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REPLY LETTER



# Comment on Gomez et. al. "Response to article by Wasserman et. al. (2018) 'Modelling the sustained use of the 13-valent pneumococcal conjugate vaccine compared to switching to the 10-valent vaccine in Mexico'"

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**ABSTRACT**

In a recent Letter, Gomez et. al. provided a critique of our original analysis estimating the clinical and economic impact of switching from the 13-valent (PCV13) to the 10-valent (PCV10) pneumococcal conjugate vaccine in Mexico. This comment addresses Gomez et. al.'s comments with additional information and clarifies potential misinterpretations.

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We thank Gomez and colleagues for their interest in our manuscript entitled "Modelling the sustained use of the 13-valent pneumococcal conjugate vaccine compared to switching to the 10-valent vaccine in Mexico".[1] While their concerns are very similar to a previously published letter to the editor,[2] to which there is a published response,[3] in order to ensure scientific accuracy we appreciate the opportunity to respond to each of their five comments.

## 1. Use of PCV10 in Mexico

Gomez and colleagues stated that our "one sided and highly limited focus narrowly addresses the sequence of PCV7 to PCV13 and improperly assume that all the health benefits observed in this period are associated with those vaccines" based on a claim that between January 2010 and December 2011 there were 2.2 million doses of PCV10 distributed to the Mexican Social Security Institute (IMSS). While PCV10 was used over a brief time in Mexico, it was never used exclusively in the national immunization program (NIP) and represented ~20% of PCV use over the shared time period and less than 5% of the total PCV use over the course of our model time horizon. Our assumption that the long-term serotype specific trends are driven by PCV7 and PCV13 use are well justified, and PCV10 was not specifically considered in the retrospective analysis.

## 2. Potential cross-reactivity of the 10-valent vaccine with 19A

Gomez and colleagues state that our "analysis appears significantly biased considering an invasive pneumococcal disease (IPD) serotype specific approach [and] the evidence of cross-protection against serotype 19A provided by PHiD-CV." This is inaccurate and does not acknowledge the novel methodology afforded from this modeling approach. Our methodology captures any observed 19A cross-reactivity of PCV10 in scenarios utilizing historic data from Finland and the Netherlands. For example, any changes in 19A disease due to cross-reactivity would be captured in surveillance data in PCV10 countries. However, because PCV10 does not provide protection against 19A pneumococcal carriage,[4] rates of 19A disease have been increasing at a population level in both vaccinated and unvaccinated populations in countries using PCV10 and recent studies have stated that PCV10 provides limited cross-reactivity with 19A.[5] Furthermore, Gomez and colleagues state that SIREVA have shown a reduction in 19A after PCV13 use,[6] but it still circulates, which is consistent with Figure 2 in our manuscript, as 19A cases have continue to persist in the PCV13 arm even at the 10 year time horizon.

It is important to reiterate that our results are consistent with observed evidence from a real world change from PCV13 to PCV10.[7] By the end of 2017, only 8 to 18 months following the change to PCV10 in the two Belgian regional immunization programs (Flanders in July 2015 and Wallonia in May 2016), a nationwide 10-fold increase in serotype 19A IPD cases in children ≤2 years of age was observed with this trend continuing into 2018.[7] This real world example further supports the assumptions used in our model.

## 3. PCV13 vaccine effectiveness against serotype 3

Gomez and Colleagues also state that "the heterogeneity of effectiveness/impact on serotype 3 observed with PCV13 appear not to have been considered." Similar to the discussion on serotype 19A, our model takes into account the heterogeneity of results for serotype 3. As seen in Figure 2 in our manuscript, serotype 3 remains a persistent serotype in adults but it has reduced slightly

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in children given the recent declines observed in the Mexico surveillance data. This is consistent with a recently published meta-analysis that found that PCV13 provides protection against serotype 3 disease with an estimated vaccine effectiveness of 63.5% (95%CI: 37.3 to 89.7).[8]

## 4. Concerns about the methodology and that these do not conform to established guidelines

Gomez and colleagues criticize our presentation of model estimation and fit of the trend regressions to historical surveillance data and that we did not sufficiently describe our inputs and methodology. On the contrary, the information is included in detailed tables of the relevant epidemiologic inputs, costs, and population parameters that influence our model estimates. The Mexico perspective was also the second publication of this methodology, for which there are additional data summarizing particular assumptions available for the reader.[9]

In our model, both PCV10 and PCV13 largely eliminate disease caused by the 10 common serotypes. As already discussed above, the difference in the 0–2 age group is driven primarily by replacement of 19A disease in the PCV10 arm, which was has been observed in numerous countries using PCV10.[4,7] In the elderly, the difference was seen in serotype 3, where replacement as high in the PCV10 arm, and residual disease remained in the PCV13 arm after 10 years.

## 5. Impact on mucosal disease

Gomez and colleagues note that we fail to acknowledge recent publications by the Pan American Health Organization (PAHO) and the World Health Organization (WHO) which state that the two vaccines produce similar levels of effect in protecting against pneumonia and IPD.[10,11] It is worth noting that both these publications are limited to children under the age of 5, do not include statistical calculations to determine non-inferiority, do not consider indirect effect or prior PCV7 use, do not include surveillance data, and do not include head-to head immunogenicity studies which have shown that PCV13 induces a statistically significantly superior immune response compared with PCV10 for 7 of the common serotypes and the three serotypes that are unique to PCV13.[12] The advisory group to WHO report that for pneumonia, there is limited evidence available due to confounding from prior PCV use and the lack of head to head studies.

Gomez and colleagues also state that our analysis fails "to consider the evidence of PCVs efficacy against pneumonia and acute otitis media." While the authors do not provide any references or note why this is the case, they then state our analysis improperly estimates "the prospective change in pneumonia and AOM based on forecasted change for IPD cases." Our analysis is conservative, focusing only on pneumonia and otitis media cases that are caused by *Streptococcus pneumoniae* rather than all-cause disease, given the concerns outlined by the advisory group to the WHO outlined above. This is based on the assumption that changes in circulating carriage would similarly cause invasive and non-invasive pneumococcal diseases. This methodology is well accepted and has been used elsewhere in the literature to predict the impact of PCVs on non-invasive disease[13-15] and the correlation between invasive and non-invasive pneumococcal disease has been well documented.[16]

In closing we thank Gomez and colleagues for their assessment of our paper. We acknowledge that results are prone to specific assumptions, and alternate assumptions could lead to alternate results, however our results were robust to numerous and rigorous sensitivity analysis. We hope that our answers brought more clarity around our analysis.

## Disclosure of potential conflicts of interest

M Wasserman, MG Palacios, AG Grajales and R Farkouh, are employees of Pfizer Inc. M Wilson and C McDade are employees of RTI Health Solutions are were paid as consultants as part of this study.

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