Letter to the Editor Regarding: “Cost-Effectiveness of the 13-Valent Pneumococcal Conjugate Vaccine (PCV13) Versus Lower-Valent Alternatives in Filipino Infants”

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In the article published in September 2021, Perdrizet et al. assessed the cost effectiveness of pneumococcal conjugate vaccine (PCV) 13-PFE versus PCV10-GSK or PCV10-SII when adopted across all regions of the Philippines [1]. The authors utilized a model that calculates the future behavior of serotype-specific invasive pneumococcal disease (IPD), serotype-specific pneumococcal pneumonia, and serotype-specific pneumococcal otitis media over a 10-year period, using historical data on serotype behaviors.

Perdrizet et al. estimated the serotype-specific IPD incidence using the serotype distribution by age group from passive laboratory-based surveillance. This was obtained from the Research Institute for Tropical Medicine between 2012 and 2019, and aimed to reflect the real-world epidemiology of pneumococcal disease in the Philippines in 2020. It should be noted that the authors used average serotype-specific data between 2012 and 2019 to build their baseline scenario. Importantly, however, the first PCV was introduced into the National Immunization Program (NIP) of the Philippines in 2015, and, thus, during the 2012–2019 period some impact of PCV vaccination was already being observed. The use of baseline epidemiologic data from a time period where PCV was already being administered introduces significant uncertainty in the forecasting of future vaccine effects.

Perdrizet et al. evaluated the cost-effectiveness of maintaining the use of PCV13 compared with switching programs to PCV10 (PCV10-GSK or PCV10-SII) within the NIP of Filipino children up to 2 years of age. In order to effectively simulate and predict the behavior of pneumococcal serotypes prior to and following vaccine introduction in the Philippines, as well as predicting the indirect effects of the vaccine, a dynamic transmission model would conventionally be used [2]. However, the authors opted to use a linear and logistic regression model [1],...
in which the model’s estimates and observations of past data were not compared, thus making it unclear to what extent the trend regression can be used to accurately predict historical and future data [1].

Additionally, the authors explored the effects of PCV13 and PCV10 infant vaccination by predicting future disease trends (IPD, pneumonia, and acute otitis media) in the Philippines via regression analysis using serotype-specific behaviors observed in the USA, Finland, Colombia, and the UK. The serotype-specific behaviors in these countries following the introduction of PCVs cannot be entirely explained by the serotype composition of the vaccine. The PCV strategies implemented in these countries (US: began PCV7 in 2000, switched to PCV13 in 2010 in a 3+1 schedule; Finland: began PCV10 in 2010 in a 2+1 schedule without previous use of PCV; Colombia: began PCV10 in a 2+1 schedule in 2012 with previous use of PCV7 in specific geographic areas since 2009; UK: began PCV7 in 2006, switched to PCV13 in 2010 in a 2+1 schedule) [3–5], as well as their PCV coverages, are very different to the PCV13 3+0 strategy adopted in the Philippines in 2015, and, therefore, these results cannot be used to extrapolate future disease trends in the Philippines.

There are a wide range of factors that contribute to the results of a PCV infant immunization program in a given country, beyond the serotype content of the vaccine. Such factors include various epidemiologic, biologic, and clinical factors: 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. Cross-protection has been demonstrated in PCVs, such that the sole presence or absence of certain serotypes may not induce disease protection or cause a lack of protection [6–8]. Therefore, using real-world data obtained following the introduction of PCVs in a given country to extrapolate the PCV effects in another country is questionable, and may result in unreliable estimations and conclusions.

Although there are no head-to-head studies evaluating the magnitude of the impact of PCVs, an observational cohort study conducted in Sweden reported no differences in overall IPD impact, irrespective of the vaccine used [9]. Since circulating pneumococcal strains that cause IPD cannot always be extrapolated to pneumonia and otitis outcomes, those estimations based on serotype distribution as part of this modeling exercise could also lead to inaccurate appraisals. The authors highlighted the switching scenario observed in Belgium, but it is important to bear in mind that other countries and regions have also established switches from PCV13 to PCV10 (New Zealand, Sweden, Quebec in Canada, Piedmont in Italy, and Morocco), mainly driven by cost-effectiveness analysis and technical parity of PCVs against overall IPD.

Finally, public health bodies, including the Pan-American Health Organization, the International Vaccine Access Center (IVAC), and the World Health Organization (WHO), have conducted systematic reviews on the effects of PCV10-GSK and PCV13; these reviews reported no significant difference between the effects of the two vaccines [10–13]. A systematic review of the literature on the impact or effectiveness of PCVs on deaths, or hospitalizations due to IPD, pneumonia, meningitis, and sepsis conducted in Latin America concluded that there was a significant impact of both PCV10 and PCV13 in the outcomes evaluated, with no evidence of superiority of one vaccine over the other on pneumonia, IPD, or meningitis hospitalization reductions in children under 5 years [10]. Additionally, a systematic review was conducted by experts convened by the WHO, including those from the IVAC at Johns Hopkins Bloomberg School of Public Health and the US Centers for Disease Control, among others, on PCV products (including unpublished data) to inform the policy review process developed by the Strategic Advisory Group of Experts on Immunization (SAGE) PCV Working Group of the WHO [11]. This review provided information on the two licensed PCV products available at the time, along with advice that countries should consider before deciding on a specific product. The SAGE PCV Working Group
reviewed the data on the optimal use of PCVs, with respect to dosing schedules and products, and concluded that both vaccines have a substantial impact in the prevention of pneumonia, vaccine-type invasive disease, and carriage [12]. It was also mentioned that no evidence of different net impact on overall disease burden was found between the two products, and PCV13 may have additional benefits in settings where disease attributable to serotype 19A or 6C is significant. In February 2019, the WHO described their position on the use of PCVs, based on the systematic review of primary evidence from the literature on the immunogenicity and effectiveness of PCV10-GSK and PCV13 against clinical disease (IPD and pneumonia) and nasopharyngeal carriage; they concluded that both PCVs were safe and effective [13, 14]. Similarly, they reported that the available evidence indicated that both products were effective in reducing overall vaccine-type IPD in both vaccinated and unvaccinated individuals. Although PCV13 contains three additional serotypes, there is currently insufficient evidence to determine whether they have an impact on overall IPD burden (vaccine type and non-vaccine type disease combined).

Therefore, the assumptions and methods used in the analysis performed by Perdrizet et al. are inconsistent with available scientific evidence. While the results of Perdrizet et al. suggest that maintaining the use of PCV13 instead of switching to PCV10 may avert 375,831 more cases, save 53,189 additional lives, gain 153,349 quality-adjusted life years (QALYs), and save PHP 12.27 billion over 10 years, the Health Technology Assessment from the Department of Health of the Philippines, conducted independently of manufacturers, concluded that shifting PCVs can result in significant savings, since PCV10 has a lower 5-year incremental program cost when compared to PCV13, thus saving the government PHP 4.04 billion over 5 years [15].

The analysis performed by Perdrizet et al. utilized a serotype-specific approach, directly extrapolated the effect of PCV introduction in other countries to the Philippines, and ignored relevant scientific evidence to reach an inaccurate and seemingly biased conclusion. Although we recognize the efforts exhibited by the authors to develop novel simulations to assess the epidemiological impact and cost-effectiveness of pneumococcal disease vaccines, the models and assumptions used are unreliable. Thus, taking into account the aforementioned concerns, the study conducted by Perdrizet et al. should be interpreted with some degree of caution.

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Donald Ray Josue, Edwin Rodriguez: employee of GSK.

**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.

**Data Availability.** Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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