An affordable pneumococcal conjugate vaccine after 20 years

as the primary outcome of a clinical trial is going to be impractical. Functional cure, as denoted by HBsAg seroclearance, could be a good endpoint. Tenofovir disoproxil fumarate might not be good enough.[9] It will take a few years before a combination of newer antiviral drugs directed at different viral targets can reapproach the challenge of a functional cure.[10]

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1 Hsu Y-C, Chen C-Y, Chang I-W, et al. Once-daily tenofovir disoproxil fumarate in treatment-naive Taiwanese patients with chronic hepatitis B and minimally raised alanine aminotransferase (TORCH-B): a multicentre, double-blind, placebo-controlled, parallel-group, randomised trial. *Lancet Infect Dis* 2021; published online Jan 29. https://doi.org/10.1016/S1473-3099(20)30692-7.

3 Terrault NA, Bzowej NH, Chang KM, Hwang JP, Jonas MM, Murad MH. AASLD guidelines for treatment of chronic hepatitis B. *Hepatology* 2016; **63:** 261–83.

4 Liaw YF, Sung JJY, Chow WC, et al. Lamivudine for patients with chronic hepatitis B and advanced liver disease. *N Engl J Med* 2004; **351:** 1521–31.

5 Chen CJ, Yang HI, Su J, et al. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. *JAMA* 2006; **295:** 65–73.

6 Iloeje UH, Yang HI, Su J, Jen CL, You SL, Chen CJ. Predicting cirrhosis risk based on the level of circulating hepatitis B viral load. *Gastroenterology* 2006; **130:** 678–86.

7 Chen YC, Chu CM, Liaw YF. Age-specific prognosis following spontaneous hepatitis B e antigen seroconversion in chronic hepatitis B. *Hepatology* 2010; **51:** 435–44.

8 Howell J, Chan HLY, Feld JJ, Hellard ME, Thompson AJ. Closing the stable door after the horse has bolted: should we be treating people with immune-tolerant chronic hepatitis B to prevent hepatocellular carcinoma? *Gastroenterology* 2020; **158:** 2028–32.

9 Chan HLY, Chan CK, Hui AJ, et al. Effects of tenofovir disoproxil fumarate in hepatitis B e antigen-positive patients with normal levels of alanine aminotransferase and high levels of hepatitis B virus DNA. *Gastroenterology* 2014; **146:** 1240–48.

10 Lok AS, Zoulim F, Dusheiko G, Ghany MG. Hepatitis B cure: from discovery to regulatory approval. *Hepatology* 2017; **66:** 1296–313.

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In *The Lancet Infectious Diseases*, Ed Clarke and colleagues[1] report a phase 3 non-inferiority trial of a new ten-valent pneumococcal polysaccharide protein conjugate vaccine (SIIPL-PCV) developed by Serum Institute of India, done in 2250 healthy infants in The Gambia. Vaccines produced by Serum Institute of India are often priced much lower than comparator vaccines from manufacturers in high-income countries, resulting in this manufacturer being a major supplier of affordable vaccines procured by UNICEF for childhood immunisation programmes in low-income and middle-income countries (LMICs).[2]

The clinical development of SIIPL-PCV is aligned with the WHO target product profile,[3] which provides guidance on how to align the development of new pneumococcal conjugate vaccine (PCV) formulations with the needs of LMICs. Included in the trial by Clarke and colleagues[1] are positive results of investigations to assess the non-inferiority of SIIPL-PCV relative to a licensed PCV in terms of safety and immunogenicity and its non-inferiority relative to a licensed PCV in terms of, and non-interference with, immunogenicity of concurrently administered vaccines. Furthermore, the study reports on lot-to-lot consistency of SIIPL-PCV.

Aligned to the target product profile, serotypes included in SIIPL-PCV were tailored to pre-PCV era data to optimise coverage against the most common serotypes causing childhood invasive pneumococcal disease (IPD) in Africa and south Asia. SIIPL-PCV serotypes differ from those in the comparator vaccine, PHiD-CV (Synflorix; GSK, Brentford, UK), in that serotypes 4 and 18C, which constituted about 4% of serotypes causing IPD in both Africa and Asia in the pre-PCV era, are replaced with serotypes 6A and 19A (6% of serotypes causing IPD in Africa and 13% in Asia).[4] The proportion of childhood IPD in the pre-PCV era due to serotypes covered by SIIPL-PCV was 72·1% in Africa and 72·8% in Asia; for PHiD-CV, the proportion was 62·7% in Africa and 70·6% in Asia (or 72·1% in Africa and 74·2% in Asia if 6A cross-protection is included); and for the licensed PCV-13 (Prevenar 13; Pfizer), the proportion was 77·2% in Africa and 78·5% in Asia (76·0% in Africa and 76·9% in Asia if serotype 3 is excluded, premised on no vaccine effectiveness against this serotype).

Although cross-reactive immunity against serotype 6A IPD has been reported for serotype 6B-containing PCVs,[5] advantages of including serotype 6A in PCVs are enhanced protection against serotype-specific IPD, reduced risk for nasopharyngeal

colonisation, promoting indirect protection in unvaccinated individuals, and induction of crossreactive immunity against serotype 6C IPD.[6] For serogroup 19, evidence is tenuous that serotype 19F (included in PHiD-CV) confers cross-reactive immunity against serotype 19A IPD, and protection mainly evolves after a booster dose.[7] The PHiD-CV vaccine is unlikely to eliminate 19A disease; hence, addition of 19A to SIIPL-PCV is likely to have more effective direct and indirect protection against 19A disease.

For **data on vaccine use and impact** see www.view-hub.org

Serotype-specific IgG of at least 0·35 µg/mL was established as a putative correlate of protection against IPD based on analyses of pooled immunogenicity and efficacy data from randomised controlled trials of the initial seven-valent and investigational nine-valent PCVs.[3,8] The WHO guidance document on non-inferiority immunogenicity assessment of new PCV formulations recommends "choosing licensed comparator(s) that have the highest number of serotypes in common with the new vaccine".[8] Hence, it is counterintuitive that the licensed 13-valent PCV (Prevenar 13), which includes serotypes 6A and 19A, was not used as the comparator vaccine in the study by Clarke and colleagues.[1] Instead, immunogenicity for serotypes 6A and 19A in SIIPL-PCV was benchmarked to the least immunogenic serotype in PHiD-CV (serotype 6B). This approach is especially problematic for serotype 19A, which is estimated to have among the highest IgG correlate of protection thresholds associated with reduced risk of IPD (1·0 µg/mL, exceeded only by serotype 19F and serotype 3; range across PCV13 serotypes being 0·14–2·8 µg/mL).[9] Consequently, extrapolating from immunogenicity studies the probable effectiveness of SIIPL-PCV against serotypes 6A and 19A would have been more reassuring had immunogenicity non-inferiority been assessed relative to Prevenar 13, for which effectiveness has been established for serotypes 6A and 19A IPD and nasopharyngeal colonisation.

For **GAVI eligibility criteria** see https://www.gavi.org/types-support/sustainability/eligibility

Notwithstanding this limitation, licensure of SIIPL-PCV and WHO prequalification for external confirmation of the quality, safety, and efficacy of the vaccine is likely to be imminent. SIIPL-PCV is projected to be priced substantially lower than Prevenar 13 and PHiD-CV, the prices of which have remained largely unchanged in high-income and middle-income countries since PCVs were first licensed in 2000. The time taken for PCV introduction into LMIC public immunisation programmes relative to when they were introduced in high-income countries was about halved compared with the 20-year lag it took for *Haemophilus influenzae* type b conjugate vaccine introduction in LMICs. Nevertheless, 55% of the annual global birth cohort in 2019 was not vaccinated against pneumococcal disease, with most infants living in LMICs where PCV introduction has been slow. Underimmunisation of children against pneumococcal disease continues to contribute to an estimated 300 000 pneumococcal deaths annually (based on 2015 estimates) in children younger than 5 years.[10] Included among the pneumococcal deaths in 2015 are 68 700 (23%) that occurred in India, where some phasing in of PCV into public childhood immunisation programmes in high-burden regions of the country commenced in 2017.

Although reasons for not introducing PCV into immunisation programmes of LMICs are multifactorial, the high cost of licensed PCVs is a key driver, and some LMICs are ineligible for funding support through Gavi, The Vaccine Alliance, which mainly supports countries with a gross national income per capita of US$1630 or less. A cheaper, effective PCV could stimulate further expansion in LMICs. Furthermore, self-funding middle-income countries that could procure PCV at lower prices could use cost-savings to introduce other vaccines or strengthen their immunisation programmes.

In accordance with the target product profile, it is also necessary that effectiveness of SIIPL-PCV be assessed against pneumococcal disease, which might provide confidence for other self-funding countries to transition from a more expensive PCV to SIIPL-PCV. Also, as higher valency (15–25 serotypes) PCVs are on the horizon, SIIPL-PCV effectiveness studies would inform whether future iterations of the SIIPL-PCV should consider an expansion in the number of serotypes to align with remaining disease-causing serotypes in LMICs.

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1 Clarke E, Bashorun A, Adigweme I, et al. Immunogenicity and safety of a novel ten-valent pneumococcal conjugate vaccine in healthy infants in The Gambia: a phase 3, randomised, double-blind, non-inferiority trial. *Lancet Infect Dis* 2021; published online Jan 28. https://doi.org/10.1016/S1473-3099(20)30735-0.

2 UNICEF Supply Division. Contract Awards for January 2019. https://www.unicef.org/supply/media/2366/file/Contract%20awards%20-%202019.pdf (accessed Dec 20, 2020).

3 WHO. Target product profile (TPP) for the advance market commitment (AMC) for pneumococcal conjugate vaccines. Feb 22, 2008. http://www.who.int/immunization/sage/target_product_profile.pdf (accessed Dec 8, 2019).

4 Johnson HL, Deloria-Knoll M, Levine OS, et al. Systematic evaluation of serotypes causing invasive pneumococcal disease among children under five: the pneumococcal global serotype project. *PLoS Med* 2010; **7:** e1000348.

5 Hicks LA, Harrison LH, Flannery B, et al. Incidence of pneumococcal disease due to non-pneumococcal conjugate vaccine (PCV7) serotypes in the United States during the era of widespread PCV7 vaccination, 1998-2004. *J Infect Dis* 2007; **196:** 1346–54.

6 Cooper D, Yu X, Sidhu M, Nahm MH, Fernsten P, Jansen KU. The 13-valent pneumococcal conjugate vaccine (PCV13) elicits cross-functional opsonophagocytic killing responses in humans to *Streptococcus pneumoniae* serotypes 6C and 7A. *Vaccine* 2011; **29:** 7207–11.

7 Hausdorff WP, Hoet B, Schuerman L. Do pneumococcal conjugate vaccines provide any cross-protection against serotype 19A? *BMC Pediatr* 2010; **10:** 4.

8 WHO. Expert committee on biological standardization. Recommendations to assure the quality, safety and efficacy of pneumococcal conjugate vaccines, Replacement of: TRS, Annex 2. 2009. https://www.who.int/biologicals/areas/vaccines/pneumo/Pneumo_final_23APRIL_2010.pdf (accessed Dec 21, 2020).

9 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.

10 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 Global Health* 2018; **6:** e744–57.

Antibiotic stewardship challenges in an evolving health-care market in China

Overuse of antibiotics has attracted increasing concerns globally. Excessive use of antibiotics is believed to be associated with the development of antimicrobial resistance, which can seriously jeopardise health-care services and patient outcomes.[1] An Article by Houyu Zhao and colleagues[2]—one of the largest studies ever conducted in China—published by *The Lancet Infectious Diseases*, revealed a concerningly high proportion of inappropriate prescriptions of antibiotics. More than 51% of antibiotic prescriptions (almost 2 million per year) from 139 public hospitals for outpatient visits were found to be inappropriate, compared with 15·3% that were deemed appropriate. China has 12 436 secondary and tertiary hospitals.[3] The total volume of inappropriate antibiotic prescriptions from secondary and tertiary hospitals could have exceeded 173 millions per year on the basis of these data.

The study was done in secondary and tertiary hospitals, where well qualified medical professionals are employed. Since 1977, China has resumed formal medical degree programmes in universities with a length ranging from 5 years for bachelor degrees to 8 years for doctoral degrees.[4] Medical positions nowadays in secondary and tertiary hospitals are likely to have almost entirely been occupied by those who hold such formal qualifications. Clearly, a shortage of formal medical education alone cannot offer a full explanation for the underlying reasons of inappropriate antibiotic use in the hospital sector.

Since 2009, the Chinese Government has launched a series of policies to curb overuse and misuse of antibiotics. The measures taken include both restrictive and persuasive interventions targeting both primary care and hospital sectors.[5] Prescribers are required to follow clinical guidelines. Primary care institutions are only allowed to source medicines within the Essential Medicines List through the regional government tendering system and dispense prescribed medicines at a price with zero mark-up. Antibiotics are categorised into so-called access and restrictive groups. Unlike their hospital counterparts, primary care doctors are often trained in vocational schools without a formal medical qualification. As a result, hospital doctors are mobilised to provide antibiotic prescribing training to their colleagues in primary care. The Government also encourages development of integrated health-care networks, in which secondary and tertiary hospitals are supposed to support and supervise the work of primary care.[6]

Despite the hard efforts, however, the interventions appear to have shown little effect. As shown in the study,[2] inappropriate antibiotic prescribing in the secondary and tertiary hospitals remained high over the period from 2014 to 2018, and there was no clear changing trend. In our studies in the primary care sector,[1,5,7,8] we found that the poor work environment such as low salaries and high dependence on bonuses, a lack of trust in health-care providers, tense

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