better to use them than not to screen for the infection at all.

Managing LTBI requires further search for tests with a high predictive value for future development of the active state and research to address system bottlenecks in programmes for screening and treating people with LTBI. A 2019 study[9] concluded that "preimmigration interferon-γ release assay screening coupled with postarrival rifampin treatment among migrants from countries with moderate to very high incidence of TB resulted in the lowest cost-effectiveness ratios".[9]

We declare no competing interests.

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Efficacy and effectiveness of ten-valent versus 13-valent pneumococcal conjugate vaccines

We note some mischaracterisations in the Comment by Shabir A Mahdi and David Goldblatt[1] on the Article by Beth Temple and colleagues.[2] As an overarching framework, the data from Temple and colleagues cannot be used for predicting vaccine performance against most clinical outcomes, since the only accepted correlate of protection for pneumococcal conjugate vaccines (PCVs) is against invasive pneumococcal disease 1 month after three primary doses during infancy. For all other outcomes (carriage, mucosal disease), schedules, ages, and doses, no such association exists; thus the interpretation of immunogenicity data remains in doubt. For example, mucosal and circulating memory B cells might be the most important mediator against carriage endpoints.

Mahdi and Goldblatt[1] stated that 13-valent PCV (PCV13) "has no effect on serotype 3 invasive pneumococcal disease", despite substantial evidence to the contrary; PCV13 has been shown to provide direct protection against serotype 3 disease in both children and adults (table).[3,4] Suggestive of even some indirect effects, the European Centers for Disease Control and Prevention (ECDC) have reported that in countries using PCV13 in paediatric immunisation programmes, the incidence of serotype 3 disease decreased by 11% among people aged 65 years and older, compared with an increase of 51% in countries that used ten-valent PCV (PCV10).[5]

With respect to serotype 19A, Mahdi and Goldblatt correctly note that low crossreactive responses to 19A might explain the reported failure of PCV10 to decrease 19A colonisation in children and its inability to provide indirect protection against 19A in unvaccinated individuals. They omit that even among vaccinated age cohorts, PCV10 might provide inadequate protection, as suggested in Belgium, which had an immediate increase in paediatric 19A

	Study type	Age	Vaccine efficacy or effectiveness (95% CI)
Invasive pneumococcal disease[3]	Meta-analysis	≤5 years	63·5% (37·3–89·7)
Clinical community-acquired pneumonia[4]*	Randomised controlled trial	≥65 years	61·5% (17·6–83·4)
Chest radiology-confirmed community-acquired pneumonia[4]†	Randomised controlled trial	≥65 years	60·0% (5·2–84·8)

*At least two of the following symptoms: cough, production of purulent sputum, or a change in the character of sputum; temperature >38°C or <36·1°C; auscultatory findings consistent with pneumonia; leucocytosis (>10 × 10^9 white blood cells per L or >15% bands); C-reactive protein value >3 times the upper limit of normal; or hypoxaemia with a partial oxygen pressure >60 mm Hg while breathing room air, regardless of radiographic findings. Reported vaccine efficacy data are for first episodes of serotype 3 community-acquired pneumonia in the modified-intention-to-treat population. †Based on adjudication by an independent and blinded committee in which two of three members agreed that a radiograph (lateral and posterior-anterior chest radiograph, if the clinical condition permitted, and otherwise an anterior-posterior image) was consistent with community-acquired pneumonia. Reported vaccine efficacy data are for modified-intention-to-treat population.

***Table*: 13-valent pneumococcal conjugate vaccine efficacy or effectiveness against serotype 3 disease**

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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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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