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# Assessing the introduction of universal varicella vaccination in the Netherlands

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**Abstract**

Although varicella is seen as a benign disease in the Netherlands, about 40,000 visits to a general practitioner (GP) are made, over 200 hospital admission occur, and 2.3 persons die on average each year. Most of this burden of disease can be prevented by universal varicella childhood vaccination. Ten years after the introduction of the single-shot, single-component varicella childhood vaccination in the USA, a major reduction in hospitalization, mortality, and burden of disease has been reported. Using our recently vaccine evaluation model for the introduction of a new vaccine in our national immunization program, we have analyzed the feasibility of universal varicella vaccination by replacing the measles–mumps–rubella (MMR) vaccine with a measles–mumps–rubella–varicella (MMRV) vaccine. After structuring and reviewing the available data, two major points of uncertainty remain: (1) the influence of universal childhood vaccination on the incidence of zoster later in life; (2) the cost-effectiveness ratio for the Dutch situation. Despite these uncertainties it is clear that universal childhood vaccination will prevent most of the varicella related GP-visits, hospitalizations, and deaths.

**Keywords:** Varicella vaccination; National immunization program; Varicella zoster virus; Herpes-zoster; Chickenpox; Shingles; Cost-effectiveness; Measles–mumps–rubella–varicella vaccine

## 1. Introduction

The decision to introduce a new vaccine in a national immunization program (NIP) is complex. Such a decision is not only made on basis of scientific data, but is also influenced by predicted cost-effectiveness and by public and political perception. To help this decision process we have recently developed a vaccine evaluation model to structure the available data for the introduction of a specific vaccine [38]. In this paper we have used this model to assess the introduction of universal childhood vaccination against varicella.

Universal childhood varicella vaccination with a single-component vaccine has been introduced in several developed countries (e.g. USA, Germany and Finland). Other developed countries have decided not (yet) to introduce this vaccine (e.g. Luxembourg) in their national immunization program (NIP) [56]. Data from different sources in the USA show a profound decrease in varicella incidence [64], ambulatory visits [16], hospitalizations [16], [64] and [84] and mortality [50] after introduction of universal vaccination in 1995. This decrease is associated with major cost-savings ($ 5 for every $ 1 spend [15] and [47]). Universal varicella childhood vaccination is also for Germany and France expected to be cost-saving [14].

The effectiveness of a single dose of the live Oka–varicella vaccine is relatively low (~80%) in comparison to single doses of vaccines against measles, mumps and rubella (>95%) [1], [13], [19], [22], [72] and [74]. Furthermore, a VZV infection comes with two faces, i.e. chickenpox during childhood, and shingles (herpes-zoster) later in life. The introduction of universal childhood varicella vaccination might have an negative effect on zoster in the mid-term (~5–40 years after introduction of universal childhood varicella vaccination [6], [29] and [71]), but positive in the long-term [6], [29], [39] and [76].

Recently, a four-fold combination vaccine in which the vaccine strains for measles, mumps, rubella are combined with the Oka–varicella vaccine strain (i.e. MMRV) has been approved in the USA [20], which will make the introduction of universal varicella vaccination easier. It is expected that both Sanofi Pasteur-MSD and GSK will obtain a European registration for such a vaccine. An MMRV vaccine is a suitable candidate to replace our currently used MMR vaccine, which is universally offered in the Netherlands to children of 14 months and 9 years of age, with a calculated mean (5 years) coverage rate of 95% (at 14 months) and 96% at (9 years). However, single dose varicella vaccination is associated with a relatively high frequency of breakthrough infections. A second varicella vaccination after 1–3 months will probably lower the frequency of breakthrough infection, but requires adaptation of our vaccination schedule. The replacement of MMR with MMRV may be complicated by potential conflicts in optimal vaccination schedules for individual components, and potential interference of immune responses and adverse events.

No structured discussion concerning the feasibility and (cost-) effectiveness of universal varicella childhood vaccination has taken place in the Netherlands. We have focused the data in our vaccine evaluation model primarily on the effects of universal varicella vaccination on chickenpox itself. The possible impact of this childhood vaccination on zoster later in life will be addressed in Section 6.

## 2. Vaccine

### 2.1. Which vaccines are available?

The only available varicella vaccine strain is the live attenuated Oka strain [27]. The Oka-vaccine, developed in Japan (Biken Institute, Japan, 1974) is licensed to several large vaccine companies (e.g. Merck (available as Varivax), and GSK (available as Varilrix). Recently, four-fold combination vaccines containing the live attenuated vaccine viruses against measles, mumps and rubella and the Oka–varicella vaccine strain (i.e. MMRV) have been tested for effectiveness [51] and [80]. These vaccine have an increased VZV content (up to 10 times as much plaque forming units of VZV), and yield comparable antibody responses for mumps and rubella, while the response against measles was slightly increased, and the antibody reaction against varicella component was somewhat decreased.

By further adjusting the formulation (a further increase of the amount of VZV plaque forming units) an equally effective MMRV-vaccine seems to be possible [65] and [66]. Two major vaccine companies are currently in the process of obtaining an European license for these four-fold MMRV-vaccines (GSK [(i.e. Priorix-Tetra)] and Merck [i.e. ProQuad]).

### 2.2. Which vaccines have been registered?

In the Netherlands only one varicella vaccine has currently been registered, i.e. Provarivax (Sanofi-Pasteur MSD), as a single dose vaccine for children from 12 months onwards. From 13 years onwards two-doses are recommended [9].

### 2.3. For which indications have the vaccines been registered?

The current single-component Provarivax vaccine is registered for use in healthy children from 12 months of age onwards.

### 2.4. What is the target population?

The Oka–varicella vaccine will be effective when given after maternally derived antibodies have waned, i.e. >~8 months of age. Children in the Netherlands are infected relatively early with VZV (50% sero-conversion is reached at 2 years of age [17]) in comparison to other European countries (e.g. Germany, 50% sero-conversion at 4–5 years [81] and [83]). The effectiveness of an earlier administration of the first MMRV dose (i.e. 9 months of age) as part of the two-doses schedule is being evaluated by GSK.

### 2.5. What factors influence the successful implementation?

Over 95% of the children receive the first MMR dose at 14 months of age, while up to 96% receive the second dose given at 9 years of age. However, the public's perception of the burden of chickenpox is low, and might negatively influence the acceptance of the MMR to MMRV transition (see also Sections Sections 2.14 and 4.13).

The MMR vaccine currently used in the Netherlands is produced by the Netherlands Vaccine Institute (Bilthoven) under license of Merck. Local vaccine production may influence the vaccine pursuing costs. The transition from MMR to MMRV vaccination at 14 months of age will not lead to an additional injection. However, when a two-dose scheme with shorter interval (i.e. 1–3 months) is preferred for MMRV vaccination, adjustment of the vaccination schedule will be required.

### 2.6. What is the protection afforded?

A single-dose of the Oka–VZV vaccine protects 95–98% of the vaccinee's against moderate to severe chickenpox infection [11], [41], [51], [62], [74] and [80] (see also Section 2.11). Oka–varicella vaccine probably also (partly) protects against zoster later in live [11] and [79], because it prevents the establishment of a latent infection of wild-type VZV.

### 2.7. What are critical determinants of the immune response associated with protection?

Parameters of protective immunity against VZV are largely unknown. After single-shot VZV immunization, serum IgG antibody responses are found to be 10–30 times lower than after natural infection. Titers of antibodies to VZV after immunization increase with time, however, presumably due to the endogenous or exogenous exposure to VZV. This eventually results in IgG titers that are similar to those after natural infection [2] and [27].

Breakthrough infections, due to wild-type VZV, are much more frequent than the number of non-responders, and breakthrough infections increase with time after vaccination (see Section 2.11).

### 2.8. What is the optimal vaccination schedule

A single dose given between 12 months and 12 years of age is the preferred vaccination schedule for the single-shot Provarivax (European-license) and the four-fold MMRV combination vaccine ProQuad (USA-license). From 13 years onwards two-doses are recommended with an interval of 4–8 weeks. For MMRV a two-dose schedule might also be considered (with a interval of 1–3 months) to reduce the number of breakthrough infections. Data obtained after universal varicella vaccination in the USA shows a reduced protection rate during the first year after vaccination (73% overall protection rate) when vaccination was given at 12–15 month, compared to vaccination at ≥15 months (99%; $P = 0.01$). However, no statistically significant difference ($P = 0.17$) was found when the follow up period was extended to 8 years (81% versus 88%) [74].

### 2.9. What is the frequency of vaccine failure?

Clinical studies from the USA show that vaccine efficacy ranges from 71 to 100% [22], and frequently wild-type chickenpox infections are reported among vaccinated children [1], [13], [19], [22], [45] and [72]. A 10-year follow-up study of VZV vaccination in the USA, showed a protective efficacy of 94.4% against moderate and severe chickenpox for a single-dose vaccination, and this increases to 98.3% when an additional vaccination was given [40]. Vazquez et al. recently reported that the overall effectiveness against moderate or severe chickenpox is 98% (95% CI: 93–99%; $P < 0.001$). There was no significant difference for children vaccinated at 15 months or younger (at 12–15 months) [74]. Furthermore, they reported a substantial and statistically significant difference between the vaccine's overall effectiveness between the first year after vaccination (97%) and the years 2–8 after vaccination (84%).

Although breakthrough is relatively frequent, the clinical signs associated with a breakthrough infection are clearly reduced (i.e. a reduced number of lesions and smaller lesions). The number of breakthroughs infections will likely be reduced after a two-doses schedule, since the antibody response are much higher after two-doses compared to one dose (see Section 2.10).

### 2.10. What is the frequency of vaccine failure when using alternative vaccination schedule?

A two-dose varicella vaccination schedule induced much higher antibodies responses (GMT) than a single dose. However, this difference was largely diminished after 1 year and no longer present at 2–8 years after vaccination [40]. Breakthrough infections were 3.3 times more frequent after single-dose

vaccination [40], but breakthrough infections result only mild clinical signs (see also Section 2.11).

### 2.11. What are risk groups for vaccine failure?

Independent factors associated with breakthrough infection of VZV single component Oka-vaccination are [21]:

- vaccination before 15 months of age;
- asthma;
- vaccination against varicella soon after the MMR vaccine (<28 days);
- time (>3 years) after vaccination.

### 2.12. Is there any interference with other vaccines?

The varicella vaccine should not be given within 28 days after the live attenuated MMR vaccine (see Section 2.11). However, by using the four-component MMRV vaccine no interference can occur.

### 2.13. Are there any contra-indications for vaccination?

Contra-indications for the Provarivax are immunosuppression, immunodeficiency and active, non-treated tuberculosis infection is a contra-indication. Immunosuppressed children are, however, often vaccinated with the Oka-VZV live vaccine, as a wild-type varicella vaccination can be life-threatening for these children [24].

### 2.14. What proportion of the target population will accept the vaccine, or has already been vaccinated?

Vaccination coverage in the Netherlands is high (see Section 2.5). In a questionnaire study on acceptance of varicella vaccination parents reported rather frequently that they did not consider vaccination against chickenpox necessary (see also Section 4.13). In combination with MMR (without the need for an additional injection), it might however be accepted relatively easy. An additional vaccination (i.e. in a two-doses schedule) might hamper acceptance.

### 2.15. Is the expected vaccination rate sufficient to reach herd immunity?

Wild-type varicella establishes a latent infection, which can result in zoster when cell-mediated immunity decreases. Zoster is found frequently in elderly, and lesions contain infectious VZV (see Section 3.5). As the vast majority of the Dutch population is latently infected by VZV (VZV sero-conversion rates are > 97% in the age 6–75 in the Dutch population without vaccination), transmission will continue for many years after vaccination, albeit on a lower level. Another factor with a negative influence on herd-immunity is the presence of a large social-geographic clustered group of people in the Netherlands who refuses vaccination on religious grounds. We expect periodic epidemics of chickenpox among the children of this community, after introduction of universal varicella vaccination. Comparable outbreaks of polio, measles, and rubella have occurred during recent decades. Furthermore, the frequency of breakthrough infections with minor

clinical signs is up to 30% after single-dose varicella vaccination, while the frequency of sub-clinical breakthrough infections is unknown.

### 2.16. What is the expected duration of protection?

Long-term data on waning VZV immunity of large numbers of vaccinated children are not available. There is a significant difference in overall protection between the first year and the period of 2–8 years after infection (see Section 2.9). Infection of VZV later in life is more serious, and associated with higher hospitalization rates, and a shift in age distribution of cases could result in a higher overall morbidity. No such increase is predicted, however, by using a dynamic mathematical model and a plausible range of values for the different efficacy characteristics of the vaccine at different levels of coverage [33].

### 2.17. What is the effect of waning immunity?

Currently, the effect of waning immunity is hard to predict, due to the dual clinical appearance of a VZV infection (i.e. chickenpox and zoster). Breakthrough infections of VZV at younger ages result almost exclusively in minor clinical signs. The absence of a wild-type latent VZV infection may reduce the incidence of zoster as most vaccinated people will no longer be carriers of wild-type VZV. If vaccine-induced immunity does indeed wane the vaccine-related reduction of zoster might be less than expected (see also Section 6). The frequency of (sub-clinical) wild-type infections will probably be less after a two-doses schedule [40].

### 2.18. Will reduced pathogen transmission lead to enhanced vulnerability of specific sub-populations?

This is an area of great concern for varicella vaccination. Circulation of wild-type VZV may help to maintain cell-mediated immunity against VZV in elderly, thus preventing the reactivation of VZV and appearance of zoster [35] and [71]. Others, however, advocate that reactivation of latent VZV is common, and stimulates the immune system endogenously. Computer models predicted a temporary increase (~5 to ~40 years after the introduction of universal childhood vaccination) of zoster incidence in elderly [6] and [29]. However, no such increase has been reported in the 7 years post-introduction period (1995–2002) in the USA [36], [37] and [63]. Although encouraging, it may be too early to draw conclusion yet, as it is relatively early (i.e. 7 years after the introduction), not all states have implemented vaccination yet, coverage was relatively low in the first years [12], and surveillance of zoster is relatively poor [75].

### 2.19. Are repeated vaccinations necessary?

The live-attenuated Oka-strain will establish a latent infection for life-time, but might not prevent (sub-) clinical superinfection of wild-type VZV. A superinfection of wild-type VZV will also lead to latency and, probably, a higher risk of zoster. Therefore, it seems justified to revaccinated to booster existing immunity, or initiate immunity in children who failed to react to the first vaccination, or did not receive it at all.

### 2.20. What is the expected vaccination coverage of repeated vaccinations?

No experience exists yet in other countries with the replacement of MMR with MMRV and possible effects in vaccination coverage. We assume that the

replacement of MMR by MMRV will not influence the vaccination coverage. However, a two-doses schedule given 1–3 months apart, might have a negative affect on vaccine coverage (see also Section 2.14).

### 2.21. What is the nature and frequency of adverse events?

The single component Oka-vaccine has a good safety profile. The most common adverse events are mild tenderness and redness at the injection site (~15 to ~20% of the vaccinees), low-grade fever (~14%) and mild chickenpox-like rashes (~4%) [78]. Furthermore, MMRV, MMR/V and MMR equally induces pain, redness and swelling at the site of vaccination [51]. In the 2 weeks following vaccination slightly higher rates of fever and rashes were found for MMR/V and MMRV in comparison to the MMR [51].

### 2.22. What are risk factors for adverse events, and what is the frequency of these risk factors?

The Oka-vaccine has been used over 20 years in immunocompromised children, but serious adverse events were extremely rare [25]. Also, USA post-licensing safety surveillance of single-component Oka-vaccine showed that serious adverse events are very rare (271/100,000), and mostly a link with vaccination could not be confirmed [82]. Non-serious adverse events were more frequent (6289/100,000), especially rashes and injection side reactions.

### 2.23. What are the consequence of adverse events?

Because MMRV vaccination is well tolerated we expect only minor incremental costs associated with adverse events after the transition from MMR to MMRV.

### 2.24. Is there any difference between presumed and observed adverse events?

We have found no data on presumed adverse events for the Oka–varicella vaccine.

### 2.25. For live attenuated vaccines: is there any chance on reversion to virulence?

Herpes viruses have a large (>100 kb) and stable DNA genome. The Oka-vaccine strain contains several independent nucleotide mutations [68]. Detailed analysis of two reported gE mutant viruses showed only limited variation between these variants and wild-type VZV [31], [32] and [68] (See also Section 3.3). No reversion of the Oka-vaccine strain is to be expected.

### 2.26. What are the costs of available vaccines?

The reference price of a single-shot VZV vaccine dose varies between $ 30 and 42 [70]. We have no indications on the price difference between MMR and MMRV, but we estimated an €35 increment for the total pursuing cost form MMR (€16, currently in the Netherlands) to MMRV (€51).

### 2.27. What are the once-only costs to implement the vaccine?

The once-only cost associated with replacement are relatively low when MMRV is given according to the current schedule for MMR. However, an additional dose will

result in higher implementation costs. Additional time for the nurse/physician to explain the rational varicella vaccine might be necessary in the period surrounding the transition form MMR to MMRV. Furthermore, it might be necessary to develop new brochures about our national immunization program.

### 2.28. What are the yearly costs to administer the vaccine?

No increase of the cost of administration are expected when MMR is replaced by MMRV. If an separate varicella-dose in the second live-year is given, the yearly cost will be considerable, which depend strongly on the vaccine pursuing costs.

### 2.29. What are the costs to monitor safety and effectiveness of the vaccine?

Safety monitoring will be performed with our passive surveillance system. As the Oka-vaccine has a good safety profile (see Section 2.21) no major additional costs are expected.

## 3. Pathogen

### 3.1. Which part of the population comes in contact with the pathogen?

Almost all individuals come into contact with VZV during early childhood. Sero-conversion in the Netherlands rates approach 100% from 7 years onwards [17].

### 3.2. What is the incidence of infection in the population?

In a Dutch epidemiologic study ($n$ = 2044) 93.0% of the 5 year-olds possessed antibodies against VZV [17]. Overall VZV-seroprevalence (from 0 to 79 years of age) is 95.6% (95% CI: 94.9–96.3%).

### 3.3. Is there any variation in pathogenicity?

Recently, three different genotypes have been recognized with a different geographic distribution [48], but they belong to the same serotype. No differences in virulence or transmissibility between strains of these different genotypes has been reported.

### 3.4. Are there interactions with other pathogens?

Bacterial superinfections of skin, lungs and bones are a frequently complication of a varicella infection. Especially severe invasive group A streptococcal infections are associated with varicella infection [43].

### 3.5. Will there be any ecological consequences after implementation of vaccination?

Just like wild-type VZV, the attenuated Oka-vaccine strain will establish a latent infection. Therefore, no effect on the availability of free sites for other pathogens is expected. Furthermore, no interaction/competition has been described for different alpha-herpes viruses such as HSV-1, HSV-2 and VZV.

### 3.6. What is the infectiveness during various stages of infection?

VZV is highly contagious, both by aerosols and direct contact with lesions of varicella and, to a lower extent, zoster [28]. In temperate climates the mean age of VZV-infection is lower than in (sub-) tropical climates [61]. This is probably due to the instability of the enveloped VZV virus at higher temperatures.

### 3.7. What are routes and mechanisms of transmission?

VZV is spread by the airborne route [44]. High levels of VZV are present in chickenpox skin lesions. Isolation of VZV from the respiratory tract is usually negative. However, spread of VZV before the appearance of skin lesions occurs, suggesting that respiratory spread can occur [30].

### 3.8. What is the relative importance of different transmission routes?

Infected people are infectious from 1 to 2 days prior of onset of rash and during the first few days of rash. Dry skin lesions do probably not harbor infectious virus [23]. The relative contribution of zoster and sub-clinical varicella infections in the transmission of VZV is unknown.

### 3.9. Does antigenic variation occur?

Very limited antigenic variation has been reported for wild-type VZV (see Section 2.25).

### 3.10. Does vaccination exert evolutionary pressure leading to the emergence of antigenic or virulence variants?

No relevant antigenic variation has been described for VZV after introduction of the Oka-vaccine. Also no reports exist of antigenic or virulence variants after immunization of immunocompressed children. Acyclovir-resistant mutants might, however, appear after prolonged acyclovir usage in immunosuppressed children [46] or aids-patients [59].

### 3.11. What are the consequences of the emerge of antigenic virulence variants on the vaccine's effectiveness?

Not relevant, see Section 3.10.

## 4. Disease

### 4.1. What is the incidence of infection, and how reliable are surveillance data?

Based upon a cross-sectional sero-epidemiology study ($n$ = 2044) almost all (>97%) people from 7 years onwards possess VZV-antibodies [17].

### 4.2. Is there a social impact of the disease?

Parents often resume from work or other social activities due to children with chickenpox. Municipal Health Centers in the Netherlands advises day-care centers, however, not to refuse children with chickenpox.

### 4.3. What are risk factors for infection?

The main risk factor for attracting a VZV infection is age. Children with diminishing levels of maternally derived antibodies (>~8 month) are becoming vulnerable for a VZV infection.

Additional risk factors in the Netherlands are a higher number of persons in the house-hold (>3 persons), lower urbanization states (<2500 addresses/km$^2$), and schools attendance of subject or other person in the household [17].

### 4.4. What is the percentage of symptomatic versus asymptomatic infections?

About three-fourth of adults who have no history of clinical varicella have detectable antibodies against varicella [42]. Furthermore, it is estimated that ~ 5% of first time VZV-infections is sub-clinical [8].

### 4.5. What are risk factors for asymptomatic infection?

We found no information on factors for asymptomatic varicella infections.

### 4.6. What part of the infections results in carriership?

VZV establishes a latent infection in nerve cells in each infected individual. Carriers are, however, normally not infectious and only moderate infectious during an episode of zoster.

### 4.7. What are risk factors for carriership?

Not relevant, see Section 4.6.

### 4.8. What is the mortality, and how reliable are surveillance data?

In the period 1996–2002 on average 2.3 deaths (range 0–4; main cause of death only) were registered in the Netherlands annually, which occurred in 50% of the cases among children less than 5 years of age [17].

### 4.9. What are the consequences of infection?

VZV is usually a benign childhood disease that occurs in children <15 years of age and lasts about 5–10 days. Symptoms are rash, itching, tiredness and fever. Secondary bacterial (e.g. Group A *Streptococcus* and *Staphylococcus*) infections may occur, sometimes causing scars. In about 10% of the cases (including immunocompromised children) complications may occur like dehydration from vomiting or diarrhoea, exacerbation of asthma or more serious complications such as pneumonia [4]. In adults the course of a varicella infection is more often complicated by pneumonia or encephalitis, sometimes resulting in persistent sequelae, or death. Varicella can also occur as a superinfection in patients who are hospitalized for some other cause. The combination of multiple risk factors increases the chance of severe or fatal disease course.

In rare cases (2%) varicella can also effect the fetus if contracted early during pregnancy (congenital varicella syndrome), leading to a newborn with skin lesions, neurologic defects, eye diseases and skeletal anomalies [60].

### 4.10. Are there any sub-populations with more severe forms of disease?

Risk factors for severe VZV infection are immunodeficiency. It has been suggested that varicella is more severe in pregnant women. However, there are data to support this suggestion [49].

### 4.11. What is the quality of life after infection?

Validated data on quality of life in mild episodic diseases is scarce. Brisson and Edmunds reported an average value of 0.76 for the health state of a child with chickenpox using an existing generic health status index (Health Utilities Index mark 2, HUI2) [7]. Smith and Roberts assumed a value of 0.4 for adults during hospitalization [67]. The quality of life in adult patients who are receiving or not receiving acyclovir were estimated to ranged from 0.65 to 0.85 [58]. Paul et al. assumed a value of 0.5 for hospitalized adults, and 0.8 for adults with uncomplicated infections [55].

### 4.12. What is the burden of disease expressed in DALYs?

In the absence of published disability weights for varicella stages, we use published quality of life values and assumed that a disability weight is one minus a quality of life weight. Assuming that the total incidence of chickenpox infections equals the birth cohort [3] the total number of infected people is estimated at 200,000/year.

Assuming a disability weight of 0.24 (i.e. 1–0.76, see Section 4.11) for a 7-days episode of uncomplicated varicella, this episode contributes to a loss of quality of life of 0.0046, compared to a year lived without such a varicella episode (see Table 1). About 190,280 of these people have no complications (95.14% [3]). The associated disease burden in the population, expressed in DALYs, is 875. Similarly, the disease burden for the different subgroups with complications and hospital admission were estimated. Finally the number of years of life lost (YLL) was computed among patients for whom varicella was the primary cause of death. Table 1 shows the total burden of disease, differentiated to the course of disease.

Table 1.

Course of chickenpox diseases and associated burden of disease

| Course of disease | Duration (days) | Disability rate (episode) | Disability rate (year) | Cases (year) | Disease burden (DALYs) |
|---|---|---|---|---|---|
| Uncomplicated | 7 | 0.24 | 0.0046 | 190280 | 875 |
| Complicated | 14 | 0.35 | 0.0134 | 9720 | 130 |
| Hospital admission | 18 | 0.60 | 0.0295 | 208 | 6 |
| Death[a] | | | | 2.3 | 120 |
| | | | | | |
| Total | | | | | 1131 |

[a] Assuming on average 52 years of life lost per fatal case.

In the period 1996–2002 on average 2.3 deaths (range 0–4) were registered in the Netherlands, at a mean age of 22 years. The associated average number of years of life lost is 52 years [10]. Since there is no good administration of the fraction of varicella-related deaths in immunocomprised patients, this figure likely underestimates the total life years lost due to varicella. Furthermore, possible long-term sequela such as disfiguring scars, mental retardation, and cartilage destruction [4] has not been taken into account, as we have no data on the incidence.

In the DALY estimate uncertainty of the assumed disability weight during an uncomplicated episode of varicella is a key variable: when for example the average quality of life weight is 0.7 in stead of 0.76, the DALY total comes at 1350. In our estimation 3/4 of DALYs, are lost by the 95% of cases who go through an uncomplicated episode of chickenpox.

### 4.13. Is there a difference between real and presumed burden of disease, and what is the public's perception of the burden of disease?

The public's perception of the burden of chickenpox is low. In a recent Dutch questionnaire study ~1/5 of the parents stated that they were willing to have their child vaccinated against varicella, while ~1/3 stated that they were not [73]. In contrast, almost all Dutch parents indicated that they were willing to have their child vaccinated against *N. meningococcus* B, which causes a comparable burden of disease in the Netherlands [18]. This difference in perception is most likely due to fact that clinical cases of for *N. meningococcus* B are often life-threatening, while almost all varicella infectious are mild. Furthermore, the media reports frequently on *N. meningococcus* B deaths.

### 4.14. What is the use of health care?

The average annual incidence of GP visits due to chickenpox is 254/100,000 (2000–2002). It was highest for 0–4 year-olds (3102/100,000). This translates into a total of ~40,000 GP-visit each year in the Netherlands [17].

The average annual incidence of hospital admissions is 1.3/100,000 using main diagnosis and 2.3 using main and side diagnosis. Based on main diagnosis the total number of in-hospital days is 1379/year. Number of hospital days due to side diagnosis is unknown [17]. Because only main diagnosis for hospital admissions was used these data are probably an underestimation.

### 4.15. What are the costs associated with health care?

A total of 40,000 GP-visits leads to total annual costs of €0.8 million based on a costs of €20.20 per visit [52]. The total number of in-hospital days was 1379 (see Section 4.14). Thus, at a cost of €359/day, the total costs for hospitalization are €0.5 million/year. The annual direct health care costs due to varicella are estimated to be €1.3 million.

### 4.16. What is the magnitude of school absenteeism?

Assuming an average disease duration of 7 days, each infected child will be absent from school for about 5 days.

### 4.17. What is the magnitude of work absenteeism?

Estimates of the number of workdays lost for varicella-infected adults vary from 5.7 to 23 days [5] and [70].

### 4.18. What is the magnitude of work absenteeism of parents and caretakers?

Most studies assumed that one of the parents lose work for 0.59–2.7 days when their child has varicella [70].

### 4.19. What are the costs associated with school and work absenteeism?

No costs are associated to school absenteeism by children. However, costs are associated to the hours of parents or other caregivers to care for their children. The value of a work hour lost depends on the age of the person. The Dutch average is about €34.50; people who take care of their children with chickenpox will however usually be younger (aged 25–34). Their work hours are valued at about €32.50. The value of unpaid work lost or time spend on informal care is €8.30/h [52].

The productivity losses [6] due to sickness leave of parents taking care of children <15 years of age (indirect non-health care costs) amount to €80 million (0.90 × 200,000 cases × 1.7 days × 8 h × €32.50). If we assume that 5.3 remaining sick days the child is taken care of by people who give up some leisure time (estimated at 1 h/day), an additional €8 million is involved (0.9 × 200,000 cases × 5.3 days × 1 h × €8.3).

As disease is more severe, and associated hospital stays are twice as long in adults compared to children [7], we assumed that the varicella-infected adults will last 14 days on average. Following the friction costs method all days may be counted as sick days, resulting in indirect non-health care costs of €27 million (0.05 × 200,000 cases × 14 days × 8 h × €24.50). This estimate assumes that 2/3 of this population would be working, and 1/3 would be without a paid job (e.g. student, housewifes, un-employed, etc.), so that the weighted value for their hours lost is 24.50 ((2/3) × 32.50 + (1/3) × 8.30). However, this may be an overestimation, because weekends are included or because some people might go back to work even when the infection is not completely cured. A more likely estimate of indirect non-health care costs in infected adults is €18 million (average of eight work days and four leisure days lost).

### 4.20. Will there be economic benefits for companies if they offer vaccination to their employees?

Because almost all employees will have had a VZV-infection during early childhood, vaccination will not be cost-effective.

### 4.21. Are there any alternative preventive measures?

It is best to acquire a VZV infection during childhood, because the severity of the clinical signs of a varicella infection is increased in adolescents and adults. Immunoglobuline preparations (VZIG) and antivirals (e.g. acyclovir) are available as prophylactics and therapeutics for immunocompromised patients or pregnant women to prevent or treat a severe varicella infection.

### 4.22. What is the effectiveness of alternative preventive measurements

Not relevant, see Section 4.21.

### 4.23. What are the costs of these alternative preventive measurements

Not relevant, see Section 4.21.

## 5. Cost-effectiveness

### 5.1. How many infections can be prevented by vaccination?

Universal childhood vaccination with high coverage rates (95%) will reduce the number of susceptible children only by 80% due to the relative high number of breakthrough infections (see also Section 2.11). A second VZV-vaccination in the second live-year can limit the number of breakthrough infection considerably (see also Section 6).

### 5.2. What are savings on costs of health care by vaccination?

From a societal perspective (including indirect non-health care cost), universal childhood varicella vaccination was mostly found to be cost saving. From the health care payer perspective varicella vaccination is often not found to be cost saving, and range from $ 11,900 to about $ 40,000 per life year saved [57] and [70]. We have ignored the effects on zoster, as there is little epidemiologic evidence to validate assumptions.

### 5.3. Are the benefits of vaccination gained by those who carry the costs?

Yes, vaccination will be offered through our NIP, which is paid by the Dutch government. The benefits of vaccination will be gained by the Dutch society, i.e. the citizens (fewer illness), the health care payer (lower health care costs) and the employers (fewer sickness leave of patients and of parents taking care of sick child).

### 5.4. How many years of life and QALYs are gained by vaccination?

Considering only the cases where varicella is the primary cause of death (average 2.3/year) and assuming 95% effectiveness in prevention of severe cases, on average 2.2 lives might be saved each year by vaccination. Assuming 95% effectiveness in severe cases (current burden of disease = 130 + 6 + 120 = 256) and 80% in mild to moderate cases (current burden = 875 DALYs, see Table 1), about 943 QALYs may be gained ($0.8 \times 875 + 0.95 \times 256$).

### 5.5. What is the time interval between vaccination and realization of health effects?

We estimate that, on average, the time interval between vaccination and health effects is about 3.6 years. For 50% of the cases the time interval between vaccination (at 14 months) and health effects will be 10 months, since 50% sero-conversion is reached at 2 years. For 45% of the cases the time interval between vaccination and health effects will be between 10 months and 10 years, since 94% of the children have sero-converted at ~10 years of age. The remaining 5% are infected in adulthood.

### 5.6. How many infections can be prevented by alternative preventive measures?

Not relevant, see Section 4.21.

### 5.7. What are savings on cost of health care by alternative preventive measures

Not relevant, see Section 4.21.

### 5.8. What is the cost-effectiveness ratio of vaccination compared with alternative preventive measures?

Not relevant, see Section 4.21.

### 5.9. Is it possible to select individuals eligible for vaccination because of enhanced risk of infection?

Antibody screening of adolescents who report not to have had chickenpox and subsequent vaccination of the VZV-seronegatives might be possible [69] and [34]. Chickenpox is, however, seen as a benign disease, and we think it will not be feasible to reach a high participation of adolescents in an amnesic and serological screening.

## 6. Discussion

Varicella is in the Netherlands seen as a benign childhood disease, despite ~ 40,000 visits to a General Practitioner, over 200 hospital admissions, and 2.3 deaths each year. With the development of tetra-valent measles mumps rubella and varicella vaccines, universal childhood vaccination against varicella becomes more feasible for the Netherlands. With the use of our recently developed vaccine evaluation model [38], we reviewed (international) data on varicella childhood vaccination.

Although a lot of data is available some points of uncertainty remain. The most important one is the effect of universal childhood varicella vaccination on the incidence of zoster later in life (see also Section 2.18). Dynamic computer modeling suggests that the incidence of zoster will be increased during a ~5 to ~ 40 years period after introduction of universal childhood vaccination [6] and [29]. The underlying assumptions of these models are, however, questioned by others [34], and to date, no increase in the incidence of zoster has been reported after the introduction of varicella-vaccination in the USA in 1995 [36], [37] and [63]. Despite this encouraging data from the USA, it seems too early to conclude that the predicted temporally rise in zoster incidence will not occur, because immunization rates were relative low in the first years after introduction (below 50% until 1999 [12]). Vaccination of elderly with Oka/VZV could boost their immunity and could possibly prevent the predicted increase in rise of zoster. A recently developed zoster-vaccine, which contains atleast 10-fold more plaque forming units of Oka/VZV than a varicella childhood vaccine, appears partial effective [53], i.e. it reduces the incidence of zoster by 51.3%, and postherpetic neuralgia by 66.5% during a 3.13 years follow-up period.

Another point of uncertainty is the cost-effectiveness ratio for VZV-vaccination in the Netherlands. Sero-conversion data suggests that the mean age of contracting varicella is in the Netherlands lower than in many other European countries. As

the severity of a varicella infection increases with the age of infection, the burden of disease might be lower in the Netherlands. This assumption is supported by the fact that we find a relative low rate of hospitalization and general practitioners visits. Another point of uncertainty is the cost associated with the transition of MMR to MMRV. The incremental cost associated with this transition are especially difficult to estimate for our country, because our current MMR-vaccine is locally produced under a special license of Merck. Furthermore, the incremental cost depend on the preferred schedule (number of doses and timing).

Often not the primary infection with VZV itself, but a bacterial superinfection with e.g. group A *Streptococcus* is the cause of GP-visits and hospitalization. This makes the estimation of the VZV-related burden of disease less reliable. Where available we have also given the incidence rates on varicella as contributing cause (i.e. side diagnosis in hospitalization). We have, however, not taken the VZV-contributing cases into account in the cost evaluation, and cost calculations are most probably an underestimation. Recently, it was shown that not only the death rates due to VZV as underlying cause, but also death rates in which VZV was a contributing cause have statistically significantly declined in younger age groups in the USA in response to universal vaccination [50]. Furthermore, a reduction in pediatric hospitalizations for varicella-related invasive group A streptococcal infections due to vaccination has been reported for the USA [54]. However, most burden of disease (≃80%) is associated with mild cases (see Table 1). So the underestimation of VZV as contributing factor to morbidity and mortality will only have a limited effect on the overall estimated burden of disease.

The live vaccine against VZV appears to be less effective than other live vaccine strains such as measles and mumps, as frequently chickenpox breakthrough infections are being reported in the USA (see Section 2.9). A second vaccination in the second live-year induces a higher cellular and humoral immune response [77] and might reduce the number of breakthrough infections considerably [26] and [40]. A second vaccination will have a relatively small effect on the burden of disease, because almost all breakthrough infections are very mild. At present, the second MMR vaccine is given around 9 years of age in our NIP. The introduction of an additional, second varicella vaccination in the second life-year has major drawbacks both from economic and from parents acceptance viewpoint (see Sections Sections 2.12 and 4.13). An alternative possibility is to give our second MMR vaccination in the second life-year in stead of around 9-year-of-live as an MMRV vaccination. The consequences of this major change in vaccination time-point on the effective protection level (herd-immunity) for measles, mumps, and rubella are, however, unknown.

In conclusion, because chickenpox runs in most children a mild course it is generally seen as a benign disease, not justifying a high priority for vaccination. Nonetheless, in some children, either due to a bacterial superinfection or not, VZV leads to severe illness, resulting in hospitalization and, in rare cases, death. Despite some uncertainties, the cost-effectiveness ratio appears favorable when indirect non-health care costs due to prevention of mild cases (i.e. by prevention of work loss by care-takers) is taken into account. So, from an economic point of view, it is the prevention of many mild VZV-cases that justifies the prevention of the much fewer severe cases. From the burden of disease perspective it is clear that universal childhood vaccination will prevent most of the GP-visits, hospitalizations and death that occur due to varicella zoster virus.

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