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Vaccines against bacterial meningitis

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Meningitis remains an important cause of morbidity and mortality among children >5 years of age and is especially prevalent in developing countries. Effective routine immunization against Hib, pneumococcus and serogroupC meningococcus has had a significant impact on both invasive disease and carriage caused by these encapsulated bacteria. The major challenge in prevention of meningitis remains the delivery of vaccines worldwide, especially to resource-poor regions with the greatest disease burden.

Introduction

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Bacterial meningitis remains an important cause of morbidity and mortality in childhood despite the implementation of childhood vaccination programmes, antibiotic use and intensive care support. The fatality rates in industrialized countries are between 5% and 10%, and are considerably higher in the developing world.1–6 Survivors often have resulting neurological sequelae, including developmental delay, hydrocephalus, sensorineural deafness and seizures.5–8 The clinical severity of meningitis depends on both the nature of the infecting organism and a number of host factors.

Many viruses are also known to cause meningitis. In England and Wales enteroviruses have become the most commonly isolated agents of viral meningitis/encephalitis since the measles, mumps and rubella (MMR) vaccine was introduced routinely in 1988, resulting in the decline of mumps meningitis.[9] Before the MMR vaccine was introduced epidemics of mumps infection had occurred in cycles; incidences of 21 per 100 000 before 1988 declined to <1 per 100 000 by 1997. Enteroviral meningitis occurs predominantly during the summer and autumn months. Disease is prevented mainly through sanitary measures. Herpesvirus is a cause of meningo-encephalitis within the neonatal population and results in severe neurological sequelae in survivors.

Neisseria meningitidis and *Streptococcus pneumoniae* cause most cases of bacterial meningitis after the neonatal period. *Haemophilus influenzae*

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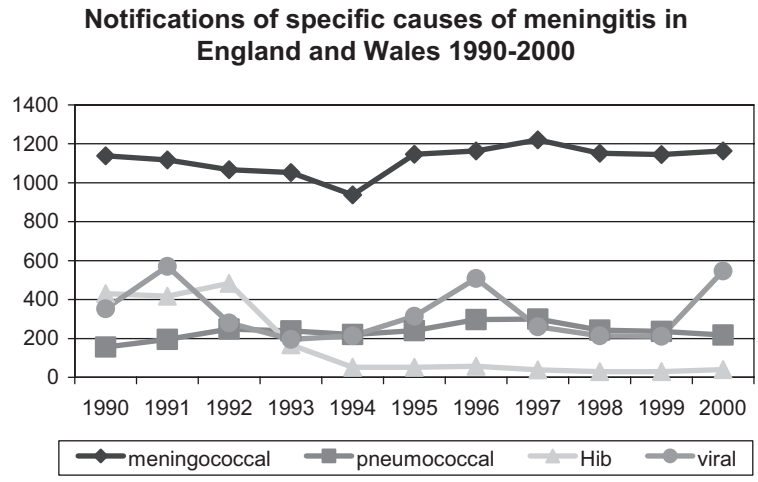

Fig. 1 Statuary notifications of meningitis causes in England and Wales 1990–2000. (Amended from 1999/2000 *PHLS Meningitis Review*, Chapter 5.).

type b (Hib), once an important cause of meningitis in children under 5, has become uncommon in industrialized countries since the introduction of the Hib vaccine from the late 1980s.[10] Group B streptococcus is the leading cause of neonatal meningitis in the UK; other causes are Gram-negative enteric pathogens and *Listeria* which account for small numbers of cases overall (Fig. 1).

Vaccines derived from the polysaccharide capsules of Hib, *S.pneumoniae* and *N.meningitidis* were first introduced decades ago. They generate T-independent immune responses, do not induce immunological memory and are not immunogenic in infants, making them unsuitable for implementation in universal infant immunization programmes. The development of protein–polysaccharide conjugate vaccines against Hib during the 1980s overcame the poor responses in infancy to the plain polysaccharides by eliciting T-lymphocyte-dependent immune responses, immunoglobulin class-switching and immunological memory. Wider use of anti-meningitis vaccines based on this technology has since become possible.[2,5]

Haemophilus influenzae type b (Hib)

Haemophilus influenzae is a Gram-negative organism that commonly colonizes the upper respiratory tract. A major virulence factor is the polysaccharide capsule with six a–f serotypes classified; serotype b is implicated in the majority of invasive disease. Hib disease is a leading

cause of mortality in the developing world and has many manifestations including meningitis, pneumonia, bacteraemia, epiglottitis, and bone and joint infections. In the majority of individuals Hib remains a harmless commensal. Disease is more common within the first 5 years of life. A number of countries now include protein polysaccharide conjugate Hib vaccines in their routine childhood immunization schedule (Fig. 2)[5,11]

Epidemiological data from a number of countries have shown significant decreases in the reported incidences of Hib meningitis following vaccine introduction (Table 1).[5] Four Hib conjugate vaccines have been developed which differ mainly in carrier protein and method of conjugation, with all four being shown to be effective against invasive disease.[12] However, these vaccines differ in their immunogenicity, and efficacy has been shown to differ between population groups[13,14] Hib conjugate vaccines have also been shown to reduce carriage and to protect unvaccinated children through herd immunity.[15,16] Recently, Hib vaccines have been included within combination vaccines in order to decrease the number of immunizations given and simplify childhood immunization programmes. However, interference has been observed, particularly in the combination of Hib with the acellular pertussis vaccines. An increase in vaccine failures attributed to this interaction led to the recent Hib catch-up campaign in the UK.[17,18] Many other countries which have

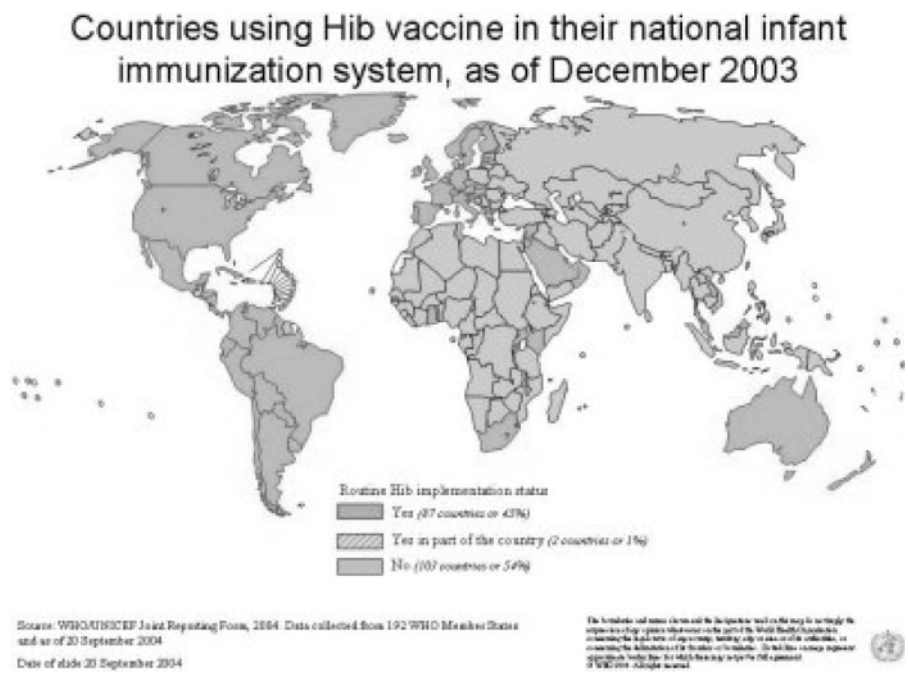

Fig. 2 WHO data for countries that have adopted Hib immunization within routine immunization programmes.

Table 1 Annual number of cases of meningitis prevented by the Hib conjugate vaccine in children aged 0–4 years

Country	No. of meningitis cases before Hib immunization	No. of meningitis cases prevented after Hib immunization
UK (1992 vs1994)	920	895
USA (1987 vs. 1995)	12 000	11 800
Chile (1995 vs. 1998)	580	560
Brazil (1988–96 vs. 1997)	29	19
Costa Rica (1992 vs. 1994)	63	40
Uruguay (1992 vs. 1995)	43	45
Australia (1992 vs. 1994)	340	300

Amended from Peltola.[5]

introduced Hib vaccine into routine vaccination schedules have done so with the addition of a booster dose in the second year of life. The main reason for this is the observation that vaccine-induced antibody wanes over time,[19,20] leading to the concern that this may be accompanied by an increase in susceptibility to disease.

In most developing countries with high infant mortality rates from Hib meningitis and pneumonia, Hib vaccination is not included in immunization schedules. However, increased uptake of vaccine is being made possible in a number of countries through the Global Alliance for Vaccines and Immunizations (GAVI), and wider use of affordable Hib may be possible through technology transfer to manufacturers in developing countries.[7] Vaccine delivery infrastructure is essential for sustainable vaccination programmes, and the evaluation of local disease burden is vital to allow cost–benefit calculations and to make the case for use of Hib vaccine in the populations with the greatest need.

Neisseria meningitidis

Neisseria meningitidis, a Gram-negative encapsulated diplococcus with inner and outer cell membranes, is classified into 12 serogroups based on the polysaccharide capsule. Five serogroups (A, B, C, W135 and Y) account for virtually all meningococcal disease.[21] In industrialized countries the incidence of invasive disease is ~1–5 per 100 000, but incidences are much higher in the developing world and during epidemics in affected populations.[8,22,23]

Serogroup A causes the majority of epidemic meningococcal infection in the African meningitis belt, amongst Hajj pilgrims and in China. Serogroup B and C meningococci were responsible for the majority of endemic meningococcal disease in European countries prior to the recent introduction of serogroup C protein–polysaccharide conjugate

vaccines.[24,25] Recently, serogroup W135 has been associated with an outbreak amongst Hajj pilgrims as well as a large epidemic in Burkina Faso during 2002 and 2003.[26–28]

Neisseria meningitidis is carried in the nasopharynx of adolescents and adults, with low carriage rates in children <10 years of age. Carriage is usually self-limiting and of variable duration. The peak incidence of invasive disease is between the ages of 6 months and 2 years, and ranges from mild disease to fulminant septicaemia leading to death within a few hours of onset. Immunosuppressed individuals, those with complement deficiency or hyposplenism and those in crowded situations are at increased risk of developing meningococcal disease.[22,23,29,30]

In several European countries and some parts of Canada, the group C glycocongugate vaccines have been adopted in the infant immunization schedule either as a three-dose course or as a single dose in the second year of life. In the UK a catch-up target campaign was also performed on children aged 4–24 months. This resulted in a dramatic decline in the incidence of group C meningococcal infection, with 97% effectiveness for ages 15–19 and 92% effectiveness for ages 2–3. In addition to the reduction in serogroup C disease, the vaccine has reduced the carriage of serogroup C meningococci inteenagers from 0.45% to 0.15%,[24,31] and thus induced herd immunity. As with Hib vaccine, the protection given by MCC vaccination is age dependent, and cohorts vaccinated at older ages seem to have longer-lasting protection than those routinely vaccinated in infancy.[32] The possibility of waning immunity in those vaccinated in early infancy may need to be considered in vaccination schedule design.

A number of trials have shown the safety and immunogenicity of both bivalent serogroups A and C and monovalent serogroup C conjugate meningococcal vaccines in adults and children. A quadrivalent ACYW conjugate vaccine is under development by a number of manufacturers and will have a major impact on non-B meningococcal disease. This vaccine has better coverage for meningococcal disease in North America, where there are high rates of group Y disease, and for travellers to regions of the world where there is an increased risk of serogroup A and W disease. This is the ideal vaccine for the meningitis belt of Africa, where outbreaks or epidemics of disease caused by A, C and W135 have been described, and for travellers and aid workers in high-risk areas.[25,33–36]

A majority of endemic disease in industrialized countries is caused by serogroup B meningococci, and vaccines against this organism are much more difficult to develop. The B polysaccharide is not immunogenic because of its chemical identity to human neural surface antigens, and attempts to improve immunogenicity could lead to the induction of autoantibodies that cross-react with glycosylated host antigens, most notably foetal brain tissue.[37] A number of different approaches to vaccine

development have been tried, but no vaccine has yet proved to be highly effective.[25,38]

Current strategies

Live vaccines

Development of immunity is thought to occur through cross-protection from commensal meningococcal species. Live-attenuated group B vaccines have been studied in animal models. *Neisseria lactamica* whole cells, outer membrane vesicles and outer membrane protein protected against challenge by meningococcal isolates representing different clonal lineages belonging to serogroups B and C.[39,40] Safety issues would need to be evaluated prior to live vaccine implementation.

Subunit vaccines

Polysacharide-based group B meningococcal vaccines. In these vaccines, the native *N*-acetyl groups on the B polysaccharide have been substituted by *N*-propionyl and conjugated to a carrier protein (recombinant PorB outer-membrane protein) in an attempt to overcome immunological tolerance. This vaccine has been shown to be immunogenic in animals and the conjugate vaccine has reached phase 1 clinical trials.[41,42] So far the vaccine has been shown to be well tolerated in adults; however, vaccine antibodies were shown to be poorly functional *in vitro*.[43] Safety concerns over autoantibody have been raised. There has been no short-term evidence of autoantibody production, but further preclinical studies are warranted.[43,44] Conjugate vaccination also has a number of cost implications.

Outer-membrane protein vesicle (OMV) vaccines. Outer-membrane vesicles contain a number of proteins which could potentially serve as vaccine candidates, with PorA being the most highly expressed and immunodominant antigen. Several efficacy trials using OMV vaccines were undertaken in the 1980s in Cuba, Norway, Iceland, Brazil and Chile, and showed efficacies of up to 80% in adults.[45–47] However, these vaccines elicited limited protection in infants and young children, and there was limited cross-protection to non-vaccine meningococcal group B strains. The OMV vaccines may have an advantage over recombinant protein vaccines as they present the conformational antigenic structures to the immune system and have demonstrated efficacy, at least in older children and adults. Further development of OMV vaccines, originally developed in Cuba, The Netherlands and Norway, is being undertaken. An OMV vaccine for children in New Zealand was introduced during 2004 for a clonal epidemic of serogroup B meningococcal disease. The New Zealand vaccine is expected to offer little cross-protection, and

Table 2 Potential vaccine candidates considered for meningococcal group B vaccination

Protein	Function
Adhesion penetration protein (App)	Autotransporter, induces antibodies after infection
Ferric binding protein (FbpA)	Iron binding
Lactoferrin binding protein (LbpA)	Lactoferrin binding
Neiserrial surface protein A (NspA)	Immunogenic surface protein
Opacity associated protein (OpA; class 5)	Adhesion, invasion
OpcA (Opc; class 5c)	Invasion, adhesion
Pilin	Adhesion
PorA (class 1 protein)	Cation porin
PorB (class 2/3 protein)	Anion porin, induces immunity
Transferrin binding protein B (TbpB)	Iron acquisition from transferrin, immunogenic in animals, not proven in humans[100,101]
Transferrin binding protein A (TbpA)	Iron acquisition from transferrin, immunogenic in animals

currently there is no evidence to support its implementation more widely.[38,46,48] Following the observation of antigenic structuring amongst hyperinvasive lineages of bacteria, a novel approach using a combination of OMVs has been suggested which may potentially offer broad cross-protection.[49]

A number of other potential outer-membrane protein vaccine candidates have been identified including NspA, a conserved protein in serotypes A, B and C. Anti-NspA monoclonal antibodies have been shown to be bactericidal but are variably expressed in pathogenic group B meningococci, resulting in inconsistent protection.[50] A number of other potential vaccine candidates are listed in Table 2. The variability in the surface proteins of *N.meningitidis* resulting from high spontaneous recombination and mutation rates as well as immunological pressure on surface-exposed epitopes means that single purified proteins are unlikely to provide a cross-protective vaccine.

Lipopolysaccharide. The advantage in employing meningococcal lipopolysaccharide (LPS) as a vaccine candidate is that there are a limited number of LPS epitopes, which are shared by all meningococci. A murine antibody directed at the core of LPS has shown high bactericidal activity as well as enhanced opsonophagocytosis. Some concerns have arisen about potential autoantibody production against erythrocytes which have a similar moiety to LPS.

Other approaches

Genome sequencing. The genome sequence of *N.meningitidis* became available in 2000 and has allowed the identification of putative surface-exposed epitopes by *in silico* analysis.[51–53] The sequence data have provided insights into the organization of the meningococcal genome and the enormous variation found at genetic level. The genetic approach is

promising in that protein vaccine candidates, which are highly conserved among all meningococcal serogroups, may be found. A number of conserved open reading frames that code for surface-exposed proteins on group A and B meningococci and a *Neisseria gonorrhoeae* strain have been identified, cloned and expressed in *Escherichia coli*. Twenty-eight of these novel proteins were shown to elicit group B antibodies, which either had bactericidal activity or bound to the bacterial surface.[54] Another approach using OMVs genetically engineered to produce protective antigens has been submitted to preclinical evaluation, with active protection in a mouse model being shown in ~10 candidates.[55]

To achieve and maintain adequate cross-protection among serogroups a new vaccine will need to contain a number of epitopes which should be both immunogenic and conserved. Although many new proteins have been described from genomic approaches, it is not yet clear whether the proteins identified in this way provide a significant advantage over the proteins described using non-genetic methods in the 1970s.

Gene expression. DNA microarray technology has recently been used in the search for vaccine targets. Hybridizing labelled RNA with fluorescent dyes to DNA fragments on the surface of a multi-array chip is used to monitor gene expression. Fluorescent signals emitted upon laser beam excitations are then quantified and define the transcriptional activity of arrayed genes *in vivo*. Microarray technology has been used to analyse gene regulation in meningococci and a number of previously unidentified genes have been discovered.[56] Sequence-tagged mutagenesis has enabled the labelling of specific meningococcal gene mutations which are crucial for survival of the organism and may help to define particular pathogenic strategies.[57]

Meningococcal group B vaccine research has progressed considerably, with a number of potential vaccine candidates being tested in animal models and entering into human trials. Quadrivalent ACWY vaccination is likely to make a large impact on non-B meningococcal disease.

Streptococcus pneumoniae

Streptococcus pneumoniae is a major cause of community-acquired bacterial pneumonia, otitis media and meningitis. It has 90 known serotypes, with a limited number accounting for the majority of invasive disease isolates in specific geographic locations. The peak rate of both colonization and invasive disease occurs during the first 2 years of life, dropping during later childhood and rising again in old age. Mortality rates from meningitis are about 25% of affected cases and are often characterized by neurological sequelae in survivors. Disease rates are particularly high at the extremes of age, in patients with underlying

chronic disease and in immunocompromised individuals, particularly those with HIV infection, where the incidence of disease is 50–100-fold higher.[1,58,59]

A 23-valent pneumococcal polysaccharide vaccine has been available since the 1970s but is poorly immunogenic in young children and has no effect on nasopharyngeal carriage. In February 2000 a 7-valent pneumococcal protein–polysaccharide conjugate vaccine was licensed for use in the USA. The first randomized controlled trial in >37 000 children showed that the 7-valent vaccine prevented 94% of invasive pneumococcal cases.[60–63] Both this trial and a smaller study in Finland found a reduction of ~6% in cases of otitis media, with an increase in otitis media caused by non-vaccine type organisms.[64] The 7-valent pneumococcal vaccine does not cover all disease-causing serotypes, prompting the development of 9-, 11- and 13-valent vaccines. However, it does produce a cross-protective serogroup response[65] extending to non-immunized adults via herd immunity decreasing the adult burden of disease.[66]

The expense of the conjugate vaccine is a fundamental disadvantage in developing countries, which carry the main burden of disease. There is already considerable evidence of replacement of vaccine serotypes by non-vaccine serotypes in mucosal carriage.[67–71] It is possible, although not certain, that other serotypes may replace invasive isolates and reduce the efficacy of these vaccines. There is also the risk that widespread conjugate vaccine use may result in increase of disease attributable to non-vaccine serotypes through genetic transformation. For this reason the development of cross-protective protein-based pneumococcal vaccines is being pursued.

Protein vaccines

As for the meningococcus, the complete genome sequence of both virulent and non-virulent isolates of *S.pneumoniae* has provided new classes of genes as potential targets for vaccine design and provided insight into the mechanisms of host–bacterial interaction.[72–74] Proteins within the pneumococcal cell membrane are known to be essential in pneumococcal pathogenicity. The most promising protein candidates so far are the well-characterized choline-binding proteins (Cbp) pneumolysin, Ply, LytA, PsaA and PspA.[75,76]

Genomic variation in 20 *S.pneumoniae* isolates has been examined using microarray technology, and a variation in up to 470 genes has been detected, most notably among the choline-binding proteins. Other genes implicated in virulence, such as NanA/B, LytA and Ply, showed little variation which suggests that they may be better potential vaccine candidates.[77] CbpA is the largest and most abundant choline-binding

protein; it functions as a surface adhesin and plays an important role in nasopharyngeal colonization.[78] Six novel mutants of CbpA constructs have been shown to affect nasopharyngeal carriage; the most promising as a potential candidate is CbpG which showed both loss of adherence to epithelial cells and decreased virulence in a sepsis model.[79]

Ply and PspA have been shown to be protective immunogens. PspA is serologically variable among pneumococcal strains but is sufficiently conserved in that immunization with a single PspA protects against strains with highly diverse serotypes. Limited trials with pneumolysin and PspA have shown that they provide partial protection against challenge with virulent pneumococci in experimental animal models,[80,81] with specific inactivation of the genes within these proteins by insertion duplication mutagenesis significantly reducing virulence in mouse models. Recently, PsaA fusion proteins have been expressed in *E.coli* and given intranasally in mouse models, resulting in mucosal antibody production.[82] However, the antigenic relatedness of pneumococcal proteins to those of other commensal streptococci needs careful evaluation in order to avoid disruption of the balance of harmless commensals in the nasopharynx and safety needs to be assessed in further detail. The Lyt proteins have also been examined as potential vaccine candidates in mouse models of sepsis and found to confer protection.[83] Other proteins with lipoprotein motifs, which are thought to be important in adhesion, have recently been identified in the streptococcal N4 genome. Three of the four proteins identified (PhtA, PhtB and PhtD) were shown to protect immunized mice from a number of streptococcal strains and therefore may be relevant in broad subtype protection.[84]

Sequence-tagged mutagenesis has also been used in pneumococcal candidate identification, and a number of novel protein candidates including IgA1 protease and adhesin PavA have been identified.[85,86]

The field of pneumococcal vaccination continues to show considerable potential, with rapid advances being made in research. Currently, heptavalent conjugate vaccines offer much promise in covering the most prevalent serotypes causing disease worldwide, with the main barrier to use being expense.

Group B streptococcus

Group B streptococcus (GBS) is a predominant cause of neonatal meningitis. It has nine serotypes, each of which has a different polysaccharide capsule. Purified polysaccharide vaccines were assessed in women in the late 1980s, but were shown to be poorly immunogenic. Whole-genome sequencing of serotypes Ia, III and V has offered new insights into GBS virulence, with potential vaccine candidates including capsular polysaccharide,

β-haemolysin, C5a peptidase, adhesins and immunogenic surface proteins. Currently, prophylactic antenatal antibiotic therapy is the main preventive strategy. The development of multivalent protein polysaccharide or conjugate vaccines would extend protection against invasive disease in the neonatal period. Conjugate vaccines have been prepared against the most prevalent GBS serotypes in the USA (types Ia, Ib,II, III and V) and Japan (types VI and VIII). Animal studies have established their efficacy, and phase 1 and 2 clinical trials undertaken in adults have shown that their administration is safe.[87,88] More recently conjugate vaccines against types IV and VII have been assessed for efficacy in a neonatal mouse model of GBS disease.[89] The safety of maternal vaccination remains unknown and it is not clear if this strategy would have any impact on late-onset GBS disease. However, these vaccines do offer the potential to decrease perinatal GBS disease and phase 3 trials are awaited.

Tuberculosis

Currently, one-third of the world's population is infected with *Mycobacterium tuberculosis*, Bacillus Calmette–Guerin (BCG), the only vaccine currently licensed for prevention of tuberculosis, is up to 77% effective against disseminated tuberculosis (TB) and ~50% effective against infectious pulmonary TB.[90,91] Its effectiveness in reducing morbidity and mortality from disseminated meningeal and miliary TB has justified its use as a neonatal vaccine. Neonatal vaccination provides protection against childhood disease, but this protection wanes over time.[92] BCG is safe and well tolerated, with adverse reactions being rare. An improved TB vaccine could be employed either for naive individuals (and would need to be at least as immunogenic and safe as BCG) or as a booster vaccine that would supplement BCG and lead to lasting immunity in adults.[93]

Leading candidates for priming vaccines include recombinant BCG, *M.tuberculosis*, *M.vaccae* or *M.microti*. In an augmented BCG vaccine deleted genes lost from the parental strain could be added or increased expression of genes already known to induce an effective immune response might be explored. Recombinant BCG is due to enter clinical trials following studies showing better protective immunity than was found with the parent strains.[94,95] Modified *M.tuberculosis* generates good protection in mouse models[96] and is safe in SCID mice. This animal model of T-cell immunodeficiency has become increasingly relevant because of the rising incidence of HIV and TB co-infection.

The advantages of a booster vaccine are that the well-established infant BCG programme could be maintained whilst the booster vaccine

would be added to maintain effective T-cell memory. Approaches include the use of a subunit vaccine which may include either a recombinant protein (ESAT-6, Ag85B) or DNA vaccination. DNA vaccination involves the vector delivery of a plasmid encoding a gene product which leads to both CD4 and CD8 responses to the target protein. Immunization with more than one gene product may be required in order to ensure broad protection,[97] and evidence suggests that efficacy is greater using the adjuvant effects of cytokines[98] or a prime/boost vector approach.[99] Assessing both the safety and the efficacy of these approaches will need to be undertaken in trials that are currently being designed (http://www.vaccinationnews.com). A major challenge in the development of a TB vaccine is the evaluation of efficacy against latent infection. There are potential risks of disease reactivation, and preclinical animal data may be difficult to interpret since the human major histocompatibility complexes are quite different. Better immunological correlates of protective immunity are also needed. However, the greatest challenge remains safe and affordable delivery to the world's poorest individuals and the impact that HIV has on the rising incidence of TB infection.

Conclusions

The impact of conjugate vaccines over the last 15 years has been substantial. Hib infection has all but disappeared in most industrialized countries that use the vaccine. Effectiveness data for pneumococcal (USA) and meningococcal (UK) conjugate vaccines highlight the possibility that conjugate vaccines could eliminate a majority of invasive bacterial disease of childhood. However, the challenge of finding a safe and immunogenic vaccine against group B meningococci is considerable, and the effect of mucosal pneumococcal serotype replacement on invasive disease post-vaccination could undermine the initial success of this vaccine.

Antigenic portions of outer membrane proteins of both *S.pneumoniae* and *N.meningitidis* are under strong immunological pressure but remain important vaccine candidates. The design of protein-based vaccines that are protective against a broad range of *S.pneumoniae* serotypes or multiple lineages of serogroup B meningococci is a major challenge.

There is huge potential for vaccine prevention of a majority of meningitis in children globally today. Despite this, the cost of the glycoconjugate meningitis vaccines and the lack of infrastructure required for their delivery means that most of the world's children will remain susceptible to bacterial meningitis.

Key points

- The use of glucoconjugate Hib vaccines has had a major impact on the incidence of Hib meningitis in developed countries. Hib vaccines have yet to be implemented in many resource-poor countries where disease burden is highest.
- Use of glycoconjugate vaccines for serogroup ACYW *N.meningitidis* could prevent meningococcal disease caused by these serogroups. However, disease caused bygroup B *N.meningitidis* accounts for a substantial proportion of meningitis and development of effective vaccination remains a considerable challenge.
- *Streptococcus pneumoniae* glycoconjugate vaccines are effective in preventing invasive disease and have had a major impact on invasive pneumococcal disease in the USA. However, limited implementation (because of expense), incomplete serotype coverage and serotype replacement could reduce the effectiveness of these vaccines.
- Tuberculosis vaccine design strategies will need to address the latency of infection, the potential for disease reactivation and potential variability in individual immune response.
- Advances through the development of genome-based strategies may have a major impact on vaccine design.
- Resource-poor countries have the highest meningitis burden but the least adequate infrastructure for vaccine delivery and production. In many countries lack of surveillance data weakens the case for vaccination, whilst mortality increases.

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