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Research Article

Distribution of Health Effects and Cost-effectiveness of Varicella Vaccination are Shaped by the Impact on Herpes Zoster

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ABSTRACT

Introduction: Varicella zoster virus (VZV) is the etiological agent of varicella and herpes zoster (HZ). It has been hypothesised that immune boosting of latently infected persons by contact with varicella reduces the probability of HZ. If true, universal varicella vaccination may increase HZ incidence due to reduced VZV circulation. To inform decision-making, we conduct cost-effectiveness analyses of varicella vaccination, including effects on HZ.
Methods: Effects of varicella vaccination are simulated with a dynamic transmission model, parameterised with Dutch VZV seroprevalence and HZ incidence data, and linked to an economic model. We consider vaccination scenarios that differ by whether or not they include immune boosting, and reactivation of vaccine virus.
Results: Varicella incidence decreases after introduction of vaccination, while HZ incidence may increase or decrease depending on whether or not immune boosting is present. Without immune boosting, vaccination is expected to be cost-effective or even cost-saving. With immune boosting, vaccination at 95% coverage is not expected to be cost-effective, and may even cause net health losses.
Conclusions: Cost-effectiveness of varicella vaccination depends strongly on the impact on HZ and the economic time horizon. Our findings reveal ethical dilemmas as varicella vaccination may result in unequal distribution of health effects between generations.

1. Introduction

Universal vaccination against acute communicable diseases such as smallpox, poliomyelitis, diphtheria, and measles have been very successful by reducing circulation of the pathogens and associated burden of disease (Ehreth, 2003). A live attenuated vaccine against varicella was developed in the early 1970s, and licensed for universal use in healthy children in the late 1980s and early 1990s. Since then, varicella vaccination has been introduced in an increasing number of countries (Bonanni et al., 2009; European Centre for Disease Prevention and Control (ECDC), 2014). Over the years, the varicella vaccine has proved effective in preventing varicella zoster virus (VZV) infection and varicella disease in clinical trials and after introduction in national immunisation programmes (NIP) (Varicella and Herpes Zoster Vaccines, 2014). Consequently, recommendations for varicella vaccination have been issued by the World Health Organization, the Centers for Disease Control and Prevention, and the European Centre for Disease Prevention and Control (Varicella and Herpes Zoster Vaccines, 2014; Marin et al., 2007; European Centre for Disease Prevention and Control (ECDC), 2015).

Even though the varicella vaccine is safe and effective, not all developed countries have included vaccination in their NIPs (Bonanni et al., 2009). This is mainly due to the low perceived severity of varicella compared to other vaccine-preventable diseases, and uncertainties about the effect of varicella vaccination on the epidemiology of diseases caused by VZV. VZV is the etiological agent of both varicella after primary infection, and of herpes zoster (HZ) after reactivation of the virus. Hope-Simpson hypothesised that HZ incidence increases when circulation of VZV in the population decreases (Hope-Simpson, 1965). This so-called exogenous boosting hypothesis is based on the supposition that lack of exogenous immune boosting in latently infected persons might increase

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their risk of HZ. The hypothesis is shored by several findings, e.g., the lower incidence of HZ in adults with children than in adults without children (Brisson et al., 2002), and the negative association between HZ incidence and increasing exposure to varicella, social contacts with children or occupational contacts with ill children (Thomas et al., 2002). There are, however, also studies that do not support this hypothesis and the issue is therefore not definitively settled (Ogunjimi et al., 2013).

Cost-effectiveness of varicella vaccination might be affected by several interacting factors. First, reducing VZV circulation by varicella vaccination might result in an increase in HZ incidence (Schuette and Hethcote, 1999; Brisson et al., 2000; Gidding et al., 2005; Karhunen et al., 2010) and an age-shift for HZ to younger ages, resulting in productivity loss. HZ in elderly is more severe than varicella in children, with patients often suffering from severe, long-lasting neurological pain (Oxman, 2000). Second, varicella vaccination will shift the average age at primary infection in unvaccinated individuals to higher ages, as is well-known from epidemiological theory and observations (Anderson and May, 1991). Since varicella is more severe in older than younger persons (Heininger and Seward, 2006), and infection during pregnancy can result in congenital varicella syndrome (Enders and Miller, 2000), these effects also need to be factored in. Third, with populations ageing in many developing countries, a (transient) increase in HZ cases is expected, which may impact on cost-effectiveness analyses. Fourth, the varicella vaccine contains a live attenuated virus, which itself can cause reactivation. However, there is limited quantitative evidence on the frequency of HZ among varicella vaccinees, especially on the long term (Heininger and Seward, 2006). Most cost-effectiveness analyses did not include such effects of varicella vaccination on HZ (Rozenbaum et al., 2008) and may therefore give too optimistic results.

With the aim to inform decision-making regarding introducing varicella vaccination, we provide a comprehensive cost-effectiveness analysis that includes the above factors. The Dutch situation is used as an example because of the good quality data reflecting the pre-vaccination situation in developed countries with a temperate climate in which varicella is in general a childhood disease. Because of the expected age-shift for both varicella and HZ, we pay special attention to generational differences by studying the incidence of both syndromes by birth cohort.

2. Methods

2.1. Data Overview

The analyses are primarily based on two large datasets. First, information on infection status is contained in a population-based serological study of 6251 samples carried out in the Netherlands in 2006–2007 (van Lier et al., 2013). Second, information on age-specific HZ incidence rates is retrieved from 7026 HZ cases reported to general practitioners in 2002–2011 (Stirbu-Wagner et al., 2011). In addition, we have made use of national demographic data of Statistics Netherlands and information on Dutch contact patterns (Mossong et al., 2008). Details are given in the Supplement.

2.2. Model Structure, Statistical Analysis, and Vaccination Scenarios

We investigate the effectiveness of universal childhood varicella vaccination using an age-structured transmission model (Guzzetta et al., 2013). First, we use data on varicella and HZ incidence to estimate all relevant transmission parameters in the pre-vaccination era. In a second step, we use the transmission model armed with quantitative parameter estimates to anticipate the impact of varicella vaccination on the age-specific incidences of varicella and HZ. We consider a two-dose varicella vaccination programme with a first dose at 12 months and a second dose at 4 years of age, as this would nicely fit in the existing NIP (Supplement). We simulate a vaccination programme starting (arbitrarily) on January 1, 2020, and analyse four vaccination scenarios, labelled A–D (Table 1). The scenarios differ by whether or not they include immune boosting (scenarios A and C with effect of boosting; B and D without effect of boosting), and whether or not reactivation of vaccine virus is included (scenarios A–B no vaccine virus reactivation; C–D with reactivation). For each scenario, we consider four vaccination coverages: 0%, 25%, 50%, and 95%. Throughout, we assume a vaccine effectiveness of 90% after one dose of varicella vaccine and 95% after two doses, which is reasonable in view of the evidence summarised by WHO (Varicella and Herpes Zoster Vaccines, 2014). We assume that after one vaccine dose there is small probability of breakthrough varicella (10% per infectious contact) that is less infectious (50%) than primary varicella, and we assume that there is no breakthrough varicella after two vaccine doses in persons who respond to vaccination. For simplicity, we do not consider potential waning of vaccine effectiveness. Demographic data of the Netherlands are applied to the modelled incidences of varicella and HZ to obtain the estimated number of cases by year, and by birth cohort. Details on the estimation procedures, model assumptions, and vaccination scenarios are given in the Supplement.

2.3. Cost-Effectiveness

We use the output of the transmission modelling with vaccination as input for the cost-effectiveness analyses. All assumptions and parameters regarding treatment costs, vaccination costs, production losses, and QALY (quality-adjusted life-year) losses are described in Data Supplement 3. Because age-shifts play an important role in the analyses, and clinical severity of varicella differs by age, we distinguish health care use and QALY loss of varicella in patients aged <15 versus ≥15 years, following Van Hoek et al. (van Hoek et al., 2012). Similarly, QALY loss of HZ is also age-dependent (van Hoek et al., 2012).

To determine cost-effectiveness of varicella vaccination, taking into account both varicella and HZ, the incremental cost-effectiveness ratio (ICER) is calculated, i.e., the difference in cost between a vaccination programme and no vaccination, divided by the difference in QALYs between a vaccination programme and no vaccination. In accordance with Dutch guidelines for pharmacoeconomic research, costs (4%) and QALYs (1.5%) are discounted from 2020 onwards (Hakkaart-van Roijen et al., 2011). We take a societal costs perspective that includes productivity loss. Costs are expressed in euros (€), at the 2012 price level.

First, the summation from 2020 onwards of the discounted *net costs* (= costs minus savings), are calculated separately for each year. The discounted net QALYs (= QALYs gained minus QALYs lost) are

Table 1
Overview of the four main vaccination scenarios implemented in the dynamic transmission model based on different assumptions about the effects of immune boosting on herpes zoster and vaccine VZV reactivation, and with various vaccination coverages.

	Vaccination scenarios[a]			
Assumptions	A	B	C	D
Boosting[b]	Yes	No	Yes	No
Vaccine VZV reactivation[c]	No	No	Yes	Yes
Vaccination coverage (%)[d]	0;25;50;95	0;25;50;95	0;25;50;95	0;25;50;95

[a] General assumptions for all scenarios:

- Two-dose varicella vaccination programme (first dose: 12 months, second dose: 4 years of age), starting on January 1, 2020;
- Vaccine effectiveness of 90% after one dose, 95% after two doses;
- Probability breakthrough varicella after one dose: 10% per infectious contact (relative infectiousness after one dose 50%), no breakthrough varicella after two doses.

[b] Yes = exogenous immune boosting has an effect on the probability of VZV reactivation, No = no effects of immune boosting.

[c] Yes = vaccine VZV is able to reactivate with the same rate as wild type VZV, No = no reactivation of vaccine VZV.

[d] 0%: baseline without varicella vaccination, 25%: conservative coverage because of expected limited acceptance of varicella vaccination due to the perceived low severity of varicella, 50%: intermediate coverage, 95%: highest coverage based on regular Dutch vaccination coverage data.