New vaccines

New combination vaccines still need a boost

A J Pollard

Perspective on the paper by Kitchin *et al* (see page 11)

Pertussis vaccination is part of the backbone of global immunisation policy because of the high rates of disease in unimmunised populations and a mortality in early infancy of about 1 in 500. Most of the world's children are immunised with whole-cell pertussis vaccines, which were used in the UK from the 1950s and have been highly effective in reducing pertussis-related morbidity and mortality. Whole-cell pertussis vaccines contain >3000 pertussis proteins as a suspension of killed organisms, can cause severe local reactions, and are associated with inconsolable crying and hospitalisations related to febrile seizures or hypotonic hyporesponsive episodes (HHE) after immunisation in infants. By contrast, acellular pertussis vaccines, containing ≤5 purified proteins (components) from *Bordetella pertussis*, are far less reactogenic than whole-cell pertussis vaccines. The decision to replace whole-cell pertussis vaccine in the UK schedule with Pediacel (DTaP-IPV-Hib; Sanofi Pasteur, Lyon, France) in 2004 was good news for infants, as it has an improved reactogenicity profile when compared with whole-cell pertussis vaccines,¹ and can be expected to lead to a marked reduction in these unpleasant severe adverse events. A similar acellular pertussis vaccine, Pentacel (DTaP-IPV-Hib), also manufactured by Sanofi Pasteur, was shown to reduce HHE-related hospitalisations by 67% and febrile seizures by 79% after introduction in Canada in the late 1990s.²

The efficacy of new pertussis-containing vaccines is difficult to evaluate in immunised populations, and protection cannot be adequately assessed using immunogenicity measures alone, as serological correlates of protection are not clear.³ In addition to Pediacel, which contains five purified pertussis proteins, there are several other acellular pertussis vaccines available, with varying numbers of components and doses of proteins in them. Extrapolation from previous studies using similar vaccines is necessary in considering whether Pediacel might provide adequate protection against pertussis

in the UK, as there are no efficacy trials using this vaccine. A Cochrane review of trials of different acellular pertussis vaccines⁴ and another systematic review⁵ provide some reassurance by concluding that acellular pertussis vaccines with ≥3 pertussis components had higher effectiveness against pertussis (80–84%) than those with one or two components.⁵ The efficacy of different whole-cell pertussis vaccines was highly variable (37–92%).⁵ Another acellular pertussis-containing vaccine, Infanrix-IPV (DTaP-IPV; Glaxosmithkline Biologicals, Rixensart, Belgium), a three-component acellular pertussis vaccine, is available for use as a preschool booster vaccine in the UK, although it is not currently recommended for use in infants. Nevertheless, this vaccine is available for primary immunisation in many other countries including Germany, France, Spain, Italy, Sweden, Switzerland, USA and Australia. The systematic reviews did not find differences in the performances of the three-component and five-component acellular pertussis vaccines. A study in Sweden in the early 1990s compared the UK whole-cell pertussis vaccine, a three-component acellular pertussis vaccine (made by Biocine, Siena, Italy) and another five-component acellular pertussis vaccine (a forerunner of Pediacel, Sanofi Pasteur, Maidenhead, Berkshire, UK) and found that the two acellular pertussis vaccines were similar in their protection against severe whooping cough in a 3, 5, 12-month schedule, but that the five-component vaccine provided better protection against mild disease.⁶ The Biocine acellular pertussis vaccine was also evaluated in Italy in a study which compared it with Infanrix, and both these three-component vaccines produced similar levels of protection using a 10, 15, 26-week schedule.⁷ However, it is difficult to draw firm conclusions with respect to the expected performance of different acellular pertussis vaccines in the UK from these data in view of variation between the studies in trial design, vaccine schedules, use of concomitant vaccines and population characteristics. Further, the differences

in formulation or manufacturing between the vaccines evaluated in the efficacy studies and the currently available products leaves uncertainty about the point estimates of efficacy that could be expected for any acellular pertussis combination vaccine used today in the UK, highlighting the need for ongoing surveillance.

Unfortunately, it seems that protective immunity after pertussis immunisation in infancy is not sustained, and booster doses are required through childhood to ensure ongoing protection of the individual and to reduce transmission to younger siblings, especially unimmunised infants. Pertussis antigens were added to the preschool booster vaccine in 2004 in the UK to improve immunity in primary school-aged children, and recommendations in the US for adolescent immunisation have been made recently.⁸ Discussion continues about optimal strategies to reduce pertussis rates in various age groups from neonates to adolescents and adults, including pregnant women,⁹ with the aim of protecting infants in the first few months of life from severe diseases. Reducing disease rates in older age groups is particularly important because transmission to infants <2 months (unimmunised) is most likely to have come from other family members.¹⁰ In the UK, this would most readily be achieved by addition of acellular pertussis to the school leaver vaccine, although the effect on disease in the UK through this strategy is not clear.

Although acellular pertussis vaccines are well tolerated, whole-cell pertussis vaccines better enhance immune responses to coadministered vaccines. Conversely, coadministration of Hib with acellular pertussis vaccines results in reduced Hib immunogenicity.¹¹ In 2000, a rise in Hib cases was associated with a switch to use of an acellular pertussis vaccine (Infanrix-Hib; DTaP-Hib) as a result of shortages of whole-cell pertussis vaccine.¹² It is assumed that this increase in Hib cases arose from a combination of the lower starting antibody levels after primary immunisation with DTaP-Hib and rapid waning over the next 12 months, causing an increase in the population of individuals in early childhood who had become susceptible again through loss of protective antibody. Similarly, the data presented here by Kitchin *et al*¹³ show a trend towards reduced Hib antibody concentration when the Hib vaccine was coadministered as part of DTaP-IPV-Hib, as compared with DTWp-Hib.

Further, in Kitchin *et al*'s¹⁴ study, there is an apparent additional reduction in Hib antibody concentration noted when

MenC-CRM vaccine is concomitantly administered (with either acellular pertussis or whole-cell pertussis), as compared with concomitant administration of MenC-TT, suggesting that MenC-CRM may exert a further pressure on immunity against Hib in the population. Similarly, we have previously described suppression of Hib immune responses by use of a concomitantly administered combination pneumococcal–MenC-CRM vaccine. However, the absence of a control group (receiving no MenC vaccine) in Kitchin's study makes interpretation of these data difficult, and it is equally possible that MenC-CRM has no effect on Hib, as found in a previous study.¹⁵ In this case, the variation is all explained through enhancement of the anti-PRP immune responses by MenC-TT. These data highlight the importance and complexity of these interactions and indicate that the immunity against Hib is not secure after primary immunisation alone.

The authors have also found that concomitant immunisation of DTaP–IPV–Hib with MenC-TT results in substantially lower MenC antibody responses than when DTwP–Hib is used. Conversely, there is little effect of DTaP–IPV–Hib on the antibody response to MenC-CRM when compared with the DTwP–Hib arm. Like Hib, MenC protection wanes very rapidly after primary immunisation in infancy,¹⁶ and the data presented by Kitchin *et al* showing a lower starting level of antibody when MenC-TT is given with DTaP–IPV–Hib may indicate that individuals and thus populations will become susceptible sooner when MenC-TT is used with Pediacel for primary immunisation. However, many countries introduced MenC vaccines without infant immunisation and gained excellent disease control¹⁷; the magnitude of the added value of infant immunisation is debatable, as long as immunity through the rest of childhood is high to provide herd immunity. Now that MenC disease is under control in the UK and booster doses of MenC at 12 months of age are to be introduced imminently, these unexpected interactions will probably be of no

clinical significance. However, the key to sustaining low levels of disease in the UK is clearly more dependent on the maintenance of immunity in the population (through booster doses of vaccine) than it is on the magnitude of the response to priming in early infancy. Conversely, it is clear that primary immunisation alone in early infancy cannot guarantee that MenC disease will stay away.¹⁶

The slightly lower immunogenicity of Hib and MenC vaccines found in this study had no marked effect on the proportions of infants whose antibody levels exceeded the protective threshold. These differences are therefore not likely to be clinically relevant in the few months after immunisation, particularly in the context of the new UK immunisation schedule (to be launched in Autumn 2006), which includes a booster dose of Hib and MenC in the second year of life that will hopefully sustain population immunity against these infections through childhood and maintain low rates of invasive disease.

Arch Dis Child 2007;**92**:1–2.

doi: 10.1136/adc.2006.106724

Correspondence to: Dr A J Pollard, Department of Paediatrics, University of Oxford, Level 4, John Radcliffe Hospital, Oxford OX3 9DU, UK; andrew.pollard@paediatrics.ox.ac.uk

AJP acts as chief investigator for clinical trials conducted on behalf of Oxford University sponsored by vaccine manufacturers (Sanofi-Pasteur MSD, Novartis Vaccines, Glaxosmithkline Biologicals, Sanofi-Pasteur and Wyeth Vaccines), and has received assistance from manufacturers to attend scientific meetings. Industry-sourced consultancies and honoraria for lecturing or writing are paid directly to an independent charity or to an educational fund held by the Department of Paediatrics, University of Oxford. He is an inventor of patents in the area of MenB vaccines.

REFERENCES

- 1 Kitchin N, Southern J, Morris R, *et al*. A randomised controlled study of the reactogenicity of an acellular pertussis-containing pentavalent infant vaccine compared to a quadrivalent whole cell pertussis-containing vaccine and oral poliomyelitis vaccine, when given concurrently with meningococcal group C conjugate vaccine to healthy UK infants at 2, 3 and 4 months of age. *Vaccine* 2006;**24**:3964–70.

- 2 Le Saux N, Barrowman NJ, Moore DL, *et al*. Decrease in hospital admissions for febrile seizures and reports of hypotonic-hyporesponsive episodes presenting to hospital emergency departments since switching to acellular pertussis vaccine in Canada: a report from IMPACT. *Pediatrics* 2003;**112**:e348.
- 3 Pichichero ME, Casey JR. Acellular pertussis vaccines for adolescents. *Pediatr Infect Dis J* 2005;**24**(Suppl):S117–26.
- 4 Tinnion ON, Hanlon M. Acellular vaccines for preventing whooping cough in children. *Cochrane Database Syst Rev* 2000;(2):CD001478.
- 5 Jefferson T, Rudin M, DiPietrantonj C. Systematic review of the effects of pertussis vaccines in children. *Vaccine* 2003;**21**:2003–14.
- 6 Olin P, Rasmussen F, Gustafsson L, *et al*. Randomised controlled trial of two-component, three-component, and five-component acellular pertussis vaccines compared with whole-cell pertussis vaccine. Ad Hoc Group for the Study of Pertussis Vaccines. *Lancet* 1997;**350**:1569–77.
- 7 Greco D, Salmaso S, Mastrantonio P, *et al*. A controlled trial of two acellular vaccines and one whole-cell vaccine against pertussis. Progetto Pertosse Working Group. *N Engl J Med* 1996;**334**:341–8.
- 8 American Academy of Pediatrics. Prevention of pertussis among adolescents: recommendations for use of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccine. *Pediatrics* 2006;**117**:965–78.
- 9 Crowcroft NS, Pebody RG. Recent developments in pertussis. *Lancet* 2006;**367**:1926–36.
- 10 Bisgard KM, Pascual FB, Ehresmann KR, *et al*. Infant pertussis: who was the source? *Pediatr Infect Dis J* 2004;**23**:985–9.
- 11 Eskola J, Ward J, Dagan R, *et al*. Combined vaccination of Haemophilus influenzae type b conjugate and diphtheria-tetanus-pertussis containing acellular pertussis. *Lancet* 1999;**354**:2063–8.
- 12 McVernon J, Andrews N, Slack MP, *et al*. Risk of vaccine failure after Haemophilus influenzae type b (Hib) combination vaccines with acellular pertussis. *Lancet* 2003;**361**:1521–3.
- 13 Kitchin N, Southern J, Morris R, *et al*. Evaluation of a diphtheria-tetanus-acellular pertussis-inactivated poliovirus-Hib vaccine given concurrently with meningococcal group C conjugate vaccine at 2, 3 and 4 months of age. *Arch Dis Child* 2007;**92**:11–16.
- 14 Buttery JP, Riddell A, McVernon J, *et al*. Immunogenicity and safety of a combination pneumococcal-meningococcal vaccine in infants: a randomized controlled trial. *JAMA* 2005;**293**:1751–8.
- 15 Halperin SA, McDonald J, Samson L, *et al*. Simultaneous administration of meningococcal C conjugate vaccine and diphtheria-tetanus-acellular pertussis-inactivated poliovirus-Haemophilus influenzae type b conjugate vaccine in children: a randomized double-blind study. *Clin Invest Med* 2002;**25**:243–51.
- 16 Trotter CL, Andrews NJ, Kaczmarski EB, *et al*. Effectiveness of meningococcal serogroup C conjugate vaccine 4 years after introduction. *Lancet* 2004;**364**:365–7.
- 17 Snape MD, Pollard AJ. Meningococcal polysaccharide-protein conjugate vaccines. *Lancet Infect Dis* 2005;**5**:21–30.