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# Response to article by Johnna Perdrizet et al.,"Cost-effectiveness analysis of replacing the 10-valent pneumococcal conjugate vaccine (PCV10) with the 13-valent pneumococcal conjugate vaccine (PCV13) in Brazil infants"

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Dear Editor,

We have read with interest the manuscript published by Human Vaccines and Immunotherapeutics entitled "Cost-effectiveness analysis of replacing the 10-valent pneumococcal conjugate vaccine (PHiD-CV) with the 13-valent pneumococcal conjugate vaccine (PCV-13) in Brazil infants" (Perdrizet et al.).[1] Although the study addresses an important topic, we believe the article may create confusion based on the assumptions used for the simulation and have unintended negative impact on public health decisions.

The model used by Perdrizet et al. forecasted future pneumococcal disease trends based on historical serotype behaviors. Given the observed historical surveillance data on serotype-specific pneumococcal disease, the model calculates future behavior of serotype-specific invasive pneumococcal disease (IPD), serotype-specific pneumococcal pneumonia, and serotype-specific pneumococcal otitis media over a 5-y time horizon. The authors calibrated the incidence of IPD in Brazil with data from the Colombian Individual Registration of Health Services (RIPS), a health benefit information system from all health maintenance organizations, because it provides a good estimation of IPD rates. Authors mentioned that both countries share population and health-care assistance similarities and had first introduced a PHiD-CV program in 2010. However, the decision of calibrating the model using the Colombian database is surprising. First, Brazil has a very well-developed online and public health-based information system (DATASUS) including, among others, the Notifiable Diseases Information System (SINAN), the Hospital Information System (SIH) and the Mortality Information System (SIM).[2] Second, a recent study designed to report the trends of all-cause pneumonia and all-cause otitis media incidence in Colombian children using RIPS before and after pneumococcal conjugated vaccine (PCV) introduction, concluded that its data could be considered less reliable leading to substantial bias. The authors also acknowledged that RIPS data quality is subject to considerable uncertainty and under-reporting is generally well recognized.[3] Besides, although some features are similar between countries (same PCV in the National Immunization Program (NIP) and same year of introduction), others are very different (the baseline pneumococcal epidemiology, years of previous PCV-7 use in NIP, PCV-7 coverage, catch up campaigns, PCV schedule (3 + 1 or 2 + 1), development of vaccine days, the effective vaccine coverage and population contact matrices), providing uncaptured factors in the simulation. Therefore, the model could optimally be calibrated with Brazilian health data.

In addition, the historical incidence of acute otitis media (AOM) was obtained from Sartori et al.[4] a study developed in the public healthcare system of Goiania, Brazil. Sartori et al. found a high impact (43.0%; 95% CI 41.4 ± 44.5%) of PHiD-CV (3 + 1 schedule) against AOM rates and they hypothesized that nontypeable *Haemophilus influenzae* (NTHi) protein D, to which PHiD-CV is conjugated, could have an effect in providing further protection against AOM caused by either *S. pneumoniae* or NTHi. It is not clear in the scenario reported by Sartori et al. how reductions on AOM rates as observed after PHiD-CV introduction (43.0%) could be maintained and even improved with the switch to PCV-13.

Perdrizet et al., based on the *Sistema Regional de Vacunas* (SIREVA) II laboratory surveillance network[5] reported that, in 2018, 40% of all registered IPD cases in children under 5 y were caused by serotype 19A and 52.3% were attributed to serotype 3, 6A, and 19A combined. Therefore, assuming in the baseline analysis that 42% of disease in children 0–2 y of age was caused by serotypes 3, 6A, and 19A, combined. The SIREVA II laboratory network was not designed to evaluate pneumococcal disease burden, instead the network was designed to characterize different bacterial strains. Furthermore, the system does not collect population denominators that would allow disease incidence calculation. Additionally, strain submission to the reference laboratory is non-systematic and voluntary and the methods for strain characterization were improved and extended over time so that the serotype distribution reported by the network should be considered carefully and the serotype prevalence used for this analysis should be considered debatable.

Perdrizet et al. evaluated the cost-effectiveness of replacing PHiD-CV with PCV-13 for vaccination of children up to 2 y of age, and they considered in their analysis both the direct and indirect vaccine effects related to herd immunity and serotype replacement. The authors used a linear and logistic regression model to simulate and forecast the complex behavior of pneumococcal serotypes prior to and post-vaccine introduction in

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Brazil. The classic tool to simulate the complexities of pneumococcal serotypes dynamics, including the indirect vaccine effects like serotype replacement and herd immunity, is a dynamic transmission model.[6] To perform a reliable valid health economic analysis, there are certain needs regarding the biological process that should be enclosed in the models to reflect how infections, demographic mortality, protection against infection, costs, and use of healthcare resources occur over time.[7] In the analytical framework used by Perdrizet et al., comparisons between the model's estimations and past data observations are not presented and therefore there is limited explanation on how well trend regressions could predict historical and future data.[1] In addition, serotype-specific regression analysis was used to forecast future disease trends based on serotype behaviors observed in the USA, UK, Canada, and Quebec in order to reflect PCV13 infant vaccination effects. The pneumococcal serotypes behavior in those countries cannot be explained solely by the serotype content of the respective PCVs. As mentioned before, the results of a PCV infant immunization program in a country is related to many other epidemiologic, biologic, and clinical features besides the serotype composition of the vaccine being used. The serotype content of PCVs may not automatically translate into disease protection against included serotypes and the absence of a certain serotype will not automatically translate into the absence of an effect, as cross-protection was demonstrated.[8–10] Therefore, the use of real-world data observed after PCV introduction in one country should not be linearly transferred to simulate the potential vaccine effects in a different country. Real-world data can be very useful to improve the estimations of PCV effects in a country, but this is not a head-to-head comparison and these experiences are not easily transferable between countries. A significant portion of the incremental effects described for PCV-13 by Perdrizet et al. are related to its indirect effects on non-vaccinated cohorts. Again, transferring the serotype replacement and herd immunity effects (indirect vaccine effects observed in non-vaccinated individuals) on vaccine types and non-vaccine types between countries when their baseline pneumococcal epidemiology, years of previous PCV-7 use in NIP, PCV-7 coverage, catch up campaigns, PCV schedule (3 + 1 or 2 + 1), development of vaccine days, the effective vaccine coverage, and population contact matrices are different, can produce a biased assessment.

Finally, the investigators affiliated to recognized public health entities such as the Pan-American Health Organization (PAHO), the International Vaccine Access Center (IVAC), and the World Health Organization (WHO) have each conducted independent systematic reviews on the direct effects described for both PCVs and concluded that there was no superiority of one vaccine over the other.[11–13] Therefore, the assumptions used in the analysis of Perdrizet et al. are inconsistent with the evidence already generated. While the results of Perdrizet et al. suggest that the switch to PCV-13 (instead of continuing the use of PHiD-CV) would likely save 172 Million Brazilian Reals (BRL) (34 Million US dollars (US$)) in serotypes 3, 6A and 19A pneumococcal cases averted over the next 5 y, a recent analysis for Brazil assuming the scenario previously described by international organizations, reports that vaccine switch would only reduce a few number of pneumococcal cases with an incremental cost of US$18 million per year.[14]

Therefore, the analysis of Perdrizet et al. appears significantly biased by using this serotype-specific approach and transferring the PCV experience from other counties to Brazil without considering the PHiD-CV evidence of cross protection against serotype 19A.[8–10] We recognize the efforts of the authors to develop simulations that evaluate the epidemiological scenarios and management costs for pneumococcal diseases, but their tools and assumptions are debatable. Vaccine impact estimations and cost-effectiveness data are crucial to inform policymakers on PCV use. Considering all these general concerns, the Perdrizet et al. study should be interpreted with caution.

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## Disclosure of potential conflicts of interest

Jorge Gómez, Javier Nieto Guevara and Thatiana Pinto are employees of the GSK group of companies. Jorge Gómez and Javier Nieto Guevara report holding shares in the GSK group of companies. Tatiana Guimarães de Noronha is an employee of Bio-Manguinhos/Fiocruz, which manufactures PHiD-CV. Jorge Gómez, Javier Nieto Guevara, Tatiana Guimarães de Noronha and Thatiana Pinto declare no other financial and non-financial relationships and activities.

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