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LETTER TO THE EDITOR

Reply to Farkouh RA et al. 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

Farkouh et al. [1] in their letter to the editor in response to the publication entitled "Cost-Effectiveness Evaluation of the 10-Valent Pneumococcal Non-typeable *Haemophilus influenzae* Protein D Conjugate Vaccine and 13-Valent Pneumococcal Vaccine in Japanese Children" [2] raise questions concerning the efficacy and effectiveness assumptions made for both vaccines.

We agree with Farkouh et al. [1] that the validity of any cost-effectiveness model relies upon both the ability of the model to reflect the reality of complex clinical and epidemiological scenarios and the quality of the input data. In the absence of head-to-head studies comparing the clinical efficacy of the two pneumococcal conjugate vaccines (PCV), validation of the assumptions used in the model is essential. In the case of our model, contrary to the opinion of Farkouh et al. [1], the assumptions are based on the most recent, publicly available clinical evidence. In reflection of the variable robustness of the available evidence, the assumptions were validated by two independent advisory boards (including one undertaken specifically to support the analysis in Japan), each consisting of prominent experts in the field. This was particularly important for

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the 13-valent PCV (PCV-13), since the data for that vaccine is largely derived from post-marketing surveillance studies that are subject to several different confounding factors, as opposed to results of randomized, double-blind clinical trials, which are considered to be of the highest standard for assessing vaccine efficacy. The latter are only available for the ten-valent pneumococcal non-typeable *Haemophilus influenzae* protein D conjugate vaccine (PHiD-CV), and data from post-marketing surveillances with PHiD-CV corroborate findings of these randomized trials.

As most of the concerns raised by Farkouh et al. [1] have already been addressed in the scenario and sensitivity analyses presented in our original publication [2], in this response we will largely discuss those assumptions which were not previously elaborated upon [2].

EFFECTIVENESS AGAINST PNEUMONIA

While the suggestion by Farkouh et al. [1] to assume that the individual effectiveness of vaccines is proportional to their serotype coverage seems straightforward, the real-world experience with various PCVs does not support such a close relationship. In fact, based on a critical appraisal of clinical evidence for all marketed as well as many investigational pneumococcal conjugate PCVs, Hausdorff et al. [3] convincingly argued that the serotype coverage of PHiD-CV and PCV-13 vaccines is an inadequate basis for making quantitative projections regarding the overall disease impact [3]. One major reason is that such a simplistic approach does not adequately account for protection against vaccine-related serotypes, while there is substantial, growing evidence in the literature that PCVs can provide substantial protection against those [3]. Moreover, randomized double-blind trials assessing efficacy against pneumonia do not suggest that higher valence vaccines, even beyond the ten-valent formulation [3], offer greater protection against clinical or radiologically confirmed pneumonia. Finally, PHiD-CV efficacy to prevent pneumonia in children was demonstrated in two large randomized, double-blind clinical trials [4, 5] and corroborated during post-marketing surveillance (for example, in Brazil [6], Finland [7], and Iceland [8]), whereas the evidence for PCV-13 is based solely on data from post-marketing surveillance studies [9–14]. As mentioned earlier, this poses difficulties in comparison, as due to a variety of factors inherent in these latter studies, such as differences in populations, schedules, uptake rates, timing and other variables that affect disease rates within an uncontrolled effectiveness or impact analysis, it is very difficult to draw meaningful quantitative or comparative conclusions.

The complexity of interpreting post-marketing impact studies is perhaps best illustrated by a study from Sweden [15] referred to also by Farkouh et al. [1], where currently both PHiD-CV and PCV-13 are used in different county councils. Differences in pneumonia hospitalization incidence were observed between the respective councils and it was suggested that this can be attributed to the difference in the valence of PCVs used [1]. However, as reported in that paper [15], the seven-valent PCV (PCV-7) was introduced in all those councils in Sweden prior to the use of higher valent vaccines, and yet the magnitude of reduction of pneumonia incidence observed during the period when only PCV-7 was used still differed markedly in those respective councils, which are currently using either PCV-13 or PHiD-CV. This observation strongly

suggests that any observed differences in pneumonia incidence between the councils mainly reflect other epidemiological factors or secular trends that differ in the two populations, rather than true differences in efficacy against pneumonia of either PCV-13 or PHiD-CV. In conclusion, the concept that overall protection is governed predominantly by serotype coverage is unsupported by the clinical evidence [3] and support the efficacy estimates used in our published model [2].

PROTECTION AGAINST CROSS-REACTIVE SEROTYPES

With respect to protection against cross-reactive serotypes not included in PHiD-CV formulation, our assumptions for vaccine effectiveness against serotypes 19A and 6A are, in contrast to the opinion of Farkouh et al. [1], largely based on data generated with this vaccine in a number of studies of robust design. Data generated with other formulations are also strongly supportive of our assumptions.

Data from various post-marketing studies provide evidence for PHiD-CV protection against serotype 19A [16]. The 82% effectiveness of PHiD-CV against 19A invasive pneumococcal disease (IPD) reported in the Brazilian case–control study [17] has been corroborated in two additional robustly designed studies in Quebec (Canada) and Finland, respectively. In the Quebec case–control study [18], the effectiveness of PHiD-CV against serotype 19A was 71%, which was statistically significant. This study, which is unique in also assessing the effectiveness of PCV-13 on 19A disease in the same study setting, demonstrated vaccine effectiveness of 74% for PCV-13 (overlapping confidence intervals with PHiD-CV) [18]. In the Finnish cohort study, a significant 62% reduction in a number of 19A IPD cases was observed following the introduction of PHiD-CV into their national immunization program (NIP) [19]. Additional data supporting the effectiveness of PHiD-CV in their NIP, including the Netherlands [20, 21] and Chile [22], as well as the functional opsonophagocytic antibody (OPA) responses against 19A (functional OPAs are generally agreed to be the mechanism of protection) have been fully described in recent reviews by Hausdorff et al. [23], Clarke et al. [24] and Mrkvan et al. [25].

Evidence from post-marketing surveillance studies indicate that PHiD-CV also prevents disease caused by serotype 6A. The cohort study in Finland also described a significant 100% (95% CI: 41%; 100%) reduction in 6A IPD cases following PHiD-CV introduction into the NIP [26]. Another example is Chile, where at least ten 6A IPD cases in children below 2 years of age were recorded annually in each of the 4 years before PHiD-CV was introduced in 2011 (average of 18 cases per year), but only five cases were reported in 2012 [22]. It should be noted that evidence for the effectiveness of PHiD-CV against serotype 6A is somewhat more limited than for serotype 19A. This is because countries where PCV-7 was implemented to NIP before PHiD-CV had little or negligible residual serotype 6A IPD due to substantial cross protection provided by the 6B conjugate in PCV-7 [3]. Studies using different schedules and conducted in different populations have also consistently demonstrated that PHiD-CV, similarly to PCV-7, elicits robust functional OPA responses against serotype 6A. Notably, the antibody levels elicited by PHiD-CV against cross-reactive serotypes 6A and 19A were especially higher in Japanese infants in comparison with other populations [27].

In summary, data generated during post-marketing surveillance, as well as the immunogenicity results from randomized double-blind studies, strongly support the validity of our assumptions made for protection conferred by PHiD-CV against infections caused by the cross-reactive serotypes 19A and 6A.

EFFECTIVENESS AGAINST ACUTE OTITIS MEDIA

Farkouh et al. [1] further question the assumptions specific to acute otitis media (AOM). A vaccine efficacy of 19% for PHiD-CV against clinically confirmed AOM was demonstrated in the large randomized, double-blind COMPAS study [4]. Corresponding data from a randomized clinical trial are not available for PCV-13. As with PCV-13, significant reductions in the burden of AOM have been observed with PHiD-CV in countries where the vaccine has been included in their NIP. For instance, a time series database analysis in Goiania (Brazil) indicated that medical visits for all-cause AOM in 2- to 23-month-olds were 45% lower after the introduction of PHiD-CV [28]. In Iceland, the annual incidence of hospital visits/admissions attributable to AOM was 24% lower in children younger than 2 years, who were born within 1 year of the introduction of PHiD-CV [8]. However, as already discussed above in the context of post-marketing surveillance studies addressing pneumonia, it is rather difficult to draw meaningful quantitative conclusions regarding vaccines used in different populations from post-marketing surveillance.

Our model therefore relies on extrapolations, made by the expert panels, of assumptions of vaccine efficacy against the major pathogens causing bacterial AOM, *Streptococcus pneumoniae* and non-typeable *Haemophilus influenzae* (NT*Hi*), derived from available randomized trials. Although the efficacy data for PCV-13 against pneumococcal AOM are lacking, it should be noted that whenever the vaccine efficacy against vaccine-type (VT) pneumococcal AOM was assessed for PCVs (PCV-7, the 7-valent conjugate vaccine with outer membrane protein carrier (7vOMP), the 11-valent pneumococcal conjugate vaccine with protein D of *Haemophilus influenzae* as a carrier (11PnPD), and PHiD-CV), it [4, 29–31] was similar, so it is reasonable to assume that it would not be a lot different for PCV-13.

With respect to efficacy against NT*Hi*-AOM, although the COMPAS trial was not powered to provide conclusive evidence, the positive point estimate of PHiD-CV efficacy against NT*Hi* (22%; 95% CI: −43%; 57%) is [4] consistent with the significant efficacy observed with the predecessor protein D conjugate formulation in the POET study (35%; 95% CI: 2%; 57%) [31]. The positive point estimates for efficacy against NT*Hi* OM observed in COMPAS and POET are in contrast with the negative point estimates observed in studies of non-protein D containing PCV formulations, including CRM conjugates [4, 29–31]. In addition, there is concordant body of pre-clinical and immunological evidence (reviewed in detail in [32, 33]), lending credence to the notion that protein D containing vaccines elicit an immunological response and offer protection against NT*Hi* AOM [34–37].

Despite that population-based studies evaluating the impact of vaccines on AOM are generally based on clinical rather than pathogen-specific diagnoses, and therefore cannot generally provide information on the impact on AOM due to NT*Hi,* further, albeit limited, evidence of PHiD-CV impact on NT*Hi* disease is emerging from some post-marketing

studies. For instance, one cross-sectional survey study has provided information on the prevalence of NT*Hi* AOM in a PHiD-CV-vaccinated population of Australian indigenous children compared with a historical cohort of children who had received PCV-7. Also, the prevalence of the more severe suppurative disease presentations were significantly lower in the PHiD-CV cohort. Moreover, the prevalence of NT*Hi* was significantly lower in the PHiD-CV cohort of children diagnosed with suppurative disease and culturing of otopathogens [38]. Although these findings need to be interpreted with the same caution as for other observational studies, they provide an encouraging sign that protein D-based vaccines may offer some level of protection against disease due to NT*Hi*.

Notwithstanding the multiple lines of evidence above, the possibility that PHiD-CV has no efficacy against NT*Hi* AOM has been explored and presented as an additional scenario in the original paper [2].

EFFECTIVENESS AGAINST IPD CAUSED BY SEROTYPE 3

Farkouh et al. [1] state that PCV-13 cannot be considered ineffective against serotype 3 because the available evidence is not conclusive at this point. We argue the contrary, because today, several years after introduction of PCV-13 into many national immunization programs, there is still no conclusive evidence that PCV-13 prevents serotype 3 disease or provides herd protection [39–50]. Some post-marketing surveillance studies report no detectable change at all in serotype 3 disease [41, 42]. Although some studies, including the latest Joint Committee on Vaccines and Immunization (JCVI) minutes from the UK [51], as cited by Farkouh et al. [1], have reported non-significant trends for reduction, it is unclear whether these observations should be attributed to the use of the vaccine, or rather represent a secular trend/natural cyclical pattern in the disease, as have been described for a number of serotypes [52], including serotype 3 as suggested in other settings [40, 53]. Indeed, the most recent published data from the UK report a non-significant vaccine effectiveness of 26% (95% CI: −69%; 68%) [44], a very wide confidence interval crossing zero and a point estimate that is remarkably lower) than the high (and significant) effectiveness estimates obtained for the other PCV-13 vaccine serotypes [44]. Nonetheless, we note that the assumption of effectiveness of PCV-13 up to 89.0% [54] against serotype 3 IPD was tested in the sensitivity analysis of our model, revealing no substantial impact on the model outcome.

HERD EFFECT

Farkouh et al. [1] question whether indirect effects for VT disease have been demonstrated and reported for both formulations, i.e., both PCV-13 and PHiD-CV. Decreases in VT disease in non-vaccinated cohorts have been observed in post-marketing studies for both PCV-13 and PHiD-CV (including Brazil, Chile, Finland and Iceland [55]). In addition, the herd effect of PHiD-CV has been more rigorously analyzed in the context of a cluster randomized double-blind study in Finland [56].

Although not mentioned by Farkouh et al. [1], the public health value of the herd effects remains an area of debate. Based on the experience with PCV-7 use, the herd effect observed for VT disease is likely to be largely or fully offset by disease caused by circulating

non-vaccine serotypes, a phenomenon called serotype replacement [57, 58]. The extent of such replacement elicited by each of the new vaccines is a remaining area of uncertainty, and therefore whether there will be differential net herd effect is currently difficult to assess conclusively [3]. In consequence, we did not incorporate herd or indirect protection in our analysis. Further discussion on the reasons why herd effects were not considered for this analysis is detailed in our original paper [2].

SUMMARY

Our analysis has considered the most up-to-date clinical evidence, placing emphasis on data from randomized double-blind controlled trials, rather than having relied on theoretical assumptions. In addition, we have consulted an external group of experts to validate each parameter that was used as base-case input into the model. We hope that the evidence provided here, in addition to what is reflected in our original paper, testifies that we have considered the strengths and weaknesses of all available data to construct a sensible and conservative base-case analysis as well as have meticulously addressed any areas of uncertainty using appropriate sensitivity and scenario analyses.

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