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LETTER TO THE EDITOR

Comment on: "Cost-Effectiveness Evaluation of the 10-Valent Pneumococcal Non-Typeable Haemophilus influenzae Protein D Conjugate Vaccine and 13-Valent Pneumococcal Vaccine in Japanese Children"

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INTRODUCTION

Shiragami and colleagues [1] have presented a cost-effectiveness model of the use of routine pneumococcal vaccination in infants in Japan using the 10-valent pneumococcal conjugate vaccine (PCV10) and the 13-valent pneumococcal conjugate vaccine (PCV13). In this analysis, the authors concluded that the routine use of PCV10 was more cost-effective than PCV13. While the analysis applies modeling methodologies that are sound, many of the assumptions presented in the paper are inconsistent with current published scientific evidence, specifically those regarding PCV13 effectiveness against serotype 3, PCV10 effectiveness against pneumonia, PCV10 effectiveness against otitis media, PCV10 cross-protection against serotypes not contained in the vaccine (serotypes 6 and 19A), and herd effects. We challenge these assumptions using previously conducted studies and data in the public domain.

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Both vaccines received approvals (PCV10 and PCV13 in the European Union in 2009 and PCV13 in the United States in 2010) based on immunologic criteria; no efficacy studies formed the licensure criteria. Therefore, early cost-effectiveness evaluations required extrapolation of immunogenicity to clinical effectiveness. We discussed the criteria under which appropriate assumptions could be formulated in a review paper [2]. In subsequent years, several efficacy and effectiveness evaluations have been conducted around the world to fully evaluate both vaccines. PCV10 data have been analyzed in 2 randomized controlled trials [3, 4], and PCV13 data have largely come from studies assessing the effectiveness of vaccination after introduction in national immunization programs initiated following the transition from the 7-valent pneumococcal conjugate vaccine (PCV7) to PCV13. Since the introduction of PCV13 in countries having a national immunization program, there has been a decline in vaccine-type invasive and noninvasive pneumococcal infections in children and adults (via herd effect) as well as a reduction of nasopharyngeal carriage after the

primary series vaccination and after a booster [5–14].

EFFECTIVENESS AGAINST SEROTYPE 3

The protection of PCV13 against invasive pneumococcal disease caused by serotype 3 is assumed by Shiragami and colleagues to be 0.00%, largely on the basis of the authors' selection of outdated Joint Committee on Vaccination and Immunisation (JCVI) minutes [15]. The most recent JCVI minutes have included a revised statement indicating that the number of serotype 3 cases has declined in the United Kingdom following the introduction of PCV13 in the UK National Immunisation Program [16]. In other countries with robust surveillance systems, positive point estimates for serotype 3 have been presented [13, 17, 18]. Although it is true that positive point estimates for serotype 3 effectiveness took longer to reach statistical significance [13], it is clear that PCV13 cannot be considered ineffective against serotype 3.

EFFECTIVENESS AGAINST PNEUMONIA

Because of high incidence and expenditures, pneumonia is a significant driver of the costs of pneumococcal infections. Assuming that PCV10 and PCV13 have equal effectiveness is inconsistent with the current evidence that serotype coverage plays an important role in the potentially preventable burden of disease. We agree with the authors that the clinical trial results of PCV7 and PCV10 against X-ray-confirmed pneumonia were similar; however, comparisons between the COMPAS study (PCV10 [19]) and the Northern California Kaiser Permanente study (PCV7 [20]) are historical. At the present time, the comparison needs to be made against PCV13, a vaccine with 6 additional serotypes compared with PCV7. In the United States, for example, after a 43% nationwide decline in hospitalizations for all-cause pneumonia in children <2 years of age was achieved with PCV7, data from Tennessee showed an additional reduction of 27% following the introduction of PCV13 [10]. In Sweden, where both PCV10 and PCV13 are used in different county councils, the number of cases of hospitalized pneumonia significantly decreased in county councils that made a transition from PCV7 to PCV13; during the same time period, no additional reductions were observed in county councils that switched from PCV7 to PCV10 [7]. The observed differences between PCV10 and PCV13 reached statistical significance [7]. Effectiveness data from France [5], Nicaragua [6], and Uruguay [21, 22] confirm additional benefits in the PCV13 post-vaccination period compared with the pre-vaccination period, not only in the incidence of uncomplicated pneumonia, but also in the incidence of cases resulting in hospitalization or complicated with pleural effusion.

Based on these recent publications and the fact that protection against disease is based on the serotypes contained in the vaccine, we believe that using serotype coverage proportional to the individual effectiveness of PCV10 and PCV13 would have been more appropriate.

EFFECTIVENESS AGAINST OTITIS MEDIA

Farkouh et al. [2] described in detail the issues specific to acute otitis media (AOM) with models of PCV cost-effectiveness. The incorrect assumptions used in the model by

Shiragami and colleagues, specifically the hypothetical effect of the vaccine against disease caused by non-typeable *Haemophilus influenzae* (NTHi) and cross-protection against the 6A and 19A serotypes, result in an overstatement of the effectiveness of PCV10 against acute otitis media. After 5 years of use, no evidence of effectiveness against NTHi has emerged from any country that has evaluated PCV10. The inclusion of the Pneumococcal Otitis Efficacy Trial (POET) from the Czech Republic in the model of Shiragami and colleagues is inappropriate because it evaluated a markedly different vaccine formulation that was never brought to market and it used a highly selective population [23, 24]. Furthermore, the confidence intervals observed for NTHi were wide, and methodological flaws were observed, such as the extraordinarily low number of otitis media cases and the low number of bacteriologically confirmed otitis media cases [25].

Two studies of all-cause AOM conducted in Finland, one assessing PCV7 and the other assessing PCV10, each found nearly the same reduction in AOM, supporting that there was no added benefit in reduction of all-cause AOM with PCV10 [26, 27]. Since the United States transitioned from PCV7 to PCV13, an additional reduction in all-cause AOM has been reported in children <2 years of age, supporting an incremental benefit of PCV13 in the reduction of AOM consistent with its broader serotype coverage [28]. As highlighted previously [2, 29], and again in the model of Shiragami and colleagues, AOM is erroneously responsible for the majority of modeled cost differences reported between the 2 vaccines. Based on the available information and the fact that protection against disease is based on the serotypes contained in the vaccine, we believe that using an effectiveness analysis that is proportional for the serotype coverage of PCV10 and PCV13 is the most appropriate approach.

CROSS-PROTECTION AGAINST SEROTYPES NOT INCLUDED IN PCV10

Early studies relied on PCV7 data to extrapolate effectiveness of the higher valent vaccines. However, after 5 years of use, a vaccine should be able to support assumptions with evidence. Considering that PCV7 and PCV10 are manufactured using different carrier proteins and conjugation chemistries, making extrapolations between these vaccines is questionable. Therefore, it is inappropriate for Shiragami and colleagues to reference a US study of PCV7 to support the contention that the serotype 6B antigen in PCV10 provides protection against serotype 6A. After 5 years of use, there should be sufficient data for PCV10 to support such a claim of protection. If these data are still not present, it is inappropriate to assume cross-protection. Evidence regarding the lack of cross-protection of PCV10 against serotype 6A is currently available [30].

More importantly, the issue of serotype 19A cross-protection is critical in Japan because serotype 19A currently represents 45% of pneumococcal serotype isolates [31], not the 25% referenced by Shiragami and colleagues. It is widely known that, during the PCV7 era, serotype 19A emerged as a dominant serotype globally. To support the claim that PCV10, which contains serotype 19F, provides cross-protection effectiveness against serotype 19A, Shiragami and colleagues referenced a case–control study of invasive pneumococcal disease in young children from Brazil by Domingues and colleagues [30], in which only a few numbers of discordant pairs supported their

findings. Although the study design was robust, the results are inconsistent with the national surveillance system in Brazil, which shows an increase in the incidence of serotype 19A invasive pneumococcal disease between 2006 and 2011 in children younger than 5 years of age [32, 33]. Domingues and colleagues concluded that "Validation of this finding in other settings is important because the point estimate of effectiveness against serotype 19A disease is higher than what might be expected based on immunogenicity data, and the 95% CI was wide. Additionally, PCV10 has not reduced 19A nasopharyngeal carriage in Kenya, where it was introduced in early 2011". As another example, in Finland, where PCV10 has been used extensively, the incidence of serotype 19A invasive pneumococcal disease continues to rise, driven mostly by disease in older groups [34]. In their analyses, Shiragami and colleagues rely too heavily on the single, unsubstantiated data point provided by the report of Domingues and colleagues. Despite an initial case–control study in the United States that demonstrated a reduction in serotype 19A disease [35], real-world experience confirms that PCV7 does not provide cross-protection against serotype 19A [36, 37]. Combined with the lack of confirmation of any 19A cross-protection in countries where PCV10 is used in a national program [38, 39], it is inappropriate to use cross-protection against 19A as a base case assumption.

HERD EFFECTS

The analyses by Shiragami and colleagues do not include any assumption regarding indirect or herd effects. Herd effects are critical for evaluating the full public health impact of vaccines. Each case of pneumococcal disease that is prevented indirectly provides an economic and health benefit while imposing no additional costs, making herd effects a powerful driver of value. For PCV13, indirect effects have been demonstrated and reported for persons older than 5 years of age in countries with pediatric immunization programs and high vaccine uptake [13, 40]. This has not been the case for PCV10, as has been clearly demonstrated in data from Finland and Chile [41, 42].

SUMMARY

Because all important assumptions used in the model are simultaneously biased toward PCV10, the model results are erroneous and misleading. Routine infant pneumococcal vaccination in Japan would undoubtedly bring substantial reductions in morbidity and mortality. However, given the current epidemiologic landscape in Japan and the current evidence, the clinical and economic gains from the use of PCV13 would, undoubtedly, far exceed those potentially observed from the use of PCV10. We urge those who conduct, critique, and consider cost-effectiveness studies to evaluate the strength of the evidence of clinical claims for the products and the influence these assumptions have on the overall findings. In addition, when performing economic predictive modeling, it is critical to provide a balanced perspective by weighing the strengths and weaknesses of all available data to construct the base case analysis.

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