-risk individuals is often difficult, and vaccination programmes that target only certain sub-populations will miss individuals who would develop pneumococcal disease. Based on the success of the US experience, universal vaccination appears to be the most effective in protecting all children, who are at risk simply because of their young age.

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Figure 1 Illustration representing proportion of children with invasive pneumococcal disease (IPD) who have a risk factor.
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