invasive pneumococcal disease after a switch from PCV13 to PCV10.[6]

In summary, for invasive pneumococcal disease due to PCV13 unique serotypes (3, 6A, and 19A), the ECDC reported that after 5 years of PCV10 or PCV13 use in the paediatric population, the incidence of serotypes 3, 6A, and 19A decreased by 37% (95% CI 22 to 50) in six PCV13 sites[5] and increased by 50% (95% CI –8 to 146) in the four sites using PCV10 (alone or with PCV13) among adults aged 65 years and older.[6]

Madhi and Goldblatt conclude that vaccine choice for direct protection against invasive pneumococcal disease might be "influenced primarily by the cost of vaccine procurement".[1] Cost is an important consideration for countries working within constrained health budgets; however, ethics, equity, and budget efficiency demand that important differences in performance—and thus in effect on morbidity and mortality—also be highlighted and considered. For PCV13 compared with PCV10, PCV13 brings not just a "perceived benefit"[1] but an actual benefit with important implications for population health.

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1 Madhi SA, Goldblatt D. The duopoly of ten-valent and 13-valent pneumococcal conjugate vaccines: do they differ? *Lancet Infect Dis* 2019; **5:** 453–54.
2 Temple B, Toan NT, Dai VTT, et al. Immunogenicity and reactogenicity of ten-valent versus 13-valent pneumococcal conjugate vaccines among infants in Ho Chi Minh City, Vietnam: a randomised controlled trial. *Lancet Infect Dis* 2019; **19:** 497–509.
3 Sings HL, De Wals P, Gessner BD, et al. Effectiveness of 13-valent pneumococcal conjugate vaccine against invasive disease caused by serotype 3 in children: a systematic review and meta-analysis of observational studies. *Clin Infect Dis* 2019; **68:** 2135–43.
4 Gessner BD, Jiang Q, Van Werkhoven CH, et al. A post-hoc analysis of serotype-specific vaccine efficacy of 13-valent pneumococcal conjugate vaccine against clinical community acquired pneumonia from a randomized clinical trial in the Netherlands. 29th European Congress of Clinical Microbiology & Infectious Diseases; Amsterdam, The Netherlands; April 13–16, 2019. P0356.
5 Hanquet G, Krizova P, Valentiner-Branth P, et al. Effect of childhood pneumococcal conjugate vaccination on invasive disease in older adults of 10 European countries: implications for adult vaccination. *Thorax* 2018; **74:** 473–82.
6 Desmet S, Verhaegen J, Van Ranst M, Peetermans W, Lagrou K. Switch in childhood pneumococcal vaccination programme from PCV13 to PCV10: a defendable approach? *Lancet Infect Dis* 2018; **18:** 830–31.

Authors' reply

Bradford D Gessner and colleagues argue that our Comment[1] contains mischaracterisations regarding the relative merits of the PCV10 and PCV13 vaccines.

They assert that predicting vaccine performance from immunogenicity data is invalid because immunological correlates of protection are relevant only to invasive pneumococcal disease. We do state this fact as a limitation of immunogenicity studies in our Comment, and we re-emphasised this point at the end and indicated the need for more studies to help understand the association between antibody concentration and endpoints of non-invasive pneumococcal disease.

Gessner and colleagues also disagree with our assertion that PCV13 has no effect on serotype 3 invasive pneumococcal disease. They cite efficacy data for PCV13 on serotype 3 when used to immunise adults, but our Comment was focused on infant immunisation and we stand by our assertion regarding the limitations of serotype 3 as a vaccine antigen in infants. When arguing for an indirect effect of PCV13 on serotype 3 disease in adults, Gessner and colleagues cite a European paper that contains data up to 2015 from diverse countries with surveillance of varying quality,[2] while ignoring more recent, publicly available data. For instance, in the UK, epidemiological data up to mid-2017 indicate that use of PCV13 in infants has had no direct or indirect effect on serotype 3 invasive disease,[3] and that carriage of serotype 3 continues.[4] The most recent US epidemiological data, from 2016 to 2017, also show no indirect effect on serotype 3 disease in adults older than 65 years.[5]

The relative merits of the PCV10 and PCV13 vaccines were recently addressed by the WHO Strategic Advisory Group of Experts, who endorsed the use of both vaccines and commented "The choice of product to be used in a country should be based on programmatic characteristics, vaccine supply, vaccine price, the local and regional prevalence of vaccine serotypes and antimicrobial resistance patterns."[6]

The global health community recognises the value of having two life-saving licensed PCVs available for childhood immunisation. Unfortunately, the cost of PCVs remains prohibitive for public immunisation programmes in many low-income and middle-income countries that do not qualify for Gavi preferential pricing and co-funding assistance. The challenge to manufacturers is to ensure affordable accessibility of PCVs to the millions of children in low-income and middle-income countries who remain unvaccinated against pneumococcus because of the sustained high cost of vaccines.

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1 Madhi SA, Goldblatt D. The duopoly of ten-valent and 13-valent pneumococcal conjugate vaccines: do they differ? *Lancet Infect Dis* 2019; **5:** 453–54.
2 Hanquet G, Krizova P, Valentiner-Branth P, et al. Effect of childhood pneumococcal conjugate vaccination on invasive disease in older adults of 10 European countries: implications for adult vaccination. *Thorax* 2019; **74:** 473–82.

3 Ladhani SN, Collins S, Djennad A, e. 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 Kandasamy R, Voysey M, Collins S, et al. Persistent circulation of vaccine serotypes and serotype replacement after five years of UK infant immunisation with PCV13. *J Infect Dis* 2019; published online April 20. DOI:10.1093/infdis/jiz178.

5 Pilishvili T. Impact of PCV13 on invasive pneumococcal disease (IPD) burden and the serotype distribution in the US Advisory Committee on Immunization Practices: Oct 24, 2018. https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2018-10/Pneumococcal-02-Pilishvili-508.pdf (accessed May 31, 2019).

6 WHO. Summary of WHO Position Paper on pneumococcal conjugate vaccines in infants and children under 5 years of age, February, 2019. https://www.who.int/immunization/policy/position_papers/who_pp_pcv_2019_summary.pdf?ua=1 (accessed May 31, 2019).

2017 ECIL 7 vaccine guidelines

We thank Laura Sticchi and colleagues[1] for their pertinent comments on the 2017 European Conference on Infections in Leukaemia (ECIL 7) vaccination guidelines for patients with haematological diseases, including haematopoietic stem-cell transplant (HSCT) recipients.[2,3] We answer their comments about antibody assessment below and address all other issues in the appendix.

See Online for appendix

Sticchi and colleagues first debate the use of antibodies for assessing vaccine immunity. The reasons our recommendations are mostly based on laboratory endpoints were explained in our Series papers:[2,3] for most vaccines, undertaking prospective trials that are powered enough to show the clinical benefit of vaccination in these populations is not possible. Until now, the largest prospective vaccine trial after HSCT included 251 patients.[4] Therefore, although prospective trials collect data on the occurrence of vaccine-preventable diseases, their primary objective is always a laboratory endpoint, except in cases of an outbreak when the infection incidence is high. We agree with Sticchi and colleagues that there are weaknesses in the use of antibodies for assessment of pre-existing immunity or vaccination efficacy, particularly for pathogens such as pertussis, which is why we did not suggest an individual assessment of anti-pertussis antibodies, although they have been assessed in prospective trials after HSCT.

Sticchi and colleagues also comment on the interest in opsonophagocytosis assays over ELISAs for assessing antipneumococcal and antipolyribosylribitol *Haemophilus influenzae* type b (Hib) antibody titres. We agree that opsonophagocytosis assays are rarely available in routine clinical practice; however, several prospective studies[4,5] have shown correlations between IgG ELISA antibody titres and opsonophagocytosis assay titres for all pneumococcal vaccine-induced antibodies assessed in allogeneic HSCT recipients. The largest study on the 13-valent pneumococcal conjugate vaccine (PCV13) in HSCT recipients, done in 54 paediatric and 162 adult patients, confirmed this strong correlation for all PCV13 antibodies, except for a small discrepancy for serotype 3 in children.[4] As for Hib anti-polyribosylribitol antibodies, we agree that their titres might sometimes not strictly correlate with their functions; however, first, after allogeneic HSCT, as we established in our 1987 publication[6] (before Hib vaccine was routine in children), an association exists between the onset of Hib disease and low anti-polyribosylribitol antibody titres assessed by ELISA,[6] irrespective of functional tests. Second, although anti-polyribosylribitol antibody titres decrease rapidly after vaccination in healthy children, nearly all those vaccinated maintain protective concentrations.[7] Finally, a large UK study using 2693 serum samples from individuals of all ages strongly suggested that anti-polyribosylribitol antibody titres at a concentration of 1 µg/mL or higher are protective of Hib disease.[8] The benefit of functional tests over ELISA is probably limited to the so-called grey zone of protection between 0·15 and 1 µg/mL in ELISA. In such a case in an HSCT recipient, without functional tests in routine practice, we would recommend a booster vaccination. In summary, we do not think functional tests are warranted in routine clinical practice (except for meningococcal immunity) because ELISAs can mostly provide useful individual patient-level information about the extent of protection, although no cutoff of protection has been established in this population.

Sticchi and colleagues question the assessment of antibodies against tetanus, diphtheria, and pertussis (Tdp) and Hib during long-term follow-up. After the initial regimen of three doses of Tdp vaccine, we recommend at least a booster programme according to the national recommendations for individuals of that age. However, the long-term (eg, 5-year) persistence of immunity after vaccination for diphtheria and tetanus after HSCT is good for tetanus but not for diphtheria, especially in patients who have extensive and chronic graft-versus-host disease.[9] Therefore, we hypothesise that high-risk patients (eg, those with extensive and chronic graft-versus-host disease, cord blood transplant recipients, or those receiving rituximab after transplant) might need boosters of vaccines earlier than is recommended in the healthy population.

Sticchi and colleagues also believe there was a contradiction between table 2 and the main text about assessment of pneumococcal antibodies,[1,2] which is not the case. In table 2, we gave the initial recommended programme for pneumococcal vaccination, and in the text we recommend the assessment of anti-pneumococcal antibodies from 24 months.