Review of Cost-Effectiveness Analyses of Varicella Vaccination: Which Model Structure Assumptions and Input Parameters Matter?

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Background

- Several reviews of cost-effectiveness analyses (CEAs) of varicella vaccination have been published.[1-5]
  - Results of these reviews suggest dynamic transmission models, compared with static models, better capture a vaccination program's impact on herd immunity, changes in the age distribution of cases, and impact of the vaccine on boosting cell-mediated immunity.[2-4] Thus, the use of static models to estimate the clinical outcomes of a vaccination program is not recommended.[2]

Objective

- To review CEAs of varicella vaccination that used a dynamic transmission model in order to assess the evidence supporting the model structure assumptions and input parameters identified as having the greatest impact on the CEA results.

Methods

- A targeted MEDLINE search was conducted to identify economic evaluation studies of varicella vaccination programs that used the outcomes from a dynamic transmission model.
  - The search strategy was limited to studies from 1985 through 2014. The search strategy was not initially limited by patient population (eg, children, adolescents, adults, and health care workers), by English language, or country of analysis (**Table 1**).
  - Studies were limited by patient population to those evaluating childhood varicella vaccination only.
  - Of 260 abstracts identified, 21 articles were selected for full-text review.

Table 1. Targeted Literature Search Strategy

Search Number	Search Terms	Number of Articles
#1	Varicella OR Chickenpox OR "Chickenpox Vaccine" [MeSH] OR "Herpesvirus 3, Human" [MeSH] OR "Chickenpox" [MeSH]	14,953
#2	"Costs and Cost Analysis" [MeSH] OR "Cost-Effective" OR "Cost Effective" OR "Cost-Utility" OR "Cost Utility"	221,246
#3	Economic	703,365
#4	#1 AND #2 AND #3	260

MeSH=medical subject heading.

Results

Identified Studies

- Of the 21 articles reviewed, 16 were CEAs of a childhood varicella vaccination program, and 5 were reviews of these economic analyses.[1-5] Two of the CEAs[6,7] were not available in English and were not reviewed.
- Therefore, 14 varicella vaccination CEAs using a dynamic transmission model are summarized. Table 2 presents an overview of the model structure, assumptions, and results of the 14 CEAs reviewed.

Summary of Varicella CEAs

- Most studies (nine) performed the economic analysis from both payer and societal perspectives, presenting results both with and without inclusion of productivity losses; three used the payer perspective only; and one used the societal perspective only.
- The models varied in the economic measure presented: three presented a benefit-cost ratio (BCR), seven presented both BCRs and cost-effectiveness (CE) ratios measured as cost per life-year (LY) gained, one presented a CE ratio only, and three presented only cost-utility ratios measured as cost per quality-adjusted life-year (QALY) gained.
- Only four of the CEAs included the possible impact of vaccination on cases of zoster via reduction in the rate of boosting cell-mediated immunity.[8-11]
  - Two were conducted by Brisson and colleagues[9,10] using their dynamic transmission model.[12]
  - Two[8,11] used a dynamic transmission model developed by van Hoek and colleagues.[13]

Summary of Varicella Economic Evaluation Studies That Used Outcomes From a Dynamic Transmission Model

Study (in Order of Publication)	Country, Currency	Varicella With/Without Zoster	Vaccination Strategy	Time Horizon	Type of Analysis	Results		Dynamic Model Reference
						Payer Perspective	Societal Perspective	
Lieu et al., 1994[14]	US 1990 US$	Varicella	< 6 years ± catch-up	30 years	Cost-benefit CE	BCR: 0.90:1 16,000/LYS	BCR: 5.40:1 NS	15
Coudeville et al., 1999[16]	France 1995 FF	Varicella	< 6 years	30 years	Cost-benefit	NS	ANB: 1,826 million	15
Brisson and Edmunds, 2002[9]	Canada 1997-1998 Can$	Varicella ± zoster	1 year w/o zoster	30 years	Cost-benefit CE	BCR:0.61:1 44,503/LYS	BCR: 5.24:1 NS	12
			1 year and catch-up w/o zoster			BCR: 0.6:1 50,866/LYS	BCR: 4.90:1 NS	
			1 year w/ zoster			BCR: 0.16:1 118,188/LYS	NS	
			1 year and catch-up w/ zoster			149,993/LYS	NS	
Brisson and Edmunds, 2003[10]	England and Wales 2001 £	Varicella + zoster	12-15 months	80 years	Cost-utility	Dominated[a]	Dominated[a]	12,17
			12-15 months and catch-up			Dominated[a]	Dominated[a]	
Banz et al., 2003[18]	Germany 1999 €	Varicella	1-1.5 years	30 years	Cost-benefit CE	BCR: 1.75:1 NS	BCR: 4.12:1 Cost saving	15
			1-1.5 years and catch-up			BCR: 1.70:1 NS	BCR: 4.10:1 Cost saving	
Coudeville et al., 2004[19]	Italy 2002 €	Varicella	1-2 years	50 years	Cost-benefit	BCR: 1.20:1	BCR: 3.50:1	12,15
			1-2 years and catch-up			NS	NS	
Coudeville et al., 2005[20]	France and Germany 2002 €	Varicella	19 months	50 years	Cost-benefit	BCR: France: 1.08:1 Germany: 2.35:1	BCR: France: 3.42:1 Germany: 3.49:1	12,15
			19 months and catch-up			Cost savings	Cost savings	
Lenne et al., 2006[21]	Spain 2004 €	Varicella	1-2 years	50 years	Cost-benefit CE	BCR: 0.91:1 3,982/LY	BCR: 3.67:1	15
			1-2 years and catch-up for 2-11 years			BCR: 0.88:1 13,312/LY	BCR: 3.77:1 8,638/LY	
Hammerschmidt et al., 2007[22]	Germany 2006 €	Varicella	11-23 months and catch-up for 2-17 years	30 years	Cost-benefit	BCR: 1.01-1.39:1	BCR: 2.40-3.27:1	15,18
Bonanni et al., 2008[23]	Italy 2002 €	Varicella	1-1.5 years	30 years	Cost-benefit	BCR: 0.67:1	BCR: 3.47:1	15
			1-1.5 years and catch-up			BCR: 0.64:1	BCR: 3.33:1	
Valentim et al., 2008[24]	Brazil 2004 BRL	Varicella	12 months	30 years	Cost-benefit CE	BCR: 0.12:1 12,248/LY	BCR: 0.21:1 11,042/LY	NS
Banz et al., 2009[25]	Switzerland 2008 CHF	Varicella	1-2 years	30 years	Cost-benefit CE	BCR: 0.30:1 1,588/LY	BCR: 1.29:1 NS	15
			1-2 years and catch-up at 11 years			BCR: 0.27:1 1,711/LY	BCR: 1.22:1 NS	
van Hoek et al., 2012[11]	UK 2007 £	Varicella + zoster	Childhood	100+ years	Cost-benefit Cost-utility	BCR: 0.59:1 35,029/QALY	NS	12,13
			Childhood and zoster vaccine in elderly			BCR: 0.40:1 22,166/QALY	NS	
Bilcke et al., 2013[8]	Belgium 2012 €	Varicella + zoster	1 dose only at 1 year	100 years	Cost-utility CE	€607-€5,600/QALY €15,000/LY	NS	13
			1st dose at 1 year, 2nd dose at 4, 6, or 11 years	100 years		1+4 years[b]: €5,781-35,240/QALY 1+11 years[c]: €5,564-32,850/QALY Any 2-dose regimen: €49,300-€74,000/LY	NS	

ANB=actualized net benefit; NS=not stated; UK=United Kingdom; US=United States.
[a] The vaccination strategy is dominated (more expensive than the current strategy and generates fewer health benefits).
[b] Vaccination at age 1 and 4 years with 95% and 90% coverage, respectively.
[c] Vaccination at age 1 and 11 years with 95% and 80% coverage, respectively.

Key Model Structure Assumptions and Inputs

- Evidence was lacking for the following model structure assumptions and input values, to which the varicella vaccination CEA results were most sensitive; perspective of analysis (ie, payer or societal), inclusion of the impact of varicella vaccination on zoster in those previously infected with varicella virus, time horizon for the CEA, and QALY loss per case of varicella and zoster.

Perspective of the Analysis

- CEA results were always more favorable when a societal perspective was taken. Varicella vaccination was typically cost-saving when including both direct and indirect costs and either cost-saving or cost-effective (defined as a CE ratio below country-specific thresholds) when including only direct costs in some studies (**Table 2**).
- The choice of perspective should depend on the requirements for the decision maker and is not evidence based.
- However, among studies conducted from the societal perspective (which included indirect costs by definition), the magnitude of the estimates of productivity loss costs varied widely across studies.
- The wide range in productivity loss costs was a result of multiple factors.
  - Wide range in the cost per day lost (12.70-326.40 in 2008 purchasing power parity adjusted dollars) using the human capital method.
    - This finding was aligned with the findings from Soárez and colleagues[3] that the value of a work day ranged widely even when adjusting country-specific wages to a common currency (purchasing power parity), highlighting the wide variation in wage scales between countries.
  - Wide range in time loss estimates per case of varicella (0.27-8.8 days for caregivers of children, 2.6-26.1 days for adults).
    - Variation in time loss estimates due to severity of disease or differences in work patterns (ie, percentage of primary caregivers or patients employed) between countries is appropriate and expected.
    - However, some variation in time loss estimates was due to differences in methodology. The lowest estimates were those based on physician and patient surveys,[16,26] and the highest estimates were those based on the average length of hospital stay.

Inclusion of the Impact of Varicella Vaccination on Zoster

- CEA results showed varicella vaccination was cost-effective when the impact was included on only varicella or when the CEA model included the impact of zoster on varicella cases for those susceptible to varicella and/or included the extent to which children vaccinated for varicella could later acquire zoster, either vaccine serotype, or any serotype. However, when an impact of varicella vaccination on increasing zoster cases in those previously infected with varicella virus was included the results were much less favorable.
  - In the two studies[8,11] using the van Hoek model,[13] childhood varicella vaccination resulted in increased costs and CE ratios that were above country-specific thresholds, indicating that varicella vaccination was not cost-effective.
  - In the two studies[9,10] using the Brisson model,[12] childhood varicella vaccination was found to be either not cost-effective or dominated (more expensive and fewer health benefits than no vaccination).
- The inclusion or exclusion of zoster in the dynamic transmission model depended on the evidence that varicella vaccination will affect the number of cases of zoster in children and adults.
  - The four CE models that included the impact of varicella vaccination on zoster cited two case-control studies from the UK that showed a correlation between exposure of adults to children with varicella and a reduced incidence of zoster.[27,28]
  - However, a recent review of the evidence for an impact on zoster cases in those previously infected with varicella virus concluded that, although most evidence indicated that there may be some increase in zoster cases attributable to vaccination, this finding was not unanimous, and the magnitude of the effect depended on many factors, including the long-term efficacy of the varicella vaccine, the importance of endogenous versus exogenous boosting, the importance of age-related declines in immunity, and the duration of effect of exogenous boosting.[29]

Time Horizon

- In the Brisson and Edmunds studies[9,10] that included the impact of varicella vaccination on both varicella and zoster, the CEA results were less favorable for all varicella vaccination programs when a 30-year time horizon was used compared with when an 80-year time horizon was used for the dynamic transmission model.
  - This point was further emphasized in the other two studies that included the impact of varicella vaccination on both varicella and zoster,[8,11] which showed using an infinite time horizon how benefits accrued many years into the future (eg, decades or centuries) could have substantial impact on the CE results and how the results generally improved with longer time horizons.
- There was lack of standardization across studies on the time horizon to use for dynamic transmission models in general and for varicella dynamic transmission models specifically. Current guidelines simply state "the time horizon should be long enough to capture all of the effects of the intervention."[30]

QALY Loss per Case

- Estimates of QALY loss per case of natural varicella (0.0027-0.004 [uncomplicated case], 0.0038-0.017 [complicated case]), per case of breakthrough varicella (20%-50% of natural case value), and per case of zoster (0.01-0.12 [younger/less severe case], 0.201-0.52 [older/more severe case]) varied among studies. This impacted only the few studies (three) that presented the results as cost per QALY gained.

Conclusions

- Future research should be prioritized for epidemic and economic parameters for which there is large uncertainty and that impact the results and, consequently, decisions about varicella vaccination programs.
- There is a lack of evidence around the impact of varicella vaccination on zoster, which has led to wide interstudy variability on the assumptions used in varicella dynamic transmission models and the relevant time horizon. Therefore, long-term evidence on the impact of varicella vaccination on zoster is needed.
- Given the importance of the societal perspective for estimating the value of a vaccine program, additional studies estimating work time loss and QALY loss for cases of varicella and/or zoster could be considered.

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