Systematic Review of Effectiveness of Varicella Vaccines: A Critical Appraisal

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Summary

In this systematic review and descriptive meta-analysis, the authors examined the post-licensure estimates of varicella vaccine effectiveness (VE) among healthy children. Publications that reported original data on dose-specific varicella VE among immunocompetent children were included. Random effects meta-analysis models were used to obtain pooled one dose VE estimates by disease severity (all varicella and moderate/severe varicella). Within each severity category, pooled VE by vaccine and by study design were assessed. The pooled 1-dose VE was 81% (95% CI 78%, 84%) against all varicella and 98% (95% CI 97%, 99%) against moderate/severe varicella with no significant association between VE and vaccine type or study design. For 1-dose, median VE for prevention of severe disease was 100% (mean 99.4%). The pooled 2-dose VE against all varicella was 92% (95% CI 88%, 95%), with similar estimates by study design. The authors conclude that one dose of varicella vaccine was moderately effective in preventing all varicella, and highly effective in preventing moderate/severe varicella, with no differences by vaccine. The second dose adds improved protection against all varicella.

Commentaries

Evidence-based Medicine Viewpoint

Relevance: Varicella (chickenpox) is an infectious disease with considerable individual and public health significance, as well as economic impact, especially in developed countries [1]. Vaccines developed to prevent serious forms of chickenpox and (hopefully) long-term complications such as herpes zoster have been available for the past few years. A program of universal coverage with Varicella vaccine was initiated in the United States 10 years ago, and the majority of efficacy data originate from that setting. In contrast, individual European countries have variable vaccination policies, despite generally acceptable efficacy and cost-effectiveness [2]. A recent systematic review confirmed the efficacy of vaccination to prevent herpes zoster in elderly people, demonstrating almost 50% reduction in incidence [3]. Although the review reported increased occurrence of side effects, most of these were not severe. Economic evaluations also suggest that vaccination to prevent varicella zoster may be cost-effective in developed countries [4,5].

However, there is also a divergent view [6] which suggests that declining varicella infection in children (on account of vaccination) reduces the 'natural boosting' effect of sub-clinical exposures in the community. Since vaccine-induced immunity is not life-long, this would necessitate booster dose(s) in later life. When the added costs are factored in, a vaccination program may no longer be cost-effective [6]. This view is supported by the detection of increased occurrence of zoster among adults, following universal vaccination programs. There is limited data on universal varicella vaccination efficacy or cost-effectiveness from developing countries [7,8]. Data from India are limited to reports of outbreaks [9,10] or trials of sero-efficacy [11,12], and thereby indirect suggestions that vaccination may be beneficial. Against this backdrop, the recent systematic review by Marin, *et al.* [13], examining the protective efficacy of varicella vaccination (*i.e* effectiveness), is both timely and relevant. Although efficacy (in research settings) has been amply demonstrated previously, this is perhaps the first systematic evaluation of vaccine effectiveness (in real world settings).

Critical appraisal: ***Table* I** presents a critical appraisal of the systematic review using standard tools [14]. Overall, the review met the major criteria for a good quality review. However, some of the methodological refinements associated with a Cochrane systematic review were not undertaken. One serious methodological limitation was the absence of quality assessment of each included study (see ***Table* I**).

TABLE I: CRITICAL APPRAISAL OF THE SYSTEMATIC REVIEW ON VARICELLA VACCINE EFFECTIVENESS [13]

Parameter	*Comment*
Validity	
Is there a clearly focused clinical question?	Although the authors did not present an explicit PICO question, the following can be discerned: What is the protective efficacy/ effectiveness (Outcome) of varicella vaccination (Intervention) versus no vaccination (Comparator) among otherwise healthy children (Population)?
What are the criteria for selection of studies?	The authors searched for publications from 1995 to mid-December 2014 (approximately ten year period) reporting protective efficacy of Varicella vaccine in immuno-competent children (age not specified). They did not restrict any study design or language.
Is the literature search method specified?	The authors presented the precise search strategy, databases searched (total four), and dates of searching. The method used suggests low probability of missing relevant publications. However, it is possible that additional unpublished data may be available with relevant Health Ministries, vaccine manufacturers, and possibly insurance companies/reimbursement agencies.
Have the identified studies been evaluated for methodological quality?	The authors included various study designs, but did not attempt to assess methodological quality of individual studies. Although sub-group analysis by study design was performed separately, no sensitivity analysis (by methodological quality) was performed. This could compromise the results as lower quality studies generally over-estimate the effect. Since methodological quality was not assessed, the additional issue of independent appraisal by multiple authors and calculation of concordance, could not be considered.
Is it appropriate to combine the results from different studies?	The Supplementary data summarizes the extracted information from each study *viz.* (*i*) Country, (*ii*) Vaccine type, (*iii*) Study design, (*iv*) Study setting, (*v*) Age of included participants, (*vi*) Sample size and (*vii*) Study period. From this data, it is difficult to judge whether all studies were appropriate for combining into a pooled analysis. However, the authors undertook additional analyses by Study design, Vaccine type, and a meta-regression including both in the model.
Results	
Were the results consistent from one study to another?	All the studies included in the meta-analysis demonstrated protective efficacy suggesting an overall consistent effect. However, there was considerable heterogeneity (I^2 88%) suggesting unexplored variations among studies. A random effects model was used in the meta-analysis.
What were the overall results of the review?	*Effectiveness for one dose of vaccine,* All Varicella: • Monovalent vaccine: 0.81 (95% CI 0.78, 0.84) • Polyvalent (MMRV) : 0.55 (95% CI 0.08, 0.78) Moderate and severe Varicella: 0.98 (95% CI 0.97, 0.99) Severe Varicella: Pooled VE not presented *Effectiveness for two doses of vaccine,* All Varicella: • Monovalent vaccine: 0.92 (95% CI 0.88, 0.95) • Polyvalent vaccine (MMRV): 0.91 (95% 0.65, 0.98)
How precise were the results?	The pooled effect had narrow confidence intervals. This was true for the combined analyses as well as all subgroup analyses (*i.e* by vaccine type and by study design).
Applicability	
Is the local population similar to the peopleincluded in the original studies?	All the studies included in the systematic review originated from developed countries with different baseline risks, variable disease burden, diverse public health priorities and health-care systems.
Is the intervention feasible in my setting?	At the present time, universal Varicella vaccination of Indian children is precluded by paucity of knowledge of disease burden, public health impact of Varicella (in childhood and later years), and unknown effectiveness and cost-effectiveness. The baseline risk would determine the number-needed-to-vaccinate even if protective efficacy of the magnitude demonstrated in this systematic review was considered.
Have all the clinically relevant results been taken into consideration?	This systematic review did not consider vaccine related adverse effects (although this may not have been the focus of the review), impact on Varicella zoster, and cost-effectiveness.
Do the benefits outweigh the potential harm?	In terms of prevention of Varicella, there is clear benefit. Harm can be assessed only after studying the factors listed above.

On the plus side, the authors used clear definitions for terms such as Varicella and disease severity. They also prudently considered relevant confounders and undertook subgroup analysis based on type of vaccine, monovalent *versus* combination (MMRV) vaccine, and type of study design. Single dose vaccination was analyzed separately from two dose regimen.

It appears that the authors did not convert outcomes from individual studies into a uniform format of relative risk (RR) or odds ratio (OR), but used a formula to calculate vaccine effectiveness (from individual study OR and RR). Therefore, NNT could not be calculated from individual studies and the pooled data. The authors rightly explored publication bias and did identify the same, which indirectly suggests that studies failing to identify/report negative results (*i.e* inadequate vaccine effectiveness) may have been missed. The authors observed that a significant number of publications were related to outbreaks, and suggested how this could impact the overall result.

The authors noted data on waning of vaccine-induced immunity over time. However, a critical issue of whether this could translate to greater episodes of Varicella in the immunized or older age groups; and/or whether it could result in increased burden of herpes zoster, was not considered.

Extendibility: Almost the entire body of evidence included in this systematic review originated from developed countries with vastly different status of population risk, epidemiological factors affecting transmission, and access to health-care. Therefore, it is not possible to directly extrapolate the favorable results of vaccine protective efficacy (*i.e* effectiveness) to our setting. Further, none of the studies was conducted in a setting that could be even considered similar.

Conclusion: Varicella vaccine appears to offer a high degree of protection against varicella; this is higher for more severe forms of the disease, and better with two doses. The results are robust irrespective of vaccine type and study design used to address the issue.

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Immunization Expert's Viewpoint

This systematic literature review and descriptive meta-analysis selected 42 studies to evaluate the vaccine effectiveness (VE) to prevent varicella with 1 or 2 doses. These studies originated from the United States (23), China (4), Germany (3), Israel (3), Italy (2), Spain (2),

Taiwan (2), Australia (1), Turkey (1), and Uruguay (1). In the final analysis, it was seen 1-dose had moderate effectiveness with 81% (95% CI 78%, 84%) to all varicella and 98% (95% CI 97%, 99%) against moderate to severe varicella. The stratified VE results of different vaccines with 1-dose showed: Varivax 82%, Varilrix 77%, other vaccines 86% and mixed/multiple vaccines 81% with 1-dose. In the meta-regression analysis, no significant association was found between VE and vaccine type [1]. Of the studies analyzed, most had 100% prevention of severe varicella, irrespective of 1- or 2-dose schedule [2].

There were eight studies with 2 doses and most of them have showed slightly better VE for all varicella. The VE of the only study with two doses of MMRV/ Priorix tetra was 91% (95% CI 65%, 98%) [1]. One of the limitations of this outcome was that the VE was assessed primarily during the outbreak, and all were clinically diagnosed which may tend to show underperformance of the vaccine [1].

The pooled VE estimates for 1-dose primarily were within the first decade. Within this time frame, some studies showed higher vaccine failure with time since vaccination (cut-off of 3,4 and 5 years), but other studies did not find this association [3-14]. Varivax showed decline of VE in 1 and 2 years after vaccination from 97% to 86%, but not subsequently after 7 years follow-up [15]. In another study at US, it showed a decline in VE from 94 % till 5 years to 88% at 5 to 9 years, and 82% after 10 years. Bayer, *et al*. [16], in their meta-analysis of outbreak data, concluded waning immunity based on data from four studies which all showed decrease in VE by time since vaccination for an average 4 to 6 years. Though most studies showed a decline in immunity, the results were not adjusted for likelihood of exposure or force of infection, which may have changed with time due to the changing epidemiology with routine vaccination program [1].

In 1995, United States adopted 1-dose routine vaccination policy, with coverage of 90% and had a significant decline (more than 90%) of varicella infection, and related hospitalization or death [17-19]. But after a decade or so, inspite of significant decline in disease and severity, there were varicella outbreaks (although less in number, smaller in size and short duration) even in highly vaccinated populations [20,21]. Hence after nearly 10 years, 2-dose schedule was adopted in the policy of United States, which further decreased the outbreaks and related hospitalizations. Spain introduced 2-dose schedules from the beginning, and reported 98.5% decline in incidence in 5 years [22].

After detailed analysis of various studies, IAP Committee of Immunization in 2011 decided to adopt the 2-dose schedule for India. Though there was no published Indian data to support the outbreak or incidence of breakthrough infection, but based on expert opinion and sporadic incidences of varicella infection post-vaccination as experienced by many, it was decided to recommend two doses to provide higher effectiveness and immunity to individuals who opted for the prevention.

Unfortunately we do not have any VE data in India, and most of the analyzed data are from high-income countries where epidemiology is different. For public policy, it would be difficult to make any recommendation based on this meta-analysis as most studies have been done in low prevalence countries.

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