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LETTER

A Response to: 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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We thank Feemster and Weiss for their interest in our study "*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*." Below we will first address their methodologic concerns and second address minor concerns.

First, Feemster and Weiss state that our "model assumed that the distribution of *S. pneumoniae* serotypes was the same across all countries and regions." However, our study leveraged country-specific serotype distributions of *Streptococcus pneumoniae* serotypes for invasive pneumococcal disease (IPD). This is clearly stated in the method section of the original paper *"Serotype coverage for children under 5 years of age was derived from nationally or regionally representative IPD surveillance systems for each country"* and was presented in Figs. 3 and 4 as well as in Supplemental Tables S1 and S2 [1]. Furthermore, a well-known limitation of estimating pneumococcal disease burden in children is the limited data availability on serotype distributions for non-invasive disease, including otitis media (OM) and pneumonia. Most studies quantifying the burden of serotype-specific pneumococcal disease are limited to IPD. As is appropriate and well accepted in pneumococcal disease modeling, we assumed that the serotype distribution of noninvasive disease would be similar to IPD but acknowledge that in certain settings there could be variation in the serotypes causing invasive and noninvasive disease [2–9].

Second, Feemster and Weiss state that "the proportion of all-cause pneumonia attributable to *S. pneumoniae* in France and South Korea was assumed to be 100%." We apologize if it was not immediately apparent in the paper; however, both France and South Korea disease incidence estimates were obtained from sources reported specifically as pneumococcal pneumonia (i.e., only pneumonias caused by *S. pneumoniae*). For the remaining countries, where specific pneumococcal pneumonia estimates were not available, we conservatively assumed 20% all-cause hospitalized and non-hospitalized pneumonia and OM were attributable to *S. pneumoniae* [10], despite observed reductions in OM and pneumonia in

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children as high as 41% [11] and 47% [12] after PCV13 introduction, respectively.

Third, a minor concern raised by Feemster and Weiss was that our model did not consider serotype-specific invasive disease potential. We acknowledge that certain pneumococcal conjugate vaccine (PCV) serotypes have a higher invasive potential, but we determined there was insufficient evidence on serotype-specific invasive disease potential to justify including it in our model. Consequently, we agree that our estimates are conservative and may underestimate the overall clinical and economic burden. Had we incorporated serotype-specific invasiveness potential in our model, this would have resulted in an increase in burden because the additional serotypes contained in 20-valent PCV (PCV20) such as 8, 10A, and 12F have a higher invasive potential [13].

Fourth, Feemster and Weiss highlighted that the model does not account for immunogenicity differences of higher valent vaccines and their impact on disease burden. To meaningfully estimate the effectiveness of higher valent vaccines, efficacy, effectiveness, or real-world impact studies are needed. Predictions based on immunogenicity are insufficient for estimating clinical impact over the short and long term. Because no vaccine efficacy, effectiveness, or impact data are available yet for PCV15 or PCV20, this study focused on the burden of disease associated with the serotypes in each vaccine.

Fifth, Feemster and Weiss also commented on the utilization of the most recent serotype-specific data in our study. We reiterate what was stated in our discussion: "Two recent studies by Hu et al. quantified the additional economic burden of PCV15 serotypes in the United States [63] and Europe [64] and found directionally similar results to our study; however, they did not include the burden of the five additional serotypes contained in PCV20. By omitting the incremental burden of PCV20-unique serotypes from their calculations, Hu et al. overestimates the burden of PCV15-unique serotypes and consequently misrepresents the vaccine-type burden of pneumococcal disease by only using PCV15-type disease as a denominator. These studies also considered pre-PCV incidence of both PCV7- and PCV13-unique serotypes, while 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. Although it is beneficial to show the overall value of a PCV program, this methodology does not reflect the current burden of disease which is perturbed by decades of PCV use. Estimating the current pneumococcal disease burden is important when policymakers must characterize which vaccines will provide robust serotype coverage and decrease the disease burden in their country, given that serotype epidemiology has changed over time and current disease rates are not analogous to pre-PCV incidence and serotype distributions. However, it remains essential that investigational higher-valent vaccines continue to protect against serotypes contained in currently licensed vaccines and avoid removing vaccine pressure, given that uncovered serotypes can rebound and cause significant disease."

Finally, Feemster and Weiss mention that our model did not include indirect medical costs, such as productivity losses among adult caregivers of children with IPD. Indeed, these costs can be important contributors to cost-effectiveness models. We agree with the authors of this letter that it is important to capture the full societal benefits of vaccination, which have been shown to be greater than the more limited direct [14, 15]. Therefore, our annual economic burden results of $118 million for PCV15 and $214 million for PCV20 can be considered conservative. In our article, we chose not to include indirect costs as most countries included in our analyses require economic evaluation performed from a health care perspective [16]. Including indirect costs will increase the annual economic burden with higher increases for higher-valent PCVs. To demonstrate the impact of including indirect costs, we performed an additional indirect cost analysis to estimate caregiver burden and loss of productivity in the 13 countries included in our analysis. In our economic evaluation, we found that indirect costs represented approximately 44% of the total costs associated with pneumococcal disease burden. The annual economic burden

increased by $92 million to $210 million for disease caused by PCV15 serotypes and by $172 million to $385 million for disease caused by PCV20 serotypes, respectively. We note that these estimates are conservative as we did not account for caregiver burden from an unpaid job, presenteeism, or direct non-medical cost such as travel-related indirect costs. More research is needed to quantify the entire societal burden including these indirect costs.

In closing, we thank Feemster and colleagues for their interest in our article and hope that our responses remove any concerns raised in their letter.

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Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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