

The duopoly of ten-valent and 13-valent pneumococcal conjugate vaccines: do they differ?



In *The Lancet Infectious Diseases*, Beth Temple and colleagues¹ report on a head-to-head comparison of the immunogenicity, in a low-income to middle-income setting (Vietnam), of the currently licenced ten-valent (PCV10) and 13-valent (PCV13) pneumococcal conjugate vaccines. The two vaccines were administered in a two-dose primary series (2 months and 4 months of age), with a booster dose at 9 months of age (a 2+1 schedule), with the primary comparison of immunogenicity between the vaccines being the proportion of recipients with serotype-specific antibody concentrations above the recommended composite putative threshold of protection developed for invasive pneumococcal disease (serotype-specific IgG concentration ≥ 0.35 $\mu\text{g/mL}$).² By this measure, PCV10 and PCV13 did not differ in immunogenicity. This finding was supplemented by assessment of the prevalence of functional antibody (opsonophagocytic index ≥ 8) post-vaccination, which was also similar between groups. The similarity of PCV10 compared with PCV13 in the 2+1 dosing schedule was evident after both the primary series and the booster dose.

The perceived benefit of PCV13 over that of PCV10 has been the superior coverage of PCV13 for three additional disease-causing serotypes (serotypes 3, 6A, and 19A). Evidence suggests that PCV13 has no effect on serotype 3 invasive pneumococcal disease,³ whereas evidence of a direct effect on serotypes 6A and 19A invasive pneumococcal disease in countries using PCV10 suggests some cross-protection.⁴ Similarly to past studies, the data in this paper show cross-reactive IgG and functional antibodies to serotype 6A and 19A in 61–67% of PCV10 recipients after a booster dose; however, these percentages were lower than the percentage (>99%) of PCV13 recipients in whom functional antibodies to these serotypes were induced. Furthermore, the geometric mean opsonophagocytic indices were 15–77 times higher for serotypes 6A and 19A after the primary series, and 23–32 times higher after the booster dose in PCV13 recipients versus PCV10 recipients. The effect of these higher titres on direct protection is unclear. The lower cross-reactive responses to 19A might explain the

reported failure of PCV10 to reduce 19A colonisation in children and provide indirect protection against 19A in unvaccinated individuals.⁵

Another important observation by Temple and colleagues¹ was that the immunogenicity of a two-dose primary series of PCV13 was similar to a three-dose primary series of PCV10 (3+0). These data indicate the potential for using three doses of PCV13 in a 2+1 schedule rather than a 3+0 schedule. This schedule could potentially address the waning of protection against serotype 1, as reported in African efficacy trials of a nine-valent PCV (including serotype 1), which only immunised with a three-dose primary series.⁶

The interpretation of results from this and other similar immunogenicity studies, however, have limitations in extrapolating to overall direct vaccine effectiveness. These limitations include the likelihood of serotype-specific differences in thresholds of antibody associated with protection against invasive pneumococcal disease;⁷ the possibility that concentrations required for protection against invasive pneumococcal disease are not the same as those required for non-invasive pneumococcal disease syndromes, such as non-bacteraemic pneumococcal pneumonia, which constitutes the largest burden of severe pneumococcal disease;⁸ and that concentrations of IgG required to protect against colonisation might be significantly higher than those required to protect against invasive pneumococcal disease.⁹ PCVs protect against the acquisition of nasopharyngeal colonisation,¹⁰ and this protection is key to reducing the transmission of pneumococci and, thus, to the indirect protection from pneumococcal disease in unvaccinated individuals. A pooled analysis, which used seroincidence as a proxy of serotype-specific colonisation, suggested that serotype-specific antibody concentrations associated with reduced odds of nasopharyngeal colonisation range from 0.50 $\mu\text{g/mL}$ (62% lower odds of imputed serotype 6B colonisation) to 2.54 $\mu\text{g/mL}$ (87% reduced odds of imputed serotype 19F colonisation).¹¹ These estimates are approximately 3.1 times higher than the respective serotype-specific threshold estimated to confer 90% reduced risk of invasive pneumococcal disease for



Published Online
April 3, 2019
[http://dx.doi.org/10.1016/S1473-3099\(18\)30785-0](http://dx.doi.org/10.1016/S1473-3099(18)30785-0)
See [Articles](#) page 497

serotypes 6B (0.16 µg/mL), and 2.2 times higher than that for serotype 19F (1.17 µg/mL).^{7,11}

In summary, Temple and colleagues' study showing non-inferiority of PCV10 versus PCV13 in terms of immunogenicity against invasive pneumococcal disease provides important endorsement of existing WHO advice on the use of PCVs for infant immunisation.¹² Furthermore, these data indicate that an individual country's decision on which vaccine to use in a 2+1 schedule to directly protect against vaccine-serotype invasive pneumococcal disease might well be influenced primarily by the cost of vaccine procurement. The effects of the differences between the vaccines in terms of absolute antibody concentrations are unclear, but might have implications for the effect of vaccines on non-invasive disease, carriage, and indirect protection for at least some serotypes. However, these questions require further study.

*Shabir A Madhi, David Goldblatt

Medical Research Council: Respiratory and Meningeal Pathogens Research Unit, University of the Witwatersrand, Faculty of Health Science, Johannesburg, 2013, South Africa (SAM); Department of Science/National Research Foundation: Vaccine Preventable Diseases, University of the Witwatersrand, Faculty of Health Science, Johannesburg, South Africa (SAM); and Immunobiology Unit, UCL Great Ormond Street Institute of Child Health, London, UK (DG) madhis@rmpu.co.za

SAM reports grants and personal fees from the Bill & Melinda Gates Foundation, and grants from GlaxoSmithKline, Pfizer, and Sanofi Pasteur outside of the submitted work. DG reports grants from GlaxoSmithKline outside of the submitted work.

Copyright © 2019 The Author(s). Published by Elsevier Ltd. This is an Open Access article under the CC BY 4.0 license.

- 1 Temple B, Toan NT, Dai VTT, et al. Immunogenicity and reactogenicity of PCV10 versus PCV13 among infants in Ho Chi Minh City, Vietnam: a randomised controlled trial. *Lancet Infect Dis* 2019; published online April 8. [http://dx.doi.org/10.1016/S1473-3099\(18\)30734-5](http://dx.doi.org/10.1016/S1473-3099(18)30734-5).
- 2 Jodar L, Butler J, Carlone G, et al. Serological criteria for evaluation and licensure of new pneumococcal conjugate vaccine formulations for use in infants. *Vaccine* 2003; **21**: 3265–72.
- 3 Ladhani SN, Collins S, Djennad A, et al. Rapid increase in non-vaccine serotypes causing invasive pneumococcal disease in England and Wales, 2000–17: a prospective national observational cohort study. *Lancet Infect Dis* 2018; **18**: 441–51.
- 4 Mrkván T, Pelton SI, Ruiz-Guinazu J, Palmu AA, Borys D. Effectiveness and impact of the 10-valent pneumococcal conjugate vaccine, PHiD-CV: review of clinical trials and post-marketing experience. *Expert Rev Vaccines* 2018; **17**: 797–818.
- 5 Isturiz R, Sings HL, Hilton B, Arguedas A, Reinert RR, Jodar L. Streptococcus pneumoniae serotype 19A: worldwide epidemiology. *Expert Rev Vaccines* 2017; **16**: 1007–27.
- 6 Klugman KP, Madhi SA, Adegbola RA, Cutts F, Greenwood B, Hausdorff WP. Timing of serotype 1 pneumococcal disease suggests the need for evaluation of a booster dose. *Vaccine* 2011; **29**: 3372–73.
- 7 Andrews NJ, Waight PA, Burbidge P, et al. Serotype-specific effectiveness and correlates of protection for the 13-valent pneumococcal conjugate vaccine: a postlicensure indirect cohort study. *Lancet Infect Dis* 2014; **14**: 839–46.
- 8 Wahl B, O'Brien KL, Greenbaum A, et al. Burden of Streptococcus pneumoniae and Haemophilus influenzae type b disease in children in the era of conjugate vaccines: global, regional, and national estimates for 2000–15. *Lancet Glob Health* 2018; **6**: e744–57.
- 9 Shiri T, Datta S, Madan J, et al. Indirect effects of childhood pneumococcal conjugate vaccination on invasive pneumococcal disease: a systematic review and meta-analysis. *Lancet Glob Health* 2017; **5**: e51–59.
- 10 Klugman KP. Efficacy of pneumococcal conjugate vaccines and their effect on carriage and antimicrobial resistance. *Lancet Infect Dis* 2001; **1**: 85–91.
- 11 Voysey M, Fanshawe TR, Kelly DF, et al. Serotype-specific correlates of protection for pneumococcal carriage: an analysis of immunity in 19 countries. *Clin Infect Dis* 2018; **66**: 913–20.
- 12 WHO. Pneumococcal vaccines WHO position paper—2012. *Wkly Epidemiol Rec* 2012; **87**: 129–44.



Control of scabies and secondary impetigo: optimising treatment effectiveness in endemic settings

Flickr/UN Women/Nam Gilbert



Scabies is more than a common parasitic skin disease¹ and health authorities in low-income and middle-income countries now recognise it as a public health issue. In 2017, WHO added scabies to the list of neglected tropical diseases for the following reasons: it is very common (point prevalence of up to 200 million),² has a substantial global burden in disability-adjusted life-years,^{3,4} has notable psychosocial and economic effects caused by stigma and work disruption, and the major sleep disturbances and damage to the skin barrier caused by scratching. *Sarcoptes scabiei* also inhibits complement pathways,

leading to streptococcal and staphylococcal superinfection of the skin.⁵

Controlling secondary bacterial pyoderms caused by scabies is crucial. Patients in tropical areas with *Staphylococcus aureus* bacteraemia and scabies have a higher mortality than those without scabies;⁶ but other life threatening infections such as cellulitis or necrotising soft tissue infection might occur, and impetigo might lead to haematuria or post-streptococcal glomerulonephritis and acute rheumatic fever or rheumatic heart disease.^{7,8}

In *The Lancet Infectious Diseases*, Lucia Romani and colleagues⁹ report on the efficacy of the

Published Online
April 4, 2019

[http://dx.doi.org/10.1016/S1473-3099\(19\)30068-4](http://dx.doi.org/10.1016/S1473-3099(19)30068-4)

See [Articles](#) page 510

For WHO list of neglected tropical diseases see http://www.who.int/neglected_diseases/diseases/en/