Bacterial meningitis in the era of paediatric vaccination against the encapsulated pathogens

Bacterial meningitis is still prevalent worldwide in spite of effective vaccines.

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Encapsulated bacterial organisms such as *Haemophilus influenzae* serotype b (Hib), *Streptococcus pneumoniae* (the pneumococcus), and *Neisseria meningitidis* (the meningococcus) are still the most common bacteria causing acute meningitis in infants and children worldwide, despite the availability of effective vaccines. Hib meningitis is estimated to have a global incidence, in the absence of vaccination, of 31 cases per 100 000 children younger than 5 years.[1] The highest incidence estimates for Hib meningitis by region are still in Africa (46/100 000), where there is no universal access to Hib vaccines. In an initiative to estimate the global burden of pneumococcal disease, O'Brien *et al.*[2] estimated the global incidence of pneumococcal meningitis in children to be 17 cases per 100 000, irrespective of HIV status. The pneumococcal meningitis incidence was estimated to be highest in Africa (38/100 000) and lowest in Europe (6/100 000). In the above two articles and an accompanying editorial, the conclusion was that Hib and pneumococcal pneumonia and meningitis cause as many child deaths as HIV/AIDS, malaria and tuberculosis combined.

Hib meningitis is estimated to have a global incidence, in the absence of vaccination, of 31 cases per 100 000 children younger than 5 years.

Meningococcal disease remains an important cause of meningitis and sepsis worldwide. The African meningitis belt extends from Ethiopia to Senegal and has cyclical epidemics occurring every 5 - 10 years, resulting in attack rates of 1 000/100 000 or higher. South Africa does not fall within the meningitis belt, and for many decades has documented endemic meningococcal disease with seasonal increases during the winter and spring months. The burden of disease shows a cyclical pattern, with increases at intervals of approximately 8 - 10 years.[3] The incidence of clinical notifications to the Department of Health has declined since the late 1980s, and for the period 1992 - 1997 was between 1 and 2 per 100 000 population.

In South Africa in 2007, pneumococcal meningitis was the predominant cause of acute bacterial meningitis in children <5 years as recorded by an active, national, laboratory-based surveillance system called GERMS-SA (Group for Enteric, Meningeal and Respiratory disease Surveillance in South Africa), followed by meningitis due to *N. meningitidis* and *H. influenzae* (Fig. 1).[4] Case fatality ratios were high for pneumococcal meningitis (28%, 44/156), while ratios were similar for meningococcus and *H. influenzae* (9%, 6/65 and 10%, 3/30 respectively).

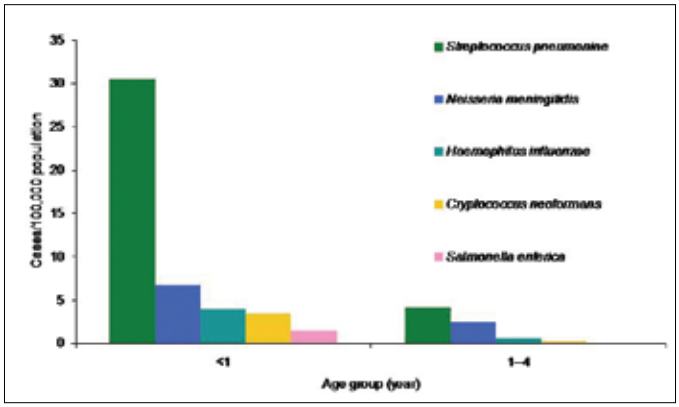

Fig.1. Age-specific incidence rates for baterial and fungal meningitis by pathogen in children <5 years old, South Africa, 2007.[4]

The polysaccharide capsule of these three encapsulated bacteria allows for their characterisation into serogroups or serotypes: more than 90 serotypes for the pneumococcus, 13 serogroups for the meningococcus (A, B, C, D, X, Y, Z, E, W-135, H, I, K and L) and 6 serotypes for *H. influenzae* (a - f). Common to all three pathogens mentioned above is that current vaccines are predominantly based on the polysaccharide capsule, and only prevent disease due to serotypes (or in the case of meningococci, serogroups) contained in the vaccine. Only the Hib vaccine is consistently monovalent, i.e. all Hib vaccines currently available are designed to prevent *H. influenzae* serotype b disease only. There are several pneumococcal and meningococcal vaccines, and each vaccine contains a different number of capsular polysaccharides (have different 'valencies'), and are designed to prevent only disease caused by the serotypes/serogroups that are contained in the vaccine.

Children younger than 2 years of age do not respond well to vaccines containing capsular polysaccharide-only antigens. However, when

polysaccharide antigens are conjugated to carrier proteins they are recognised as T-cell-dependent antigens and induce good antibody responses and immunological memory in infants.[5] For this reason polysaccharide vaccines are still used to prevent disease due to meningococcus and pneumococcus, as older children and adults continue to be at risk of disease due to these pathogens. Newer meningococcal and pneumococcal polysaccharide-protein conjugate vaccines have, however, made it possible to prevent disease in infants. Hib polysaccharide vaccine is no longer available (infants are the predominant age group at risk of Hib disease), and only polysaccharide-protein conjugate Hib vaccines are available worldwide. Another important feature of conjugate vaccines is their ability to induce mucosal immunity, i.e. the ability to induce immunity that prevents the new acquisition of vaccine serogroups/serotypes in the nasopharynx (carriage). It is this ability to reduce asymptomatic nasopharyngeal carriage in vaccinated individuals that has resulted in the demonstrated effect of reduction of disease in unvaccinated individuals, the so-called indirect effect. This article will focus on the vaccines relevant to infants – the newer generation of polysaccharide-protein conjugate vaccines.

Pneumococcus

South Africa's mortality rate in children under 5 years has increased over the last decade, from 60 deaths per 1 000 live births in 1995, to 69 deaths per 1 000 in 2005.[6] Neonatal illness, childhood infections such as pneumonia and diarrhoea, and HIV/AIDS are estimated to each cause 30% of all these child deaths.[6] *S. pneumoniae* is the most common bacterial cause of pneumonia among both HIV-infected and HIV-uninfected children.[7] The pneumococcal polysaccharide-protein conjugate vaccine (PCV) has been identified as an important public health intervention to prevent these deaths due to pneumococcal disease in developing countries.[8] *S. pneumoniae* also causes invasive diseases, which may manifest as bacteraemia (including cases of bacteraemic pneumonia), meningitis, septic arthritis and peritonitis. In addition, a large proportion of pneumococcal disease occurs in mucosal surfaces, e.g. otitis media and sinusitis. A study in South Africa calculated rates of 349/100 000 for invasive pneumococcal disease (IPD) in children <1 year in 1996/1997.[9] Although pneumococcal strains may be characterised into more than 90 serotypes, the majority of disease is due to fewer than 15 of these serotypes. Disease-causing serotypes may also vary over time and by geographical location.

An efficacy of >80% for a 7-valent vaccine (PCV7, Pfizer (previously Wyeth Pharmaceuticals), containing serotypes 4, 6B, 9V, 14, 18C, 19F and 23F PCV) against IPD has been documented in two large vaccine trials in the USA using a dosing schedule of 2, 4 and 6 months with a booster dose at 12 - 15 months.[8] Another conjugate vaccine, targeting 11 serotypes, PCV11 (GlaxoSmithKline Biologicals), demonstrated efficacy to reduce any episode of otitis media by 58% (95% confidence interval 2 - 57%), in a study with otitis media as the primary endpoint.[10] New formulations of PCV7 and PCV11 made by the same manufacturers but covering 13 and 10 serotypes, respectively, are becoming available; one of these vaccines will probably replace PCV7 in South Africa in late 2010 or 2011. In an attempt to avoid the need to conduct large efficacy studies for different endpoints for new PCVs, the scientific community has identified methods of comparing different vaccines based on immunogenicity measures.

The African meningitis belt extends from Ethiopia to Senegal and has cyclical epidemics occurring every 5 - 10 years resulting in attack rates of 1 000/100 000 or higher.

In Africa, similar studies have also demonstrated PCV to be efficacious. These trials used the vaccination schedule at 6, 10 and 14 weeks, without a booster dose, and a PCV made by the same manufacturer as PCV7, but additionally containing serotypes 1 and 5 (PCV9) was used.[11,12] The African studies with PCV9 demonstrated high efficacy for prevention of vaccine-serotype disease (92% (44 - 99%) in The Gambia,[12] and 83% (39 - 97%) among HIV-uninfected children in South Africa[11]), and in South Africa, good efficacy even among HIV-infected children (65% (24 - 86%)).[11,13] PCV9 never became a licensed product as the manufacturer later replaced it with a vaccine that contains 13 serotypes (PCV13), including those serotypes mentioned above, and in addition serotypes 7F, 3, 6A and 19A.

PCV7 was introduced in the infant immunisation programme in the USA in 2000. Substantial reductions of all IPD were documented within a year of introduction among children targeted for vaccination (69% reduction from 188 cases per 100 000 children <2 years in 1998 - 1999, to 59 cases per 100 000 population in 2001).[14] Reductions in disease have also been documented among individuals not vaccinated, demonstrating the potential for this vaccine to prevent disease by a herd or indirect effect.[15] Conjugate vaccines induce mucosal immunity, preventing the new acquisition of vaccine-serotype pneumococci in the nasopharynx.[16] This effect on carriage reduces the number of children who are carriers of pneumococci, and decreases the chance of transmission to other at-risk individuals. These indirect effects may, however, be more limited among individuals with co-morbid diseases, including HIV infection.[17]

The USA introduced PCV7 in a 3-dose infant schedule with a booster dose in the second year of life. Most other countries have introduced PCV7 as a 2- or 3-dose primary series during infancy, with a booster dose given at 11 - 18 months.[5] Immunogenicity data support the equivalence of 2 compared with 3 primary doses during infancy, and there are additional data from the USA confirming that fewer than 3 doses of PCV7 during infancy may still be effective.[18] Norway introduced PCV7 vaccination at 3, 5 and 12 months, and estimated vaccine effectiveness in the first 2 years of the programme to be 74% (57 - 85%).[19] In the UK, a 2-plus-1-dose schedule has also resulted in a decline in vaccine-serotype IPD.[20] In Quebec, implementation of a 2-plus-1 schedule resulted in a significant reduction in pneumonia hospitalisations (13% decrease of all-cause pneumonia admissions compared with the period before vaccine introduction).[21] A recent study demonstrated that a 2-dose infant schedule resulted in significant reductions of vaccine-serotype pneumococcal carriage in the second year of life, although less so than a 2-dose schedule with a booster at 11 months when carriage was assessed at 18 months.[22] Similar reductions in colonisation for both schedules were however observed at 2 years of age.[22] Therefore, the indirect effects of these vaccines may still be demonstrated with these reduced-dose schedules.

Carriage studies have documented the increase in carriage of non-vaccine serotype pneumococci following vaccination with PCVs,[16] and carriage with these serotypes may extend to their household contacts. Non-vaccine-serotype IPD has increased in some populations, and has also been noted among HIV-infected individuals.[23] As few low- and middle-income countries have introduced PCVs, data on serotype replacement in these settings are lacking.

PCV7 (Prevenar®, Pfizer) was registered in South Africa in 2005, but only made available through the private health care sector. In 2008, the vaccine was introduced in the public sector as part of the routine infant immunisation programme in one health district in the Eastern Cape. PCV7 was officially launched nationally in April 2009; however, not all clinics in all provinces are as yet administering this vaccine. Only children born after 15 February 2009 (6 weeks old or younger on 1 April 2009) were eligible for PCV7. No catch-up vaccination was planned in 2008 and 2009. PCV7 was introduced in the routine infant immunisation programme as a 2-dose primary series at 6 and 14 weeks of age and a booster dose at 9 months of age. A schedule including a booster dose was adopted in part because data from South Africa indicated that the long-term efficacy of PCV9 against vaccine-serotype disease waned among HIV-infected children, from 65% (24 - 85%) 2.5 years post-vaccination[11] to 39% (-8% - 65%) by 6 years of age in the absence of a booster dose of PCV.[13] Plans are to roll over to PCV13 (Pfizer) or change over to PCV10 (GlaxoSmithKline Biologicals) containing serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F, in 2011. Using data from active laboratory-based surveillance for IPD in 2006 in South Africa, the proportion of serotypes causing IPD included in PCV7 was 70% in infants <1 year, 74% for PCV10 and 83% for PCV13.[24] Serotyping of pneumococcal isolates causing meningitis in children <5 years identified 78% (281/360) as serotypes in PCV-7.[4]

Children younger than 2 years of age do not respond well to vaccines containing capsular polysaccharide-only antigens.

Haemophilus influenzae serotype b

Hib meningitis is a severe disease with recently estimated global case fatality rates ranging from 22% to 67%.[1] In countries with routine Hib vaccination, Hib is no longer the most important cause of bacterial meningitis in children.[25] The introduction of conjugate vaccines for the prevention of Hib disease in children has substantially reduced burden of disease in developed countries and in developing countries where it has been introduced.[5] However, although conjugate Hib vaccines have been available since 1989, due to the high cost of the conjugate vaccines they are used in only a limited number of developing countries.

Newer meningococcal and pneumococcal polysaccharide-protein conjugate vaccines have, however, made it possible to prevent disease in infants.

Hib conjugate vaccines are highly effective against invasive disease and may prevent up to 25% of radiographically confirmed pneumonia,[5] although the organism remains under-recognised as a cause of severe disease and death in developing countries. These vaccines have reduced effectiveness among HIV-infected children.[26] The vaccine-preventable burden of Hib disease, however, is likely to be greater among the HIV-infected than among uninfected children due to much higher rates of Hib disease.[27]

South Africa was the first country in Africa to self-finance the incorporation of Hib vaccine into the routine childhood immunisation programme since July 1999. Population-based studies in South Africa had previously demonstrated rates of invasive Hib disease of 170/100 000 infants less than 1 year of age, approximately 60% of these patients presenting with meningitis.[28,29] National laboratory-based surveillance for invasive Hib disease was established concurrently with Hib vaccine introduction to document the impact of routine vaccination on Hib disease and demonstrated significant declines in cases of invasive disease in the years following introduction of Hib conjugate vaccine. Hib cases declined by 65% in children less than 1 year of age, from 55 cases in 1999 - 2000 to 19 cases in 2003 - 2004.[30] Overall, more than half the cases (52%) presented with meningitis.

Conjugate Hib vaccines prevent the new acquisition of nasopharyngeal carriage, and this feature of conjugate vaccines has resulted in protection being extended to unvaccinated individuals, the so-called indirect effect.[5] Hib disease is rare in comparison with Hib carriage, and in unvaccinated populations the prevalence of carriage in children <5 years was reported to be approximately 5%. In Africa, prevalence of carriage has been found to be similar, or slightly higher at approximately 10 - 20%. The indirect effect has been demonstrated in Africa, where in The Gambia reduction in Hib disease was greater than predicted by vaccine coverage and efficacy alone.[31]

Meningococcus

Since the early 1970s polysaccharide meningococcal vaccines have been used throughout the world. No randomised controlled efficacy trials were conducted for the newer meningococcal conjugate vaccines. These vaccines have been licensed on the basis of safety and immunogenicity data. Recent routine immunisation of infants with a polysaccharide-protein conjugate monovalent serogroup C vaccine in the UK has been successful,[5] while a quadrivalent conjugate vaccine is recommended for routine use in adolescents in the USA.[32]

***S. pneumoniae* is the most common bacterial cause of pneumonia among both HIV-infected and HIV-uninfected children.**

In South Africa, the age group at greatest risk for disease is children <1 year of age, although there were some differences by serogroup.[33,34] The incidence rate of reported laboratory-confirmed meningococcal disease increased from 1999 to 2002, and serogroup A, most prevalent in Gauteng Province, was the only serogroup of viable isolates to increase significantly.[33] More recently we have noted a decline in serogroup A disease, but an increase in disease caused by serogroup W-135.[34] Serogroups B, C and Y are also important serogroups causing disease in South Africa.

No routine or large-scale use of any meningococcal vaccines is standard in South Africa. Two polysaccharide meningococcal vaccines are available in the country: the quadrivalent vaccines (containing serogroups A, C, W-135 and Y), Mencevax $ACW_{135}Y$®, GlaxoSmithKline (registered in 2003) and Menomune® – A/C/Y/W-135, sanofi pasteur (2007). Vaccination is used for at-risk populations and in response to small outbreaks of disease, particularly in

institutions. No polysaccharide-protein conjugate meningococcal vaccines are registered in South Africa. In addition, there are currently no vaccines for prevention of serogroup B disease registered in South Africa. In the future, conjugate meningococcal vaccines will become registered in the country and should play a role in preventing meningococcal disease in infants.

Serogroup A meningococcus has historically been dominant in the African meningitis belt, but the region is affected by other serogroups, including C, W135, and X. In 2001, the MVP (Meningitis Vaccine Project) was created, centred on a partnership between PATH (Programme for Appropriate Technology in Health) and the WHO (World Health Organization), with the aim of eliminating meningococcal epidemics in Africa.[35] The MenAfriVac vaccine is a serogroup A conjugated vaccine. Phase I studies in India have shown that the product is safe and immunogenic. Phase II and II/III studies are being carried out in 1 - 29-year-olds in Africa (Mali, Senegal, The Gambia), India, and in African toddlers (12 - 24 months old). This vaccine has the potential to prevent future disease and epidemics due to serogroup A meningococcus in a region most affected by meningococcal disease.

South Africa was the first country in Africa to self-finance the incorporation of Hib vaccine into the routine childhood immunisation programme since July 1999.

Conclusions

The above conjugate vaccines have great potential to prevent both meningitis and pneumonia in infants. Their routine use needs to be encouraged in as many countries as possible.

The optimal schedule and the age at which infants should be vaccinated is still being determined, and a variety of strategies are likely to be effective.

Future vaccines against the above bacteria will hopefully not be based on the polysaccharide capsules and will allow broader protection across serotypes and serogroups.

References

1. Watt JP, Wolfson LJ, O'Brien KL, *et al.* Burden of disease caused by *Haemophilus influenzae* type b in children younger than 5 years: global estimates. *Lancet* 2009; 374: 903-911.
2. O'Brien KL, Wolfson LJ, *et al.* Burden of disease caused by *Streptococcus pneumoniae* in children younger than 5 years: global estimates. *Lancet* 2009; 374: 893-902.
3. Bikitsha N. Meningococcal meningitis in South Africa. *Epidemiological Comments* 1998; 24: 2-9.
4. Meiring S, Cohen C, Govender N, *et al.*, for GERMS-SA. Bacterial and fungal meningitis amongst children <5 years old, South Africa, 2007. *S Afr J Epidemiol Infect* 2009; 24: 30.
5. Trotter CL, McVernon J, Ramsay ME, *et al.* Optimising the use of conjugate vaccines to prevent disease caused by *Haemophilus influenzae* type b, *Neisseria meningitidis* and *Streptococcus pneumoniae*. *Vaccine* 2008; 26: 4434-4445.
6. Bradshaw D, Chopra M, Kerber K, *et al.* Every death counts: use of mortality audit data for decision making to save the lives of mothers, babies, and children in South Africa. *Lancet* 2008; 371: 1294-1304.
7. Zar HJ, Madhi SA. Pneumococcal conjugate vaccine – a health priority. *S Afr Med J* 2008; 98: 463-467.
8. Pneumococcal conjugate vaccine for childhood immunization – WHO position paper. *Wkly Epidemiol Rec* 2007; 82: 93-104.
9. Karstaedt AS, Khoosal M, Crewe-Brown HH. Pneumococcal bacteremia during a decade in children in Soweto, South Africa. *Pediatr Infect Dis J* 2000; 19: 454-457.
10. Prymula R, Peeters P, Chrobok V, *et al.* Pneumococcal capsular polysaccharides conjugated to protein D for prevention of acute otitis media caused by both *Streptococcus pneumoniae* and non-typable *Haemophilus influenzae:* a randomised double-blind efficacy study. *Lancet* 2006; 367: 740-748.
11. Klugman KP, Madhi SA, Huebner RE, Kohberger R, Mbelle N, Pierce N. A trial of a 9-valent pneumococcal conjugate vaccine in children with and those without HIV infection. *N Engl J Med* 2003; 349: 1341-1348.
12. Cutts FT, Zaman SM, Enwere G, *et al.* Efficacy of nine-valent pneumococcal conjugate vaccine against pneumonia and invasive pneumococcal disease in The Gambia: randomised, double-blind, placebo-controlled trial. *Lancet* 2005; 365: 1139-1146.
13. Madhi SA, Adrian P, Kuwanda L, *et al.* Long-term immunogenicity and efficacy of a 9-valent conjugate pneumococcal vaccine in human immunodeficient virus infected and non-infected children in the absence of a booster dose of vaccine. *Vaccine* 2007; 25: 2451-2457.
14. Whitney CG, Farley MM, Hadler J, *et al.* Decline in invasive pneumococcal disease after the introduction of protein-polysaccharide conjugate vaccine. *N Engl J Med* 2003; 348: 1737-1746.
15. Direct and indirect effects of routine vaccination of children with 7-valent pneumococcal conjugate vaccine on incidence of invasive pneumococcal disease – United States, 1998-2003. *MMWR Morb Mortal Wkly Rep* 2005; 54: 893-897.
16. Mbelle N, Huebner RE, Wasas AD, Kimura A, Chang I, Klugman KP. Immunogenicity and impact on nasopharyngeal carriage of a nonavalent pneumococcal conjugate vaccine. *J Infect Dis* 1999; 180: 1171-1176.
17. Lexau CA, Lynfield R, Danila R, *et al.* Changing epidemiology of invasive pneumococcal disease among older adults in the era of pediatric pneumococcal conjugate vaccine. *JAMA* 2005; 294: 2043-2051.
18. Whitney CG, Pilishvili T, Farley MM, *et al.* Effectiveness of seven-valent pneumococcal conjugate vaccine against invasive pneumococcal disease: a matched case-control study. *Lancet* 2006; 368: 1495-1502.
19. Vestrheim DF, Lovoll O, Aaberge IS, *et al.* Effectiveness of a 2+1 dose schedule pneumococcal conjugate vaccination programme on invasive pneumococcal disease among children in Norway. *Vaccine* 2008; 26: 3277-3281.
20. Health Protection Agency (HPA). Infectious Diseases: Pneumococcal Diseases, 2009. Available at: http://www.hpa.org.uk/web/HPAweb&Page&HPAwebAutoListName/Page/1203008863939 (accessed 17 July 2009).
21. De Wals P, Robin E, Fortin E, Thibeault R, Ouakki M, Douville-Fradet M. Pneumonia after implementation of the pneumococcal conjugate vaccine program in the province of Quebec, Canada. *Pediatr Infect Dis J* 2008; 27: 963-968.
22. van Gils EJ, Veenhoven RH, Hak E, *et al.* Effect of reduced-dose schedules with 7-valent pneumococcal conjugate vaccine on nasopharyngeal pneumococcal carriage in children: a randomized controlled trial. *JAMA* 2009; 302: 159-167.
23. Flannery B, Heffernan RT, Harrison LH, *et al.* Changes in invasive pneumococcal disease among HIV-infected adults living in the era of childhood pneumococcal immunization. *Ann Intern Med* 2006; 144: 1-9.
24. von Gottberg A, de Gouveia L, Quan V, for GERMS-SA. Vaccine-preventable invasive pneumococcal disease, South Africa, 2006. *S Afr J Epidemiol Infect* 2007; 22: 95-96.
25. Schuchat A, Robinson K, Wenger JD, *et al.* Bacterial meningitis in the United States in 1995. Active Surveillance Team. *N Engl J Med* 1997; 337: 970-976.
26. Madhi SA, Kuwanda L, Saarinen L, *et al.* Immunogenicity and effectiveness of *Haemophilus influenzae* type b conjugate vaccine in HIV infected and uninfected African children. *Vaccine* 2005; 23: 5517-5525.
27. Madhi SA, Petersen K, Madhi A, Khoosal M, Klugman KP. Increased disease burden and antibiotic resistance of bacteria causing severe community-acquired lower respiratory tract infections in human immunodeficiency virus type 1-infected children. *Clin Infect Dis* 2000; 31: 170-176.
28. Madhi SA, Petersen K, Khoosal M, *et al.* Reduced effectiveness of *Haemophilus influenzae* type b conjugate vaccine in children with a high prevalence of human immunodeficiency virus type 1 infection. *Pediatr Infect Dis J* 2002; 21: 315-321.
29. Hussey G, Hitchcock J, Schaaf H, *et al.* Epidemiology of invasive *Haemophilus*

influenzae infections in Cape Town, South Africa. *Ann Trop Paediatr* 1994; 14: 97-103.

30. von Gottberg A, de Gouveia L, Madhi SA, *et al.* Impact of conjugate *Haemophilus influenzae* type b (Hib) vaccine introduction in South Africa. *Bull World Health Organ* 2006; 84: 811-818.
31. Adegbola RA, Secka O, Lahai G, *et al.* Elimination of *Haemophilus influenzae* type b (Hib) disease from The Gambia after the introduction of routine immunisation with a Hib conjugate vaccine: a prospective study. *Lancet* 2005; 366: 144-150.
32. Bilukha OO, Rosenstein N. Prevention and control of meningococcal disease. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 2005; 54: 1-21.
33. Coulson GB, von Gottberg A, du Plessis M, Smith AM, de Gouveia L, Klugman KP. Meningococcal disease in South Africa, 1999-2002. *Emerg Infect Dis* 2007; 13: 273-281.
34. von Gottberg A, du Plessis M, Cohen C, *et al.* Emergence of endemic serogroup W135 meningococcal disease associated with a high mortality rate in South Africa. *Clin Infect Dis* 2008; 46: 377-386.
35. LaForce FM, Ravenscroft N, Djingarey M, Viviani S. Epidemic meningitis due to Group A *Neisseria meningitidis* in the African meningitis belt: a persistent problem with an imminent solution. *Vaccine* 2009; 27 Suppl 2: B13-B19.

In a nutshell

- Vaccine to prevent disease due to encapsulated bacteria like meningococcus, pneumococcus and *Haemophilus infuenzae* serotype b are based on their polysaccharide capsules.
- Different vaccines will contain different numbers of serogroups or serotypes.
- The polysaccharide-only vaccines do not work in infants less than 18 months of age.
- Polysaccharide-protein conjugate vaccines work in infants, inducing a memory response to booster doses and mucosal immunity.
- Two polysaccharide-protein conjugate vaccines are currently part of the routine immunisation programme in South Africa: Hib (*Haemophilus influenzae* serotype b) and PCV7 (7-valent pneumococcal conjugate vaccine).