Early Human Development 86 (2010) 695–701

Contents lists available at ScienceDirect

Early Human Development

journal homepage: www.elsevier.com/locate/earlhumdev

Challenges in immunisation against bacterial infection in children

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ARTICLE INFO

Keywords:
Conjugate vaccines
Haemophilus vaccines
Herd immunity
Immunologic memory
Meningococcal vaccines
Pneumococcal vaccines
Premature infant

ABSTRACT

Polysaccharide-encapsulated organisms such as *S. pneumoniae*, *H. influenzae* type b and *N. meningitidis* are the leading causes of serious invasive bacterial diseases and pneumonia in children. The use of conjugate vaccines in developed countries has markedly decreased the burden of disease and mortality from these organisms through direct protection of the immunised and through herd immunity. Although conjugate vaccines are highly immunogenic, antibody levels after immunisation in early infancy wane, leading to the need for programmes which include booster doses. Understanding the generation of long-term immunity could lead to improvements in vaccine formulation and scheduling with the ultimate goal of providing more sustained protection. Prematurity is a risk factor for disease caused by polysaccharide-encapsulated bacteria and the available data indicate that preterm infants should be immunised according to their chronological age to provide early protection.

1. Introduction

Infections caused by the encapsulated bacteria *Streptococcus pneumoniae* (pneumococcus), *Haemophilus influenzae* type b (Hib) and *Neisseria meningitidis* (meningococcus) are important causes of childhood mortality worldwide. More than 14 million episodes of serious pneumococcal disease and about 800,000 deaths in children under the age of five occur annually [1–3]. In this age group, Hib causes more than 8 million cases of serious disease and about 370,000 deaths each year [4,5]. *N. meningitidis* is thought to account for approximately 500,000 cases and 50,000 deaths each year in all ages [6]. The majority of the morbidity and mortality due to these three pathogens occurs in developing countries.

In the United Kingdom, protein-polysaccharide conjugate vaccines were introduced into the infant immunisation schedule (Hib vaccine in 1992, serogroup C meningococcal vaccine in 1999 and pneumococcal vaccine, covering 7 serotypes of *S. pneumoniae*, in 2006) successfully reducing the burden of invasive disease due to these bacteria [7–9].

2. The diseases and nasopharyngeal carriage

2.1. S. pneumoniae

Streptococcus pneumoniae is a major public health problem worldwide causing high levels of morbidity and mortality in young children who suffer pneumococcal pneumonia, meningitis and septicaemia. More common but less severe manifestations of pneumococcal infection are otitis media, sinusitis and bronchitis [2,3], which collectively place a huge burden on health services. Worldwide the highest burden of disease is suffered by children under the age of 5 years and the elderly. Individuals with immune deficiency, especially HIV infection, have a high rate of pneumococcal disease. *S. pneumoniae* is an encapsulated diplococcus and is divided into at least 91 serotypes. This classification is based on a type-specific immune response directed at the pneumococcal polysaccharide capsule, which results in a swelling of the capsule that in turn can be seen under a microscope (Quellung reaction). The resistance of *S. pneumoniae* to commonly used antibiotics is a growing problem worldwide and emphasizes the importance of preventing pneumococcal disease through immunisation [10–13]. Pneumococci are frequently and asymptomatically carried in the nasopharynx of healthy individuals with the highest colonisation rates being among young children, who are thought to be the main transmitters in the population [14,15]. Pneumococcal acquisition starts in the first few weeks of life [15]. Neonatal infections due to *S. pneumoniae* including early and late–onset sepsis as well as otitis media are relatively unusual events, but are associated with considerable morbidity and mortality. The source of transmission in these cases is not clear and the affected infants do not have obvious perinatal risk factors in the majority of cases [16].

2.2. H. influenzae type b

Encapsulated *Haemophilus influenzae* strains can be divided into six different serotypes with type b being responsible for almost all

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doi:10.1016/j.earlhumdev.2010.08.010

cases of invasive disease in children. Hib is now rare in countries with an immunisation programme and the greatest burden of Hib disease is in resource-poor countries with no immunisation programme. Invasive diseases such as pneumonia and meningitis occur primarily in children younger than 2 years and have a high fatality rate, even in countries with good medical resources. Less frequent manifestations are infections of the epiglottis, soft tissues, joints and various other sites [4,5]. Human pharyngeal carriers are the only reservoir and transmission vector for the organism. Asymptomatic nasopharyngeal carriage rises rapidly after birth and is highest in preschool children [14]. Despite introduction of the Hib conjugate vaccine in the UK, colonisation rates in school-aged children remained high in a recent study (~4%), indicating that this cohort may be an important reservoir for ongoing transmission [17]. Overall, conjugate Hib vaccines protect both those who are immunised and the unvaccinated by reducing carriage and inducing herd immunity [18,19].

2.3. N. meningitidis

Neisseria meningitidis is a leading cause of meningitis and fulminant septicaemia and is a significant public health problem particularly in developing countries. There are at least 13 different polysaccharide types, five of these accounting for approximately 90% of infections worldwide. Disease incidence and serogroup distribution vary geographically and temporally. Serogroups B and C predominate in Europe, serogroups A, C and W135 account for the majority of disease in Asia and Africa, and serogroups B, C and Y predominate in the Americas [20]. The highest disease rates occur during epidemics in the meningitis belt of sub-Saharan Africa. Endemic disease occurs worldwide and predominantly affects children, adolescents and young adults. Case-fatality is high but varies widely depending on the clinical presentation. The human nasopharyngeal mucosa is the only natural reservoir for *N. meningitidis* and nasopharyngeal carriage rather than disease is the normal outcome of meningococcal colonisation [6,20]. Carriage rates are highest amongst adolescents and young adults, carriage being very rare in children under 10 years of age. A UK study compared the carriage rates of 14,000–17,700 students aged 15–19 years old before and after introduction of the meningococcal conjugate vaccine. The proportion of individuals carrying group C meningococci fell from 0.42% to 0.09% over the 2 year study period demonstrating that meningococcal conjugate vaccines protect against carriage of serogroup C meningococci [21].

3. Vaccine effectiveness

Hib and pneumococcal conjugate vaccines were licensed after showing efficacy in large-scaled randomised controlled trials. In contrast, efficacy trials were not conducted for serogroup C meningococcal conjugate vaccines, which were licensed on the basis of safety and immunogenicity data. Phase III trials of Hib vaccines conjugated to different carrier proteins showed 83–100% protection against invasive Hib infections following 2–3 doses in infancy. Estimates of efficacy were even higher after a booster dose in the second year of life [22]. In addition, efficacy of 21% against all-cause pneumonia was demonstrated in a trial of Hib vaccine conjugated to a tetanus toxoid carrier protein in The Gambia [23]. The 7-valent pneumococcal conjugate vaccine was first introduced in the US in 2000 after demonstration of efficacy (94%) against invasive disease [24] and against episodes of WHO X-ray defined pneumonia (25%) [25]. Moderate protection against otitis media of around 55–65% has also been shown in several efficacy studies [26]. For group C meningococcal conjugate vaccines, short-term effectiveness of 95% was shown soon after its implementation in the routine UK infant immunisation programme in 1999 (as a 2–3–4 month schedule), although effectiveness of the MenC vaccine fell to low levels 1 year or more after the infant immunisation series in the absence of a booster [8]. Updated data from this cohort of children who received a 3-dose infant immunisation schedule (without a booster) are now available showing 97% vaccine effectiveness within 1 year of vaccination and 68% >1 year after vaccination [27]. Children immunised at other ages appear to have more sustained protection in the effectiveness studies [8,27] but this may not be sustained as immunity has waned [28].

4. Mechanisms of immunity

The principal aim of immunisation against encapsulated bacteria is to prevent the vaccinated individual from developing (invasive) disease caused by the organism. In the short term, this can be achieved by the induction of antibodies in the serum or on the mucosal surface that prevents colonisation or microbial invasion of the organism. The balance in the importance of mucosal and systemic immunity in preventing disease in the individual is unknown. Long-term and population protection against encapsulated bacteria depends mainly on three mechanisms: persistence of functional antibodies after immunisation, maintenance of immunological memory and herd immunity.

4.1. Protection through functional antibodies

Vaccine-induced protection is mediated by specific functional antibodies that either block adherence of the pathogen at mucosal surfaces or kills the organism in the blood immediately after invasion. Hib, meningococcal and pneumococcal conjugate vaccines are successful examples of vaccines that induce such antibody-mediated protection, preventing both mucosal colonisation and invasive disease. In the blood, protection is thought to arise as a result of either antibody directed complement-mediated bacteriolysis (*N. meningitidis* and *H. influenzae*) or opsonophagocytic killing of the bacteria (*S. pneumoniae*). There have been different correlates of protection identified for each pathogen, which are generally derived from population studies [29]. In the case of group C meningococci, the serum bactericidal assay (a functional assay involving assessment of the bacterial killing power of immune sera in the presence of exogenous complement) is used as a correlate of protection and an absolute IgG antibody concentration is used for Hib and *S. pneumoniae*.

4.2. Immunological memory

In addition to generation of specific antibodies by vaccination, immunological memory may also be an important mechanism of protection, particularly after antibody levels have waned. There is good evidence that most individuals who receive a dose of a conjugate vaccine develop immunological memory, defined as an anamnestic response to a booster dose of a vaccine. In theory, B cell memory could provide a prompt uplift in protection mediated by a rapid increase in high avidity functional antibody which rises above the level that was achieved after priming [30]. It appears that infants with a higher initial B cell response have greater antibody persistence at one year of age suggesting that the magnitude of priming, at least in infancy, determines later responses [31]. Unfortunately, in individual cases for whom the incubation period is short the memory response, which takes several days, may be too slow to provide protection [32,33]. It is now believed that immunological memory alone does not guarantee protection [34] though it may be important for those individuals who acquire an organism that has a long incubation period, giving time for a rise in protective antibody before invasive disease intervenes. These considerations indicate that maintaining serum antibody levels above the protective threshold by use of booster doses of vaccine might be particularly important when antibody levels wane.