Modeling Cost-Effectiveness of Universal Varicella Vaccination With Different Varicella Vaccines in the United Kingdom

To the Editor—We read with interest the article by Akpo et al [1] comparing the cost-effectiveness of varicella vaccination in the United Kingdom (Varilrix, Priorix-Tetra, GSK, Belgium [V-GSK] and Varivax, ProQuad, Merck & Co, Inc, Kenilworth, NJ, USA [V-MSD]). This is an important contribution to the literature demonstrating value of varicella vaccination; however the use of predicted efficacy inputs for 1-dose V-MSD may not accurately reflect the actual vaccine performance and cost-effectiveness, considering availability of observed efficacy and effectiveness data.

Efficacy inputs are among the key drivers of the cost-effectiveness of any intervention. The authors derive 1-dose efficacy inputs of 78% for V-MSD from a methodological study using a statistical model [2] relating immunogenicity data (varicella-zoster virus antibody titer, >5 glycoprotein enzyme-linked immunosorbent assay units per milliliter, 6 weeks after vaccination) to long-term disease breakthrough. The efficacy estimate reported [2] was based on antibody titer with predicted efficacy of 94.0% for all ages and 87.2% in younger children (n = 326; median age, 13 months). However, Akpo et al [1] used predicted efficacy of 78% from sensitivity analysis that was included to illustrate the impact of a 2-fold decrease in antibody titer on efficacy (from 88% to 78%) in children who were vaccinated at age 18 months.

While immunogenicity data can be used as a correlate of protection, using predicted efficacy based on antibody titers alone is a limitation given actual efficacy data is available for V-MSD. Several randomized control trials (RCTs) and observational studies have been published, demonstrating the long-term efficacy [3–6] and effectiveness of V-MSD [7–9]. Kuter et al [3], in an RCT with 10 years of follow-up, showed that 1-dose efficacy of V-MSD was 94.4% (95% confidence interval, 92.9%–95.7%), and 2-dose efficacy was 98.3% (97.3%–99.0%).

Akpo et al [1] did not include the data showing higher efficacy of 1-dose V-MSD [3], with the rationale that this RCT was conducted in children aged 12 months to 12 years and noting that older children may experience a lower risk of infection. However, the average age in this RCT was 4.43 years, supporting efficacy in younger children. Another RCT showed that the seroconversion rates for V-MSD by age groups were comparable—98% for age 12–15 months, 97% for 16–23 months and 2–4 years, and 95% for 5–12 years—with efficacy of 86% for all ages [4]. Two other RCTs (average age of children, 3.6 years and 15 months) showed 1-dose efficacy of V-MSD of was 88.5% and 90.5%, respectively [5, 6]. Similarly, literature reviews, meta-analyses and surveillance studies with up to 14 years of follow-up have shown 1-dose effectiveness for V-MSD ranging from 81% to 100%, depending on disease severity [7–9] (Table 1).

The incremental cost-utility ratios reported in the publication showed marginal differences (at most 15%) between the 2 vaccines across all scenarios and time horizons. Given the sensitivity of incremental cost-utility ratio estimates to small changes in utility gains, results regarding the relative cost-effectiveness of different vaccines need to be interpreted with caution. Sensitivity analyses of relevant data sources for efficacy parameters are warranted to comprehensively test the performance and cost-effectiveness of these vaccines.

Notes

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Table 1. Summary of Key Literature on the Efficacy and Effectiveness of Varivax Vaccine (1 or 2 Dose)

Study	Varivax Vaccine, 1 or 2 Dose	Study Design	Patient Ages, Range (Mean)	Follow-up Period, y	Efficacy/Effectiveness, %
Kuter et al (2004) [3]	Both 1 and 2 dose	RCT	12 mo to 12 y (4.4 y)	10	1 Dose: 94.4 (95% CI: 92.9– 95.7); 2 doses: 98.3 (97.3–99.0)
White et al (1991) [4]	1 Dose	RCT	12 mo to 17 y (3.9 y)	1	86
Vessey et al (2001) [5]	1 Dose	RCT	12 mo to 12 y (3.6 y)	7	88.5 (95% CI: 80.9– 96.1)
Shinefield et al (2002) [6]	1 Dose	RCT	12 mo to 6 y (1.3 y)	5	Group A: 90.5 (95% CI: 86.2–95.0); group B: 88.9 (83.7–93.7)
Baxter et al (2013) [7]	1 Dose	Prospective cohort	≥12 mo	14	90 (range, 75–90)
Marin et al (2016) [8]	1 Dose	Meta-analysis	Variable	Variable	82 (95% CI: 79–85) (against all varicella)
WHO SAGE (2014) [9]	1 Dose	Literature review	Variable	Variable	Median: 83 (range, 44–100) (against all varicella)

References 3–6 are efficacy and references 7–9 are effectiveness.
Abbreviations: CI, confidence interval; RCT, randomized control trial; SAGE, Strategic Advisory Group of Experts on Immunization; WHO, World Health Organization.

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Reply to Pawaskar et al.

To the Editor—The commentary by Pawaskar et al. focused on the vaccine efficacy (VE) of the monovalent OKA/Merck vaccine. In our study, the 10-year GSK OKA/recombinant-immunotoxin (OKA/RIT) VE of 67.2% [1] was used, compared to Chan et al.'s 78.0% estimate [2] for the OKA/Merck vaccine. We wish to clarify why the 10-year OKA/Merck VE of 94.4% [3] was considered inappropriate, with emphasis on vaccination age, dose level (plaque-forming units [PFU]) and effectiveness studies.

The Kuter et al. [3] study was a 10-year follow-up of Weibel et al. [4], in which subjects aged 1–12 years (mean age, 4.43 years) received a 17,430 PFU-containing formulation. In the study by Povey et al. [1], children aged 12–22 months (mean age, 14.2 months) received the OKA/RIT vaccine with a potency of 1,995 PFU.

Studies by GSK and MSD suggest that older age at vaccination leads to a lower risk of varicella and a higher VE. Varis and Vesikari [5] demonstrated a lower VE with OKA/RIT vaccinees aged 10–18 months (64%) versus vaccinees aged 19–24 months (82%). Chan et al. [2] showed that at 5gp enzyme-linked immunosorbent assay, the risk of varicella infection decreased by ~ 80% in children aged 5.5 years versus children aged 1.5 years. Comparisons at equivalent titers indicated that the varicella infection risk decreased by ~ 73% in children aged 4.43 years versus children aged 14 months.

VE differences resulting from varying dose levels need to be highlighted as higher doses (10,000–17,000 PFU) are associated with better protection than lower doses (1,000 PFU) [5, 6]. This is illustrated by a crude comparison of the 100% OKA/Merck VE after 9 months of follow-up in Weibel et al. [4] with the 86% VE at 1 year in White et al. [7], in which the OKA/Merck dose ranged between 1,000 and 1,625 PFU among enrollees with a mean age of 3.98 years. Similarly, Kuter et al. [8], in a 7-year follow-up of Weibel et al. [4], with enrollees aged 4.7 years on average reported that 95% of vaccinees remained varicella-free following household exposure. This VE rate could be compared with Vessey et al.'s VE of 88.5% [9] over a 7-year period in enrollees with a median age of 3.6 years, with vaccine doses of 2,900–9,000 PFU and household exposure. The currently licensed monovalent OKA/Merck vaccine contains at least 1,350 PFU, which limits comparisons with prelicensure VE studies.

Overall, the bias risk with Kuter et al.'s VE in a comparative analysis with the OKA/RIT vaccine can be limited with Chan et al.'s VE estimate of 78.0% [2], for the reason previously reported, acknowledging limitations inherent to the absence of head-to-head efficacy studies across similar age groups and dose levels. A meta-analysis of observational studies by Marin et al. [10] reported a pooled 1-dose VE of 81% (95% confidence interval, 78%–84%) against any varicella with no differences by vaccine, in agreement with our conclusion on predicted similar effectiveness between GSK and MSD varicella-containing vaccines.

Conclusively, we believe that the most accurate VE estimate was used for the OKA/Merck vaccine. Importantly, both vaccines effectively reduce the varicella burden, with GSK varicella-containing vaccines potentially being more cost-effective.

Notes

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