Letters

Pneumococcal conjugate vaccine is efficacious and effective in reducing the burden of pneumonia

While Chowdhary & Puliyel[1] are correct that there has been a non-significant reduction in clinically diagnosed pneumonia in the vaccine-efficacy trials conducted to date, their assertion that pneumococcal conjugate vaccine (PCV) does not reduce severe pneumonia or reduce mortality in the Gambia is fundamentally flawed. Updated estimates indicate that there are 155.8 million clinical episodes of pneumonia globally, which contribute to approximately 1.9 million deaths, 70% of which occur in Africa and south-east Asia.[2] The major drawback in evaluating the efficacy of PCV against "clinical pneumonia" is the lack of specificity of this clinical outcome measure that was designed for case management of pneumonia. The choice of clinical pneumonia as an endpoint is therefore biased in favour of high sensitivity, at the expense of specificity, in contrast to the more specific endpoints usually used in vaccines efficacy trials. Indeed, a large proportion of the cases that meet the case definitions for clinical pneumonia have a low positive predictive value and are, therefore, not pneumonia.[3] In the case management strategy, one accepts a level of over-treatment because of the important mortality reduction benefits. Nevertheless, that pneumococci contribute to significant pneumonia-related mortality is evident in the success of the WHO case-management strategy of pneumonia, which is premised upon early antibiotic therapy especially targeting *S. pneumoniae* and

is associated with a 36% reduction in pneumonia-mortality.[4]

On the other hand, radiologically-confirmed pneumonia is a relatively more specific measure of bacterial pneumonia and so efficacy of vaccine on this outcome measure is a better indicator of effect on pneumonia mortality. This outcome was indeed the primary outcome measure for determining efficacy of the vaccine against pneumonia, rather than the less specific measure of clinical pneumonia. The vaccine trials were thus not powered to measure efficacy against clinical pneumonia and it is not surprising that the efficacy estimate did not reach statistical significance. Furthermore, low specificity of the outcome measure leads to misclassification and a substantial underestimation of vaccine efficacy.[5]

The case fatality ratio in the Gambia trial was significantly greater in children with radiologically-confirmed pneumonia (3%) compared with clinical pneumonia cases that do not fulfil the criteria of radiologically-confirmed pneumonia (0.8–1.2%) even with access to antibiotic therapy.[6] In the absence of antibiotics, this difference may have been even greater. Radiologically-confirmed pneumonia accounts for as much as 16.7–34% of cases of clinical pneumonia,[6–8] The higher case fatality rate of radiologically-confirmed pneumonia and the higher impact of vaccine on this clinical outcome suggests that the impact of vaccine is more than a "minimal" contribution. Additionally, PCV is able to reduce pneumonia with an abnormal chest X-ray, but not defined as "radiologically-confirmed", by 1.2–7% to 30–32% when the specificity of this outcome is improved for bacterial pneumonia by using a C-reactive protein of ≥ 40 mg/l as an adjunctive marker.[9,10] Thus, the impact of vaccine on true pneumonia and pneumonia mortality is substantially greater than is indicated by the efficacy against "clinical pneumonia".

Additionally, vaccine-efficacy trials may underestimate the public health benefit of vaccines, as indicated by the indirect herd-protection observed following introduction of PCV into the United States of America[11] and, more recently, the 39% reduction in the burden of clinical pneumonia hospitalization after PCV-introduction,[12] compared to a non-significant 7% reduction in northern California during the vaccine-efficacy trial.[13] It is only through the phased introduction of PCV, which has been shown to be safe and efficacious in children from diverse settings, that the true public health benefit of PCV would be realized in developing countries. This would however need to be coupled with robust surveillance systems to evaluate changes in the epidemiology of pneumonia before and after its introduction in representative populations of different regions of the world.

The mortality benefit in the Gambian study was not evident only within 1 week of vaccination, but in fact mainly from 12 months onward when 238 (72.1%) of the 330 PCV-recipients' deaths and 289 (73.5%) of the placebo recipients' deaths occurred.[14] The rate of mortality within 7 days of *any* dose of study vaccine (n = 12; 0.15%) and placebo (n = 15; 0.18%; P = 0.55) did not differ between the two groups, and their reported incidence calculations are incorrect. The higher rate of reactive airway disease observed in the South African study was not evident upon subsequent analysis following extended follow up of the cohort until an average of 6.3 years of age (S Madhi, personal communication). Additionally, the higher initially reported risk (1.3 per 1000 children) needs to be weighed against the net reduction of disease prevented, which was 3.6 per 1000 child years against radiologically-confirmed pneumonia alone.[15]

In conclusion, while we agree with the assertion that the use of PCV in developing countries needs to be weighed in relation to its cost and benefit, we believe that the potential benefit of PCV in developing countries is beyond question, as indicated by the WHO recommendation on PCV.[16] Nevertheless, it is essential that the introduction of PCV be coupled with adequate surveillance at least in representative communities of regions in which it is introduced to fully establish the potential to public health of the vaccine. ■

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