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The epidemiology of varicella and herpes zoster in The Netherlands: Implications for varicella zoster virus vaccination

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Abstract

We studied the epidemiology of varicella (chickenpox) and herpes zoster (shingles) in The Netherlands to assess the desirability to implement routine varicella zoster virus vaccination in The Netherlands. Data on seroprevalence of varicella zoster virus in the general population (1995–1996), consultations of general practitioners for varicella (2000–2002) and herpes zoster (1998–2001) and hospital admissions due to varicella (1994–2001) and herpes zoster (1994–2001) in The Netherlands were analysed. The seropositivity increased sharply with age from 18.4% for both 0- and 1-year-olds, to 48.9%, 59.0%, 75.7% and 93.0% for 2-, 3-, 4- and 5-year-olds, respectively, and varied between 97.5% and 100% for older age groups. The average annual incidence of GP-consultations amounted to 253.5 and 325.0 per 100,000 for varicella and herpes zoster, respectively. The incidence of hospital admission due to varicella and herpes zoster was 1.3 (2.3 including side diagnosis) and 2.7 (5.8) per 100,000, respectively. Whilst for varicella, the incidence of GP-consultations and hospital admissions were highest in childhood, for herpes zoster, these were highest in elderly. Insight into epidemiology of varicella zoster is needed for the assessment of the desirability of introduction of routine varicella zoster vaccination.

Keywords: Varicella zoster virus; Vaccination; Epidemiology; Population-based seroprevalence study; Hospital admissions; General practitioners

1. Introduction

The varicella zoster virus (VZV) causes two distinct diseases, varicella (chickenpox) and herpes zoster (shingles). Chickenpox is generally regarded a benign disease. However, complications like bacterial superinfections of the skin and acute neurological disorders can occur. Furthermore, latent infection of varicella zoster virus established during chickenpox can be reactivated (e.g. by aging, immunosuppresion) and results in shingles.

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Some European countries are now considering introduction of routine VZV vaccination in their national immunization programmes. Recently, Germany and Sicily have included VZV vaccination in their routine vaccination schedule [1].

The European Working Group on Varicella (EuroVar) recommended routine VZV vaccination for all healthy children between 12 and 18 months and to all susceptible children before their 13th birthday, in addition to catch-up vaccination in older children and adults who have no reliable history of varicella and who are at high risk of transmission and exposure. This policy was recommended only when a very high coverage rate could be achieved [2]. The group stated that this could be reached with a measles–mumps–rubella–varicella (MMR–V) combined vaccine. In The Netherlands, the vaccine coverage for MMR amounts to 95% at 2 years of age [3].

Insight into the epidemiology of varicella and herpes zoster in The Netherlands is essential to assess the desirability of introduction of universal VZV vaccination. Subsequently, it will also be relevant to formulate an appropriate strategy for delivery of the vaccine. The present paper aims to describe the epidemiology of varicella and herpes zoster in The Netherlands. Data on seroprevalence of VZV in the general population, consultations of general practitioners (GPs) and hospital admissions for varicella and herpes zoster are presented.

2. Methods

2.1. Data sources

2.1.1. Population-based seroprevalence study

In The Netherlands, between October 1995 and December 1996, a population-based serum bank was established of 8359 individuals. The primary aim of the study was to obtain insight into the immunity of the population against diseases included in the National Immunization Programme. Details of the study design have been published elsewhere [4]. A total of 40 municipalities were selected with sampling probabilities proportional to population size. Within each of these 40 municipalities, an age-stratified sample of 380 individuals was drawn from the population register. The age strata were 0, 1–4, 5–9, …, 75–79 years. In each of the first two strata, 40 individuals were sampled, while in each of the following strata, 20 individuals were sampled. Subjects were requested to give a blood sample, fill out a questionnaire and bring vaccination certificates.

For serology of varicella zoster virus, a sample was drawn from this serum bank. For those below 14 years of age, two sera per municipality were sampled per age in years, while for those aged 15 years and above, two sera were randomly sampled per 5-year-age group.

For 204 individuals below 5 years of age, enough serum was left to test varicella virus. In total, the sample which could be used for serological testing of varicella included 2044 sera. Serological testing was performed with the VZV IgG ELISA kit (Human GmbH, Wiesbaden, Germany) according to the manufacturer's instructions. Serum samples were measured as independent duplicates diluted 1:100 and titers were calculated with the internal positive controls which were calibrated against the WHO International Reference Preparation for anti-VZV IgG.

Frequencies within each municipality were weighted by the proportion of the age group in the population. To produce national estimates, the weighted frequencies were averaged over the 40 municipalities [5].

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Logistic regression analysis was conducted to determine whether any of the following variables were independent predictors of seropositivity for varicella virus after adjustment for age group: gender, educational level, country of birth, number of persons in the household, nursery attendance by participant or other person in the household, primary school attendance by participant or other person in the household and urbanization of the municipality.

The educational levels of those aged 17 years or more and of one of the parents (parent with the highest level) for those aged less than 17 years, were classified as "low" (primary school, lower vocational or lower general secondary education), "intermediate" (intermediate vocational or intermediate general secondary and higher general secondary education) and "high" (higher vocational secondary education and university education). The following categories for degree of urbanization were used: "very high" (>2500 addresses/km^2), "high" (1500–2500), "moderate" (1000–1500), "low" (500–1000), and "none" (<500). Country of birth was categorized as "The Netherlands" versus "other", number of persons in the household as "at least four persons" versus "between one and three person per household", nursery attendance was classified "both participant and other person in household attend a nursery", "only participant attends a nursery", "only other person in household attends a nursery" and "none of the persons in the household attends nursery". Same classes were used for school attendance.

2.1.2. Consultations of general practitioners

The Netherlands Institute of Primary Health Care (NIVEL) has coordinated the activities of a sentinel surveillance network of 43 general practices since 1970. These practices cover 1% of the Dutch population, a sample representative of the national population in terms of age, sex, and degree of urbanisation. The general practitioners in the NIVEL sentinel network weekly registered patients who consulted them for chickenpox in the period 2000–2002 and patients who consulted them for zoster in the period 1998–2001 [6]. The age groups were 0, 1–4, 5–9 and further 5-year-classes till 85 years and above. Only for herpes zoster consultations, information on gender was available.

2.1.3. Hospital admission

The number of hospitalizations with varicella (ICD-9 052; ICD-10 B01) and herpes zoster (ICD-9 053; ICD-10 B02) as main and/or side diagnosis in the period 1994–2001 were obtained form the registry of Prismant (National Health Care Registry). The age groups were 0, 1–4, 5–9 and further 5-year-classes till 85 years and above. In addition to age, information on gender was available. For main diagnosis, information on the number of hospital days was available.

2.1.4. Death registration

Deaths due to varicella (ICD-10 B01) or herpes zoster (ICD-10 B02) according to the (prime cause of death) registration of Netherlands Statistics in the period 1996–2002 were used.

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3. Results

3.1. Seroprevalence of varicella zoster virus

3.1.1. Age- and gender-specific seroprevalence

The seroprevalence of varicella zoster virus antibodies amounted to 95.6% (95% CI 94.9–96.3%) in persons 0–79 years of age (Fig. 1). The seroprevalence was slightly lower for men 93.6% (95% CI 92.2–95.0%) compared to women 95.6% (95% CI 94.7–96.5%). The seropositivity increased sharply with age from 18.4% for both 0- and 1-year-olds, to 48.9%, 59.0%, 75.7% and 93.0% for 2-, 3-, 4- and 5-year-olds, respectively. The seroprevalence amounted to 25%, 17%, 13% and 26% for infants aged 3–5 months (no infants <3 months in the sample), 6–11 months, 12–17 months and 18–23 months, respectively. The seroprevalence varied between 97.5% and 100% for 5–9- to 75–79-year-olds.

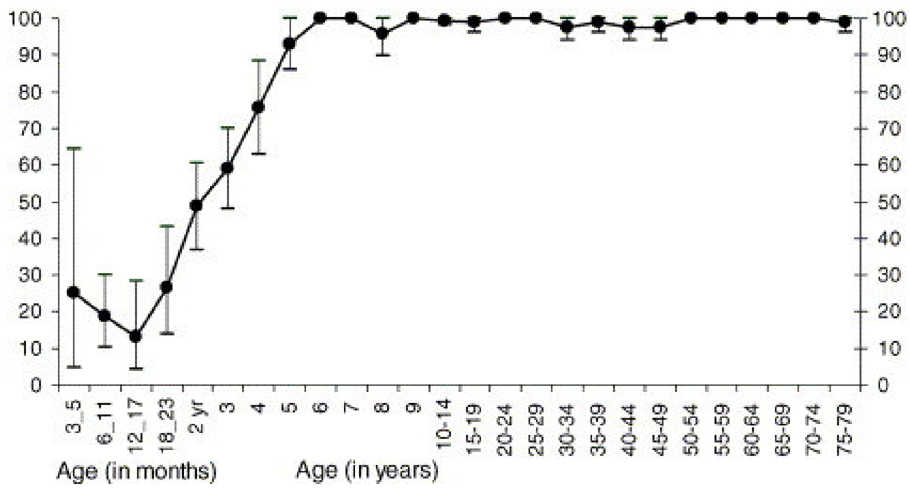

Fig. 1. Age-specific seroprevalence (and 95% confidence intervals) of varicella zoster virus in the general population (0–79 years) in The Netherlands (1995–1996) (for those less than 2 years of age, age is given in months).

3.1.2. Independent predictors for seropositivity of varicella zoster virus

In addition to age group, urbanization of less than 2500 addresses/km^2 versus at least 2500 addresses/km^2 (odds ratio 2.1; 95% CI 1.1–3.7), at least four persons in the household versus less than four persons in the household (odds ratio 1.8; 95% CI 1.1–3.1) and school attendance of both participant and other person(s) in the household versus 'no school attendance or school attendance of either participant or other person(s) in the household' (odds ratio 2.8; 95% CI 1.1–7.0) were independent predictors for seropositivity of varicella zoster virus. Gender, educational level, nursery attendance and country of birth were not independently associated with seropositivity of varicella zoster virus.

3.2. Disease burden of chickenpox

3.2.1. GP-consultations

The average annual incidence of chickenpox estimated from the consultations of GPs amounted to 254 per 100,000 (i.e. 202, 240 and 318 per 100,000 for the years 2000, 2001 and 2002, respectively). The average annual incidence based on chickenpox consultations was highest for 0–4-year-olds and it sharply decreased for older age classes. While a slight increase was observed for 20–34-year-olds, it decreased again afterwards.

3.2.2. Hospital admissions

The average annual incidence of hospital admissions due to chickenpox amounted to 1.3 per 100,000 (main and side diagnosis 2.3) in the period 1994–2001 and varied between 1.1 (2.0) and 1.6 (2.8) per 100,000 per year (Table 1). The incidence was for all years somewhat higher for men compared to women and amounted for the period 1994–2001 on average to 1.6 (2.7) and 1.1 (2.0) per 100,000, respectively.

Table 1.

Age-specific average annual incidence of GP-consultations (2000–2002, per 100,000) and hospital admissions (1994–2001, per 100,000) due to varicella and the hospitalization rate

Year	**GP-consultations 2000–2002**	**Hospital admissions 1994–2001 (main diagnosis)**	**Hospitalization rate (%) (main diagnosis, based on GP-consultations)**	**Number of hospital days (average per admission) (main diagnosis)**	**Hospital admissions 1994–2001 (main and side diagnosis)**	**Hospitalization rate (%) (main and side diagnosis, based on GP-consultations)**
0	3101.8	25.2	0.8[a]	286 (5.8)	39.2	1.3
1–4	3014.5	12.0	0.4	523 (5.6)	22.4	0.7
5–9	908.3	1.9	0.2	122 (6.8)	3.3	0.4
10–14	97.3	0.2	0.2	17 (7.3)	0.4	0.4
15–19	32.1	0.1	0.5	10 (7.4)	0.3	1.0
20–24	46.0	0.6	1.3	45 (7.0)	0.9	1.9
25–29	64.7	0.7	1.0	60 (7.3)	1.0	1.6
30–34	51.0	0.7	1.4	79 (8.4)	1.0	2.1
35–39	21.9	0.5	2.3	45 (7.0)	0.7	3.1
40–44	24.0	0.2	1.0	27 (9.3)	0.3	1.3
45–49	10.9	0.3	2.6	46 (14.3)	0.4	3.9
50–54	7.5	0.1	1.9	12 (8.1)	0.2	2.9
55–59	14.4	0.1	0.8	10 (11.7)	0.2	1.4
60–64	5.8	0.3	5.2	24 (11.1)	0.4	7.7
65–69	6.5	0.2	3.3	18 (13.0)	0.5	7.0
70+	4.6	0.2	5.3	56 (17.2)	0.4	9.1
Total	253.5	1.3	0.5	1379 (6.5)	2.3	0.9

[a] That is 25.2 (per 100,000) hospital admissions divided by 3101.8 (per 100,000) GP-consultations × 100% = 0.8%.

The average age-specific incidence in this period was highest for those less than 1 year of age and those aged 1–4 years of age. For older age classes, it decreased. A slight increase in the incidence was observed for 20–39-year-olds. The slightly higher average annual incidence for men compared to women was observed for all age groups with the exception of those aged 15–19 years (main diagnosis).

3.2.3. Age-specific estimations of hospitalization rate and number of hospital days for varicella

In Table 1, the hospitalization rate is given. The rate is calculated by dividing the age-specific incidence according to GPs by the incidence according to hospital admissions. In addition, the annual number of hospital days are given together with average number of days per admission. In general, both the hospitalization rate and average number of hospital days per admission increases with age. The hospitalization rate was lowest for 5–14-year-olds. The annual number of hospital days was highest among those less than 10 years of age, particularly among 1–4-year-olds.

3.2.4. Deaths due to varicella

In the period 1996–2002, on average two deaths (range 0–4) were registered annually. Of these, 50% occurred among those under 5 years of age.

3.3. Disease burden of herpes zoster

3.3.1. GP-consultations for herpes zoster

The annual incidence of herpes zoster based on GP-consultations amounted to 320–330 (average 325) per 100,000 in the period 1998–2001 (Table 2). The incidence was for all years higher for women (355 per 100,000) compared to men (290 per 100,000).

Table 2.

Age-specific average annual incidence of GP-consultations (1998–2001, per 100,000) and hospital admissions (1998–2001, per 100,000) due to herpes zoster and the hospitalization rate in 1998–2001

Year	**GP-consultations**	**Hospital admissions (main diagnosis)**	**Hospitalization rate (%) (main diagnosis, based on GP-consultations)**	**Number of hospital days (average per admission) (main diagnosis)**	**Hospital admissions (main and side diagnosis)**	**Hospitalization rate (%) (main and side diagnosis, based on GP-consultations)**
0	42.5	1.1	2.7[a]	13 (5.8)	1.3	3.0
1–4	97.5	1.0	1.0	52 (6.4)	1.3	1.4
5–9	170.0	0.7	0.4	59 (9.1)	1.1	0.6
10–14	155.0	0.5	0.3	46 (9.2)	0.8	0.5

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Year	GP-consultations	Hospital admissions (main diagnosis)	Hospitalization rate (%) (main diagnosis, based on GP-consultations)	Number of hospital days (average per admission) (main diagnosis)	Hospital admissions (main and side diagnosis)	Hospitalization rate (%) (main and side diagnosis, based on GP-consultations)
15–19	187.5	0.6	0.3	39 (7.3)	0.8	0.4
20–24	177.5	0.5	0.3	44 (9.7)	0.8	0.5
25–29	185.0	1.0	0.5	100 (8.1)	1.6	0.8
30–34	227.5	0.8	0.4	123 (11.4)	1.4	0.6
35–39	190.0	1.1	0.6	107 (7.8)	1.7	0.9
40–44	337.5	1.0	0.3	90 (7.7)	1.8	0.5
45–49	335.0	1.1	0.3	115 (8.8)	2.4	0.7
50–54	390.0	2.4	0.6	211 (7.7)	4.5	1.2
55–59	547.5	3.8	0.7	277 (8.6)	7.2	1.3
60–64	657.5	4.5	0.7	305 (9.5)	9.3	1.4
65–69	645.0	5.8	0.9	354 (9.6)	13.8	2.1
70–74	745.0	8.5	1.1	423 (14.4)	20.9	2.8
75–79	720.0	13.5	1.9	870 (15.0)	32.5	4.5
80–84	775.0	18.8	2.4	787 (19.2)	46.0	5.9
85+	835.0	19.4	2.3	723 (18)	44.5	5.3
Total	325.0	2.7	0.8	4739 (11.2)	5.8	1.8

[a] That is 1.1 (per 100,000) hospital admissions divided by 42.5 (per 100,000) GP-consultations × 100% = 2.7%.

In general, the incidence increased with age (Table 2). Among those aged 40–79 years, the incidence for women was higher compared to men, while little difference was found for the remaining age groups.

3.3.2. Hospital admissions for herpes zoster

The average annual incidence of hospital admissions due to herpes zoster in the period 1994–2001 was 3.1 per 100,000 (main and side diagnosis 6.8). The incidence was higher in the period 1994–1997 (main diagnosis 3.6 per 100,000; main and side diagnosis 7.8) compared to the period 1998–2001 (2.7 and 5.8 per 100,000; Table 2). The incidence increased with age from 50 to 54 years onwards (Table 2). The incidence of hospital admissions was somewhat higher for women compared to men in all years. The incidence for men and women amounted to, respectively, 3.2 (7.2) and 4.0 (8.4) per 100,000 in the period 1994–1997 and to 2.2 (4.9) and 3.1 (6.6) per 100,000 in the period 1998–2001. The gender difference was mostly due to higher incidence among women in oldest age groups from 80 years and above. For younger age groups, the incidence differed only slightly and was not consistently higher among women.

3.3.3. Age-specific estimations of hospitalization rate and number of hospital days for herpes zoster

The hospitalization rate in the period 1998–2001 using GP-consultations in this period was similar for men and women. The rate was highest among those less than 4 years of age and those 65 years and above, particularly for those aged 75 years and above. Among those aged 5–49 years of age, the hospitalization rate was lowest.

Both the annual number of hospital days and the average number of days per admission increases with increasing age, particularly from 70 years of age onwards.

3.3.4. Deaths due to herpes zoster

In the period 1996–2002, on average 18 deaths per year were registered (range 13–26). Nearly all deaths were among individuals aged 60 years and above (97%).

4. Discussion

Our study suggests that the epidemiology of varicella and herpes zoster in The Netherlands differs from that in other Western countries. This is likely to be relevant when considering VZV vaccination strategies. Firstly, the age-specific profile of VZV shows that the mean age of infection in The Netherlands is rather low in comparison to other countries [7], [8], [9], [10], [11] and [12]. After waning of maternal antibodies in the first year of life, at the age of 3 years almost 60% of the children are VZV seropositive, whilst at least 90% of children aged 5 years has VZV-antibodies. For older children and adults, the seroprevalence in our study is above 97%. The reported seroprevalence according to age was lower for other countries; i.e. 46% for 5-year-olds [7], 85% for 5–9-year-olds [10] and [12], 82–83% for 10–14-year-olds [8] and [9] and 94% for 10–11-year-olds [11]. Secondly, the incidence of general practitioner consultations [13], [14] and [15] and hospital admissions [15] and [16] for varicella are lower in our country compared to those reported by others. For Scotland [13], Spain Basque, Spain Castilla, England and Wales [14] the total incidence of general practitioners consultations ranged between 280 and 570 per 100,000 in comparison to 250 per 100,000 in our country as well as Portugal [14]. For Canada and UK, the GP-consultation rate was higher (about three times with range 1.5–6 times) for all reported age groups with the exception 0–4-year-olds in UK (2345 and 3414 versus 3000–3100 per 100,000 in our study) [15].

The overall incidence of hospitalization amounted to 2.7 per 100,000 for Spain [16]. For UK and Canada, the highest age-specific incidence of about 72 and 38 per 100,000 was reported for 0–1- and 2–4-year-olds in comparison to 39 and 22 for 0- and 1–4-year-olds in our study [15]. For older age groups, the incidence ranged for UK and Canada between 1 and 11 per 100,000 in comparison to 0.3–1 per 100,000 in our study [15]. The hospitalization rate and mean days of hospital stay were rather similar to that reported by others [15].

Based on literature, we hypothesized that the steeper age-specific seroprevalence curve could be associated with nursery attendance and high population density in The Netherlands [7], [8], [12] and [17]. However, in our study, nursery attendance was not independently associated with higher prevalence of VZV-antibodies. In accordance with our findings, Wutzler et al. concluded that higher numbers of pre-school children attending nursery or day care centers in the new federal states of Germany in comparison to old federal states was not associated with higher seroprevalence in childhood [11]. Significant variations in incidence from year to year have been described for various countries [17] and [18]. We had no data on GP-consultations (2000–2002) in similar period as the serum collection (1995–1996). Therefore, we could only use hospital admission data – that showed less variation than GP-consultations – to check whether or not during or shortly before the data collection incidences have been higher and thereby affecting the seroprevalence. The hospital admissions in this period did not show a higher incidence.

In contrast to others who either reported no difference between rural and urban regions [12] and [19] or reported a higher seroprevalence in urban regions [20], we found an unexplained lower seroprevalence in municipalities with very high urbanization degree (i.e. >2500 addresses/km^2). Heininger et al. found a (univariate) higher seroprevalence in adolescents in rural communities compared to urban communities [19]. However, this association was related to a higher number of siblings in rural compared to urban areas. In our study, we found that in addition to urbanization degree also household composition with at least four persons was independently associated with seropositivity for VZV. Also, school attendance of either the participant or other person(s) in the household was an independent predictor for seropositivity of VZV showing the relevance of transmission at schools in varicella epidemiology.

No independent association was found for gender, educational level and country of birth which is in agreement with some other findings [12] and [19]. In a Swiss study, a lower seroprevalence was found for foreign citizens older than 12 years compared to native individuals [7]. The small dip in seroprevalence at 8 years of age is in agreement with the speculation by Aebi et al. that it might represent a transient loss of detectable antibodies by some individuals [7].

Although lower overall incidences of varicella were observed, the shape of the age-specific incidence curve in The Netherlands is similar to other countries, i.e. showing that the incidence of GP-consultations and hospital admissions was highest among children under five [15] and decreased in older individuals. This is consistent with our seroprevalence data, and suggests that pre-school and school-age mixing are important in the transmission of varicella. The small peak observed in GP-consultations and hospital admissions for 25–34-year-olds is likely to indicate contacts with young children who have high infection frequency. The higher hospital admission rate (per GP-consultation) and average length of hospital stay (per case) among elderly confirm increased severity of varicella with increasing age. In combination with high transmission of varicella zoster virus in The Netherlands, this implies that vaccination coverage needs to be high to avoid a risk of increased incidence of severe varicella in older age groups. While MMR coverage is high (95%) in our country, in a recent study, it was reported that only 22% of parents were willing to vaccinated and that 33% that they would not vaccinate their child against varicella [3] and [21].

For herpes zoster, the incidence based on GP-consultations is similar to other reports [15] and [22], while the incidence of hospital admissions is lower than that reported from some other countries [15]. For UK and Canada, the reported incidence of hospital admission was about twice as high for those less than 65 years of age (range UK and Canada for different age groups 1–13 versus 0.8–9.3 per 100,000 for The Netherlands). Among those aged 65 years and above, the incidence of hospital admissions amounted to 148 and 86 per 100,000 for UK and Canada, while for The Netherlands it increased from 13.8 per 100,000 for 70–74-year-olds to a maximum of 46 per 100,000 for 80–64-year-olds.

The disease burden due to herpes zoster is higher in comparison to varicella for the number of GP-consultations (about 30%) but in particular for the number of hospital admissions (200%) and the number of hospital days (>300%). The burden of herpes zoster is lowest for those aged 5–24 years. It is somewhat higher for those less than 5 years of age and those between 25 and 50 years. The burden increases for older adults (50+) and is particularly high for elderly (75+).

Data presented on the epidemiology of varicella zoster will be useful in assessing the desirability of introduction of routine varicella zoster vaccination. A cost-effectiveness analysis for VZV vaccination is not yet available for The Netherlands [23]. An overview of Thiry et al. of cost-effectiveness analyses of VZV vaccination shows that when indirect costs were included, VZV vaccination of infants was cost saving in most cases. When only direct medical cost are considered vaccination is deemed cost effective in most studies [24]. Cost-effectiveness analysis based on dynamic modelling using combination vaccine MMR–V (i.e. Priorix-Tetra, GSK) or ProQuad (Merck)) could show whether cost-effectiveness in the Dutch situation is acceptable considering the often-cited threshold of € 20,000, which is regarded as acceptable in preventive medicine in The Netherlands [25]. Furthermore, given the high disease burden of zoster in The Netherlands, assessing the cost-effectiveness of herpes zoster vaccination with the probably soon available herpes zoster vaccine seems useful [26] and [27].

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