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Commentary

Of novel analytic approaches and impactful findings… and an opportunity to pose more questions

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Childhood pneumococcal disease in South East Asia and the Western Pacific Region accounted for approximately 60% of the global annual burden of 9.18 million cases in 2015 [1]. Although cost-effectiveness analyses on inclusion of pneumococcal conjugate vaccine (PCV) in childhood immunization programmes in Asian countries demonstrated that it would be cost-saving in 22 of 25 studies [2], by 2018 only 17% of children in South East Asia and 13% in the Western Pacific Region were vaccinated with at least three doses of PCV [3]. The lag of widespread introduction of PCV into childhood immunisation programs in the Asian region could be due to the paucity of studies characterising the burden of pneumococcal disease and effectiveness of PCV in this region.

In *The Lancet Regional Health – Western Pacific*, Weaver et al [4] used a test-negative study design at a single facility in Lao People's Democratic Republic, to investigate the effectiveness of a 13-valent PCV against hypoxic pneumonia in hospitalised children. Vaccine-effectiveness (VE) against hospitalisation for hypoxic pneumonia was 37% (95% Confidence Interval [CI]: 6–57%) in the propensity score adjusted analysis. These VE estimates are similar to those observed against hypoxic pneumonia in other low income African settings, undertaken in The Gambia (61%; 95% CI: 52–68%) and Malawi (47%; 95% CI: 5–70%), which involved more resource intensive ecological/time-series study designs [5,6].

Vandenbroucke and Pearce designate the test-negative study design as representing a special class of case-control study, which uses "other patient" controls [7]. In the test-negative approach, cases and controls undergo the same clinical and diagnostic work-up for the same reasons, but the controls differ from the cases based on a crucial clinical or diagnostic criterion. By sampling hospitalised children with acute respiratory infections as was done in Weaver et al's [4] study, potential biases arising from different health seeking behaviours were minimised, and assurance that children included in the study arose from the catchment area that is served by the facility was maximised [7]. Whilst possibly useful for outcomes with high sensitivity and specificity, e.g. seasonal influenza vaccine effectiveness against confirmed influenza among individuals presenting with syndromic influenza-like illness; whether the test-negative approach is appropriate for evaluation of PCV is unclear. Underpinning the utility of the test-negative approach is the assumption that the intervention (i.e. PCV in this study) is unlikely to have an effect on the "outcome" characterising the "control" group.

The test-negative approach was previously proposed for evaluation of VE of an experimental 14-valent pneumococcal capsu-

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lar polysaccharide vaccine against vaccine-serotype invasive pneumococcal disease (IPD) in adults, using non-vaccine serotype IPD as the control group [8]. This was, however, prior to the recognition of the increased susceptibility of PCV-vaccinated individuals to replacement disease from non-vaccine serotypes. This could confound VE analysis of PCV against IPD using such an approach. The use of a test-negative approach is further complicated when investigating for VE against non-specific outcomes such as clinically diagnosed pneumonia with and without hypoxia, both of which are caused by multiple pathogens. The key assumptions lending to the use of this approach in the context of PCV and hypoxic pneumonia would be: i. PCV-serotype pneumococci are the leading cause of hospitalisation for hypoxic pneumonia; ii. PCV-immunization will have little effect on non-hypoxic pneumonia. Neither of these assumptions are, however, correct. The multi-centred PERCH study which included settings where there was limited or no childhood PCV immunization, demonstrated that the majority of hospitalizations for severe and very-severe (including hypoxic) childhood pneumonia are due to respiratory viruses rather than pneumococci [9]. Furthermore, in the GABRIEL Trial, hypoxic pneumonia was associated with two viral pathogens (human metapneumovirus and respiratory syncytial virus), but not with pneumococcus [10]. Additionally, PCV VE against radiologically confirmed pneumonia was similar in The Gambia for cases managed as outpatients (proxy for non-hypoxia; VE 30%; 95% CI: 15–43%) compared to hospitalised cases (proxy for severe disease and hypoxia; VE 42%; 95% CI: 30–53%) [11].

In the current era of focus on optimisation of resources for maximum research outputs, often in the context of a pressing need to achieve clinically meaningful and valid trial outcomes, innovative study designs such as the test-negative approach may hold promise. However, further corroboration of the test-negative approach for evaluating PCV VE against hypoxic pneumonia (or even radiologically confirmed pneumonia) is warranted. This could include possibly simulating this analytical approach from available data sets such as the PCV9 randomized controlled trials that were undertaken in The Gambia and South Africa which provided the “gold-standard” evidence for PCV efficacy against clinically and radiologically confirmed pneumonia in low- and middle-income settings.

Declaration of Competing Interest

Dr. Moore has nothing to disclose. Prof Madhi reports grants from BMGF, Pfizer, GSK, Minervax, and Sanofi outside the submitted work.

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