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LETTER

Letter to the Editor Regarding "Clinical and Economic Burden of Pneumococcal Disease Due to Serotypes Contained in Current and Investigational Pneumococcal Conjugate Vaccines in Children Under Five Years of Age"

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In a recent article, Wasserman et al. used a decision-analytic model to estimate the clinical and economic burden of pneumococcal disease attributable to *Streptococcus pneumoniae* serotypes contained in current and investigational pneumococcal conjugate vaccines (PCVs) in children ≤ 5 years of age [1]. We would like to highlight some methodological limitations that may affect interpretation of the model results.

The model used by Wasserman et al. utilized recent data on the serotype-specific burden of invasive pneumococcal disease (IPD) from countries where either the 10-valent PCV (PCV10) or 13-valent PCV (PCV13) are already widely in use. The authors state "we only considered the most recent serotype coverage and burden of disease to characterize the remaining burden of vaccine-preventable pneumococcal disease rather than historical estimates" [1]. We argue that this approach does not acknowledge the potential for newer vaccines to have reduced serotype-specific immunogenicity compared with PCV10 or PCV13, which could result in an increase in the disease burden caused by the serotypes shared with these two PCVs.

Wasserman et al. state that analyses based on the current burden of disease are important for policymakers to understand which vaccines will decrease the disease incidence in their country. We commend this approach but believe that a comprehensive model should also take into account the potential for reemergence of serotypes covered by existing PCVs. A model that does not incorporate historical as well as recent data risks overestimating the potential effect of certain PCVs on disease burden. Analyses of the impact of other childhood vaccines have incorporated historical data on prevaccine disease incidence [2, 3]. In previous analyses, we used a Markov model to estimate the total value of the 15-valent PCV (PCV15 [V114]) using historical data on the burden of PCV13 serotypes prior to the introduction of PCV13, as well as current data on non-PCV13 serotypes included in PCV15 [4, 5]. This approach recognizes the importance of maintaining protection against serotypes in existing PCVs, as well as broadening protection against other serotypes.

There is already some evidence for an increasing burden of disease caused by vaccine

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serotypes. During the 7-valent PCV (PCV7) era, the prevalence of pneumococcal disease caused by serotype 19F significantly decreased [6]. However, since the introduction of PCV13, carriage and disease caused by serotype 19F has reemerged [6–8]. This effect may be linked to reduced immunogenicity of PCV13 when compared with PCV7, which has been observed in the clinical trial setting [9]. Additionally, the overall burden of IPD has plateaued in many countries in recent years, partially driven by disease caused by the PCV13 serotypes 3 and 19A [10, 11]. Further reductions in immunogenicity or effectiveness with newer PCVs could have the potential to lead to increased disease burden from the serotypes shared with existing PCVs.

The model used by Wasserman et al. includes other assumptions that may limit the applicability of the outputs. First, the model assumed that the distribution of *S. pneumoniae* serotypes was the same across all countries and regions. Although the model included age and country-specific incidence rates of pneumococcal disease outcomes stratified based on local serotype coverage for each PCV, these inputs were not serotype specific. Dominant serotypes are known to differ across regions. For example, in Europe, some of the most common non-PCV13 serotypes isolated from confirmed IPD cases in 2018 in children < 5 years of age were 24F, 8, 12F, 10A, and 23B [10], whereas, in the USA in 2017, the most common serotypes were 22F and 33F [7]. Given that the analysis included countries from Europe, North America, Southeast Asia, and the Western Pacific, inclusion of serotype distribution in the model could have substantially altered outputs.

Second, the model used by Wasserman et al. did not account for differences in serotype distribution across clinical outcomes of pneumococcal disease. Certain PCV serotypes, such as serotypes 1, 7F, 19A, 8, 12F, 22F, and 33F, have greater potential for invasive disease than others [12] and, therefore, may be responsible for a higher clinical and economic burden. This omission could result in an underestimation of the potential impact of PCVs that address these serotypes.

Third, the validity of the sensitivity analysis that assumed cross-protection of PCV20 to serotype 15C, due to inclusion of serotype 15B in the vaccine, should be interpreted with caution. As the authors themselves acknowledge, there is currently no clear evidence to support cross-protection, other than genetic homology of 15C with serotype 15B. Cross-protection cannot be assumed based on cross-reactivity. For example, serotype 19F in PCV7 elicits cross-reactive binding antibodies to serotype 19A, but there is no corresponding functional antibody response; thus, cross-protection is not achieved [13].

A further minor methodological limitation of the model used by Wasserman et al. is the exclusion of indirect medical costs, such as productivity losses among adult caregivers of children with IPD, which can be important contributors to cost-effectiveness models. In addition, the proportion of all-cause pneumonia attributable to *S. pneumoniae* in France and South Korea was assumed to be 100%. Although the authors state that conservative estimates were used in instances where data were not available, these assumptions are clearly an overestimation. Data from these countries are limited, but available data from similar settings suggest that a much lower proportion of childhood pneumonia cases are attributable to *S. pneumoniae* [14, 15], closer to the values used for other countries in the model (20–38%).

In summary, by only presenting the incremental value of non-PCV13 serotypes in their model, the findings of Wasserman et al. do not represent the total value of the PCVs assessed. Furthermore, not incorporating geographical and clinical differences in serotype distribution, as well as the use of non-evidence-based assumptions for sensitivity analyses, limits the accuracy of their estimates.

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