Distribution of health effects and cost-effectiveness of varicella vaccination are shaped by the impact on herpes zoster

Supplementary Information

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1 Data and vaccination schedule

1.1 VZV seroprevalence

The prevalence of VZV by age (Figure 1 of the main text) is based on Dutch serological data, derived from the second cross-sectional population-based serosurveillance study (PIENTER 2), conducted among people aged 0-79 years in the Netherlands in 2006/2007 [1]. The seroprevalence of VZV in the PIENTER2 study is quantitatively very similar to the seroprevalence in the earlier PIENTER1 study (conducted in 1995/1996), indicating little change of the age at infection with VZV over the period 1996-2006 [2]. To avoid the interference of maternal antibodies we only include the 6,251 samples of participants aged 6 months or older. We have not used sentinel General Practitioner (GP) data because it is known that 32% of varicella cases in the Netherlands do not contact their GP [3]. The VZV seroprevalence data is provided in Data Supplement 1.

1.2 Herpes zoster incidence

Sentinel data on the incidence of GP consultations due to herpes zoster (HZ) by age (Figure 1 of the main text) in the period 2002-2011 (based on 7,026 HZ cases) are provided by NIVEL, the Netherlands Institute for Health Services Research [4]. We assume that the majority of HZ patients consult their GP because it is a painful condition. Because HZ complaints are highly specific and accompanied by typical lesions, with a positive predictive value of clinical judgment estimated at 90.8% (95%CI: 87.3% – 94.3%), we expect that misclassification of the diagnosis by the GP occurs infrequently [5, 6]. Therefore, we use the sentinel GP data as a proxy for the total incidence of HZ in the Dutch population. The HZ incidence data is provided in Data Supplement 2. An overview of the data is presented in Figure S1, and shows no clear increase or decrease in any age group over the study period.

1.3 Demography and contact structure

To be able to take into account future population changes, and to enable study of differences in VZV disease burden by birth cohort, we use national demographic data from Statistics Netherlands (CBS) instead of a hypothetical cohort. For the period 1950-2014, we use the actual population size by age on January 1st of each year (http://statline.cbs.nl). For the period 2015-2060, we use CBS population forecast data. From 2060 onwards, we assume a stationary population based on the situation in 2060, due to lack of prognosis data beyond this date. Figure S2 shows the demographic pyramid in 1950, 2000, 2050, and 2100. Data on social
Figure S1. Overview of the yearly herpes zoster incidence in the Netherlands over the period 2002-2011, stratified by age.

Contact patterns are retrieved from the POLYMOD study [7]. We use the mixing matrix of a recent re-analysis of the data (unpublished data; J van de Kassteele, van J van Eijkeren, J Wallinga). Since no contact information is available beyond the age of 79 years, we assume that 80-100 year old persons have the same contact patterns as 79 year old persons. The mixing matrix is available on request.

1.4 Costs and QALY losses

All parameter values regarding the costs and quality-adjusted life-years (QALY) lost of the cost-effectiveness analyses are collected in Data Supplement 3.

1.5 Vaccination schedule

Table S1 shows the current vaccination schedule of the Netherlands. In order not to overburden the population with additional vaccination moments, it is considered likely that potential varicella vaccination (two doses) will be administered either around the age of 1 year (e.g., 11 and 14 months), or the first around the age of 1 year (11 or 14 months) and the second at 4 years.
Figure S2. Overview of the demographic pyramid of the Dutch population in the years 1950, 2000, 2050, and 2100 (blue: males; orange: females). Each bar represents a five-year age group (i.e. 0-4 years, 5-9 years, 10-14 years, etcetera). Demographic data (up to 2014) and projections (from 2015 onwards) are from Statistics Netherlands (CBS). Modelled numbers of VZV infections and herpes zoster cases are based on incidence predictions of the transmission model using the demographic population structure of the Netherlands.

2 Methods

2.1 Model structure

Our model is based on an earlier model by Guzzetta and colleagues [8]. Tenet of the model is that with each immunological boosting event individuals are passed to the next in a sequence of classes with boosted immunity. In the following we denote by $S(t, a)$ the density of uninfected (susceptible) individuals at time $t$ of age $a$, and by $L_i(t, a, u)$ the density of latently infected individuals in class $i$ ($1 \leq i \leq n$) at time $t$ of age $a$ and time since last infection or boosting $u$. The time and age-dependent force of infection is given by $\lambda(t, a)$, and the parameters $z$ and $\rho_i(a, u)$ represent the probability of boosting given an infectious contact, and the age- and time-since-boosting dependent reactivation rate, respectively. The age-dependent mortality rate is given by $\mu(a)$. Using these notational
| Age   | Vaccinations                                      |
|-------|--------------------------------------------------|
| 0 months | HepB-0 (infants with HBsAg positive mother)       |
| 2 months | DTaP-IPV-Hib-HepB-1+PCV-1                        |
| 3 months | DTaP-IPV-Hib-HepB-2                             |
| 4 months | DTaP-IPV-Hib-HepB-3+PCV-2                       |
| 11 months | DTaP-IPV-Hib-HepB-4+PCV-3                       |
| 14 months | MMR-1+MenC                                      |
| 4 years | DTaP-IPV-5                                      |
| 9 years | DT-IPV-6+MMR-2                                  |
| 12 − 13 years | HPV-1+HPV-2 (girls only)                 |

Table S1. Overview of the vaccination schedule of the Netherlands from January 2014 onwards. HepB: hepatitis B vaccine; HBsAG: Hepatitis B surface antigen; DTaP: diphteria-tetanus-acellular pertussis vaccine; IPV: inactivated polio vaccine; Hib: Haemophilus influenzae type b vaccine; PCV: pneumococcal conjugate vaccine; MMR: measles-mumps-rubella vaccine; MenC: meningococcal C-conjugate vaccine; HPV: human papillomavirus vaccine. For details, see http://www.rivm.nl/Onderwerpen/Onderwerpen/R/Rijksvaccinatieprogramma.

conventions, the model dynamics in the absence of vaccination is specified by a set of partial differential equations:

\[
\frac{\partial}{\partial t} + \frac{\partial}{\partial a} \] 
\( S(t,a) = - (\lambda(t,a) + \mu(a)) S(t,a) \)
\[
\left( \frac{\partial}{\partial t} + \frac{\partial}{\partial a} + \frac{\partial}{\partial u} \right) L_i(t,a,u) = - (\rho_i(a,u) + z\lambda(t,a) + \mu(a)) L_i(t,a,u) \)
\[
\lambda(t,a) = \beta \int_0^M c(a,a')\lambda(t,a')S(t,a')da' ,
\]

with appropriate boundary and initial conditions. Notice that in the above we have made use of the so-called short disease approximation [9]. Figure S3 gives a schematic of the model.

Figure S3. Schematic of the transmission and disease model without vaccination. This model is used for estimation of parameters using VZV seroprevalence data and HZ incidence data. After reactivation from one of the latent classes \( (L_i) \) individuals are removed from the system.
In the epidemiological analyses, we assume type I mortality (everybody lives to an exact age of \( M \) years), taking \( M = 100 \) yr. Hence, we have

\[
ex \left( - \int_0^a \mu(a') \, da' \right) = \begin{cases} 
1 & \text{if } a \leq M \\
0 & \text{if } a > M .
\end{cases}
\]

Throughout, we assume frequency-dependent mixing [10, 11]. Demography of the host population is taken into account in the economic analysis, based on the VZV and herpes zoster incidences predicted by the transmission model (see main text and below).

As in earlier studies we assume that the reactivation rate \( \rho(a, u) \) increases exponentially with age \( a \) from \( a_0 = 45 \) yr onwards, and with time since infection or last boosting event \( u \). Hence, we take

\[
\rho_i(a, u) = \rho_0 q^{i-1} e^{\max(\theta_a, a_0) a + \theta_u u}.
\]

In the above, \( \rho_i(a, u) \) represents the reactivation rate in infected persons who have been boosted \( i - 1 \) times, \( \rho_0 \) is the reactivation rate just after infection or boosting, \( \theta_a \) and \( \theta_u \) determine the exponential increase in the reactivation rates, and \( q \) is the overall reduction in the probability of boosting per additional boosting event. Notice that in contrast with the earlier study of Guzzetta and colleagues we slightly simplify the overall reduction of boosting by dropping the factor 2 in the exponent of \( q \), leading to a more transparent interpretation of the parameter \( q \) as the per event reduction in the probability of boosting.

Finally, for computational reasons the number of classes cannot be infinite and must be set to a small predefined value. Here we choose \( n = 5 \), as early analyses showed that the results are not noticeably impacted by increasing \( n \), e.g., to \( n = 8 \) (not shown).

### 2.2 Endemic equilibrium

For the statistical analysis we assume that the population is in endemic equilibrium. At equilibrium, the age- and time-since boosting-dependent partial differential equations can be solved recursively. The solution is expressed in terms of the equilibrium force of infection \( \lambda(a) \), the boosting parameter \( z \), and the reactivation rates \( \rho_i(a, u) \), and is given by

\[
S(a) = S(0) \exp \left( - \int_0^a \lambda(a') \, da' \right)
\]

\[
L_1(a, u) = \lambda(a - u) S(a - u) \exp \left( - \int_{a-u}^a z \lambda(a') + \rho_1(a', a' - a + u) \, da' \right)
\]

\[
L_i(a, u) = z \lambda(a - u) L_{i-1}(a - u) \exp \left( - \int_{a-u}^a z \lambda(a') + \rho_i(a', a' - a + u) \, da' \right),
\]
where \( i = 1, \ldots, n, 0 \leq a \leq a, \) and \( L^*_i(a) = \int_0^M L_i(a, u')du' \) is the age-dependent density of latently infected persons in boosting class \( i. \)

Using the above, the probability \( \pi(a) \) that a person of age \( a \) is infected and seropositive is given by

\[
\pi(a) = 1 - S(a),
\]

and the incidence of herpes zoster at age \( a \) is given by

\[
i(a) = \sum_{i=1}^n \int_0^M \rho_i(a, u')L_i(a, u')du'.
\]

Notice that the above equations for \( L_i \) can be solved recursively in terms of the force of infection \( \lambda(a) \), the reactivation rates \( \rho_i(a,u) \), and other parameters, starting with \( S(a) \) and \( L_1(a,u) \). Hence, an explicit albeit complicated expression for the incidence of herpes zoster (2) can also be obtained. After discretisation, the above equations (1) and (2) form the basis for statistical inference using seroprevalence and herpes zoster incidence data.

### 2.3 Statistical inference

Statistical analysis of the VZV prevalence and herpes zoster incidence data is based on discretised versions of equations (1) and (2). We take a two-step approach in which we first estimate the force of infection and basic reproduction number \( R_0 \) given VZV seroprevalence data, and then estimate the reactivation parameters \( (z, \rho_0, \theta_a, \theta_u) \) using the estimate of the force of infection. This is done to keep computation times within reasonable bounds, and because preliminary analyses indicate \( R_0 \) is strongly identified by the seroprevalence data. Our exposition closely follows earlier studies [12, 13], with the simplification that we assume from the onset that there is a fixed number of \( M = 100 \) age-groups of a year.

#### 2.3.1 Estimation of the force of infection

In the following we use a \( M \times M \) mixing matrix \( wC = q(c_{ij}) \) \( (1 \leq i,j \leq M) \), in which \( q \) is a proportionality parameter reflecting the probability of infection given contact between an infected and susceptible individual. We discretise the population into 100 age-groups of a year. The \( j \)th age group contains the age interval running from \( [j-1,j) \). Within each age group \( j \) the force of infection \( \lambda_j \) is assumed constant. Hence, the probability that an individual of of age \( a \) with \( a \in [j-1,j) \) is infected is given by

\[
\pi(a) = 1 - \exp\left(-(a-j+1)\lambda_j - \sum_{k=1}^{j-1}\lambda_k\right),
\]
and the force of infection $\lambda_i$ is given by

$$\lambda_i = w \sum_j c_{ij} \left[ \exp \left( - \sum_{k=1}^{j-1} \lambda_k \right) - \exp \left( - \sum_{k=1}^{j} \lambda_k \right) \right],$$

(4)

where we have made use of the fact that we assume type I mortality.

If we denote by $1_i$ the indicator variable for seropositivity ($1_i = 1$ if sample $i$ is seropositive and $1_i = 0$ if sample $i$ is seronegative) and by $a_i$ the age of the individual corresponding to sample $i$, then the Bernoulli log-likelihood of the serological data is given by

$$\ell_{VZV}(w|\mathbf{d}_{VZV}) = \sum_{i=1}^{n} \left( 1_i \log(\pi(a_i)) + (1 - 1_i) \log(1 - \pi(a_i)) \right),$$

(5)

where $n = 6,251$ is the number of samples and $\mathbf{d}_{VZV}$ represents the VZV seroprevalence data. Notice that the serological data contains information on the proportionality parameter $w$ (and hence the basic reproduction number, see below), but not the reactivation parameters ($\zeta, \rho_0, \eta_a, \eta_u$).

Now for each particular value of $w$ the set of equations (4) can be solved to yield forces of infection $\lambda_i (1 \leq i \leq M)$. These, in turn, are used to compute $\pi(a_j)$ for all $j$ and subsequently the log-likelihood of the varicella seroprevalence [12, 13, 14]. The value of $w$ that maximises the log-likelihood is the maximum-likelihood estimate $\hat{w}$. Confidence bounds of $\hat{w}$ are determined using the chi-squared approximation of the profile likelihood.

A more intuitive parameter than $w$ is the basic reproduction number $R_0$, which represents the expected number of secondary cases produced by one infected person in a fully susceptible population. $R_0$ is given by the spectral radius of the matrix $w\mathbf{C}$ [9]. Therefore, the maximum likelihood estimate of the basic reproduction number, $\hat{R}_0$, can immediately be identified from the maximum likelihood estimate $\hat{w}$, and below we only present $\hat{R}_0$.

As an aside, we would like to mention that, in principle, the herpes zoster data also contain information on $R_0$. However, maximisation of the joint serological and herpes zoster likelihood (see below) is computationally challenging. Moreover, preliminary analyses suggest that estimates of the basic reproduction number and the forces of infection are strongly identified by the serological data and weakly by the herpes zoster data (results not shown).

### 2.3.2 Estimation of reactivation parameters

In a manner similar to the above discretisation of the probability of infection (3), discretised expressions for the incidence of herpes zoster (2), $\iota_i$, in age groups $i (i = 1, \ldots, M)$ can be obtained [12, 13]. The result is messy, does not yield analytical insight, and is not presented here.
Next, estimates of the reactivation rate parameters \( (q, \rho_0, \eta_0, \eta_a) \) in the full model are obtained by maximisation of the conditional Poisson log-likelihood

\[
\ell_{HZ}(q, \rho_0, \eta_0, \eta_a | \hat{R}_0, \mathbf{d}_{HZ}) = \sum_{i=1}^{M} \left( n_i \log (N_i \iota_i) - N_i \iota_i - \log (n_i!) \right),
\]

where the index \( i \) runs through all age groups, \( n_i \) and \( N_i \) are the number of zoster cases and total number of person-years in age group \( i \), and \( \mathbf{d}_{HZ} = (\mathbf{n}, \mathbf{N}) \) represents the herpes zoster incidence data. The total numbers of zoster cases and person-years in age groups up to 100 years are \( \sum_{i=1}^{100} n_i = 7,021 \) and \( \sum_{i=1}^{100} N_i = 2,049,120 \), respectively.

Parameter estimates and confidence bounds for the estimates are obtained by Markov chain Monte Carlo (MCMC). Specifically, we use a straightforward random-walk Metropolis scheme with updating in blocks and using normal proposal distributions with the current value as mean and standard deviations tuned to achieve acceptance rates in the range of 10% – 50%. Convergence of chains is assessed visually. A sample of \( 2,500 - 5,000 \) is obtained, and parameter estimates presented below and in the main text pertain to the individual sample with highest likelihood. 95% confidence limits of the parameters are obtained by taking the 2.5 and 97.5 percentiles of the sample. All programs for statistical analysis have been coded in Mathematica 9.9.

### 2.4 Vaccination

#### 2.4.1 Model structure

Our vaccination model is based on an extension of the basic model without vaccination (Figure S3), with parameters as estimated above. Hence, the model is fully compatible with the epidemiological data in the pre-vaccination era, and interprets the pre-vaccination era by different boosting models. The model takes into account the possibility of one or two vaccination doses, makes the assumption that a fraction of individuals who have been vaccinated once may not respond at all to the vaccine (i.e. we take primary vaccine failure after one vaccination into account) or may be partially protected against VZV infection (i.e. we take into account that the vaccine provides partial protection after a single dose). After two vaccinations, we assume that a small fraction of individuals still do not respond to the vaccine (i.e. primary vaccine failure), and we assume that those who do respond are fully protected against infection (i.e. there is no partial protection after two doses). Figure S4 gives a (simplified) schematic of the extended model with vaccination. The set of partial differential
equations describing the model dynamics is given by

\[
\begin{align*}
\frac{\partial}{\partial t} S(t,a) &+ \frac{\partial}{\partial a} S(t,a) = - (\lambda(t,a) + \mu(a)) S(t,a) \\
\frac{\partial}{\partial t} L_i(t,a,u) &+ \frac{\partial}{\partial a} L_i(t,a,u) = - (\rho_i(a,u) + z\lambda(t,a) + \mu(a)) L_i(t,a,u) \\
\frac{\partial}{\partial t} V_0(t,a,u) &+ \frac{\partial}{\partial a} V_0(t,a,u) = - (g\lambda(t,a) + \mu(a)) V_0(t,a,u) \\
\frac{\partial}{\partial t} V_i(t,a,u) &+ \frac{\partial}{\partial a} V_i(t,a,u) = - (\sigma_i(a,u) + z\lambda(t,a) + \mu(a)) V_i(t,a,u) \\
\lambda(t,a) &= \beta \int_0^M c(a,a')\lambda(t,a') (S(t,a') + fV_0(t,a')) da'
\end{align*}
\]

with \( i = 1, \ldots, n \) and appropriate boundary and initial conditions. Pulse vaccination at ages \( a_1 \) and \( a_2 \) is included in the above by transferring individuals from classes \( S(t,a) \) to \( V_0(t,a) \) and \( V_1(t,a) \), and from \( V_0(t,a) \) to \( V_1(t,a) \). Hence, for successful primary vaccination we have

\[
\begin{align*}
S(t,a_1^+) &= S(t,a_1^-) (1 - p q_1) \\
V_0(t,a_1^+) &= p q_1 S(t,a_1^-)
\end{align*}
\]

where \( p \) is the vaccination coverage and \( a_1 \) the vaccination age, and \( q_1 \) represents the take of the first vaccination. In a similar manner, the transfer of individuals with successful primary vaccination after the second vaccination and the transfer of individuals who respond to secondary vaccination after unsuccessful primary vaccination are given by

\[
\begin{align*}
V_0(t,a_2^+) &= 0 \\
S(t,a_2^+) &= S(t,a_2^-) (1 - p (1 - q_1) q_2) \\
V_1(t,a_2^+) &= V_0(t,a_2^-) + S(t,a_2^-) p (1 - q_1) q_2
\end{align*}
\]
In words, a fraction \( p q_1 \) of the population will have partial immunity after the primary vaccination bout, while all persons with partial protection after the first vaccination will be vaccinated a second time, resulting in full protection. A fraction \( p (1 - q_1) \) of the population does not respond to the first vaccination (primary vaccine failure), and of those a fraction \( q_2 \) responds to the second vaccination. Hence, primary vaccine failure after two vaccinations occurs in a fraction \( (1 - q_1) (1 - q_2) \) of vaccinated persons.

### 2.4.2 Vaccination scenarios

In the scenario analyses we focus on models that differ by whether or not they include exogenous boosting of immunity by contact of latently infected persons with persons acutely infected (i.e., children with a varicella episode), and by whether or not the vaccine virus is able to reactivate. Scenario A incorporates immune boosting and assumes that there is no reactivation of vaccine virus. Scenario B assumes that there is no immune boosting and no reactivation of vaccine virus. Scenario C assumes that there is immune boosting and reactivation of vaccine virus. Finally, Scenario D assumes that there is no immune boosting but there is reactivation of vaccine virus.

Vaccination studies based on Scenarios A and C are based on parameter estimates of models with full boosting (Model M1 of Table S3), while vaccination studies of Scenarios B and D without boosting are based on models without immune boosting (Model M5 of Table S3). Table S2 gives an overview of vaccination parameters.

### 2.4.3 Numerical integration

Numerical integration of the partial differential equations of the model with vaccination are based on a realistic age-structured (RAS) version of the model, with age- and time-since-boosting classes of 1 year (e.g., [15, 16]). Hence, the partial differential equations (PDEs) reduce to a (large) set of ordinary differential equations (ODEs). Specifically, the PDE for the susceptible class reduces to a set of 100 ODEs for the relative frequencies of susceptible persons in 100 age classes, and each of the PDEs for the latently infected classes reduces to a set of \( 100 \times 100 = 10,000 \) ODEs. At the end of each year, all persons in age class \( i \) and boosting class \( j \) are transferred to age class \( i + 1 \) and boosting class \( j + 1 \). Vaccination in our model is assumed to take place at the beginning of each year.

To numerically solve the resulting set of ODEs efficiently without having to resort to time-consuming integration schemes (e.g., [17, 18]), we assume that the forces of infection \( \lambda_i \) (\( i = 1, \ldots, 100 \)) are constant in a small time interval...
| Parameter | Value | Explanation |
|-----------|-------|-------------|
| $p$       | 0−0.95 | vaccination coverage |
| $f$       | 0.50  | relative infectiousness of breakthrough infection after vaccination |
| $g$       | 0.10  | relative susceptibility of persons with partial vaccine protection |
| $q_1$     | 0.90  | vaccine take after one vaccination |
| $q_2$     | 0.50  | added take after two vaccinations |
| $1 − q_1$ | 0.10  | primary vaccine failure after one vaccination |
| $(1 − q_1)(1 − q_2)$ | 0.05 | primary vaccine failure after two vaccinations |
| $p q_1$   | 0−0.855 | population fraction with partial protection after one vaccination |
| $p(1 − (1 − q_1)(1 − q_2))$ | 0−0.9025 | population fraction effectively protected after two vaccinations |
| $\sigma(a,u)$ | 0 (Scenario A,B), $\rho(a,u)$ (Scenario C,D) | reactivation rate of vaccine virus |
| $z$       | est. (Scenario A,C), 0 (Scenario B,D) | fraction of infectious contacts that would lead to boosting |

Table S2. Overview of vaccination parameters considered in the dynamical modelling. Other parameters are estimated using VZV seroprevalence and HZ incidence data. Transmission parameters $\rho(a,u)$ and $z$ of models with immune boosting (Scenarios A,C) are estimated in model M1 (Table S3, Table S4 for details). Transmission parameters of models without boosting (Scenarios B,D) are estimated in Model M5 (Table S3).
of length $\Delta t$. For constant forces of infection the set of ODEs is linear, and can be solved explicitly and efficiently by matrix operations acting on the state variables ($S_i$, $L_i$, and $V_i$), yielding updated values of the state variables. The updated state variables are subsequently used to obtain updated forces of infection. For sufficiently small $\Delta t$ this procedure yields a proper numerical solution of the RAS model. We tested the performance of these procedures using various values of $\Delta t$, and found that a time step of $\Delta t = 0.25 \ yr^{-1}$ yields a solution that is very close to the one when using a smaller time step of $\Delta t = 0.125 \ yr^{-1}$. Moreover, the equilibrium when running the model without vaccination produces a result that is very close to the explicit solution of the PDEs of the model without vaccination (2). In all simulations we therefore used a time step of $\Delta t = 0.25 \ yr^{-1}$. Run times of the model remain under 4 hours on a standard personal computer for a simulation of 350 years (starting in the year 1850 without vaccination, initiating vaccination in 2020, and ending in the year 2200). All programs have been coded in Mathematica 9.9.

3 Additional results

The essence of our scenario analyses are presented in the main text. Here we present a number of sensitivity analyses, thereby underpinning our results. We give additional results for the estimation procedures (Section 3.1), the epidemiological dynamics in the presence of vaccination (Section 3.2), and the cost-benefit and cost-effectiveness analyses (Section 3.3).

3.1 Parameter estimation and model comparison

Statistical analysis of the serological and zoster incidence data using transmission models indicates that the full model with immune boosting fits the data substantially better than models without age-dependencies in the reactivation rate, models without time-since-boosting effect, or models with soft boosting or no immune boosting at all (Table S3). Maximum likelihood estimates of the parameters of the best-fitting model are presented in Table S4. In all models, the basic reproduction number is estimated at $\hat{R}_0 = 8.7$ (95% CI: 8.1 – 9.3), indicating that VZV is highly infectious during primary infection. Figure S5 shows the estimated force of infection with 95% confidence bounds associated with $\hat{R}_0$. The force of infection increases rapidly from 0.16 $yr^{-1}$ in the youngest children (0-1 year old) to 0.55 $yr^{-1}$ in 4-5 year old children, and then decreases to low values at the age of 20 years. Secondary peaks are observed in 30-40 and 60-70 year old persons, corresponding to high contact rates of persons in these age groups with their children and grandchildren.
| Model       | Description                          | $l^*$ | Parameter estimate (95%CI)                      |
|------------|--------------------------------------|-------|------------------------------------------------|
| M1         | full model                           | -396  | $\hat{x} = 0.51$ (0.48 - 0.53)                  |
|            |                                      |       | $\hat{q} = 0.099$ (0.092 - 0.15)                |
|            |                                      |       | $\hat{\rho}_0 = 0.0045$ yr$^{-1}$ (0.0040 - 0.0047) |
|            |                                      |       | $\hat{\theta}_a = 0.14$ yr$^{-1}$ (0.11 - 0.15)  |
|            |                                      |       | $\hat{\theta}_u = 0.0038$ yr$^{-1}$ (0.0035 - 0.0042) |
| M2         | soft boosting ($q = 1$)              | -439  | $\hat{x} = 0.0033$ (0.0 - 0.069)                |
|            |                                      |       | $\hat{\rho}_0 = 0.0021$ yr$^{-1}$ (0.0020 - 0.0022) |
|            |                                      |       | $\hat{\theta}_a = 0.043$ yr$^{-1}$ (0.040 - 0.048) |
|            |                                      |       | $\hat{\theta}_u = 0.0066$ yr$^{-1}$ (0.0044 - 0.0088) |
| M3         | reactivation independent of age ($\theta_a = 0$) | -661  | $\hat{x} = 0.021$ (0.0 - 0.037)                  |
|            |                                      |       | $\hat{q} = 0.18$ (0.027 - 0.21)                 |
|            |                                      |       | $\hat{\rho}_0 = 0.0011$ yr$^{-1}$ (0.0010 - 0.0012) |
|            |                                      |       | $\hat{\theta}_u = 0.033$ yr$^{-1}$ (0.031 - 0.034) |
| M4         | reactivation independent of time since boosting ($\theta_u = 0$) | -452  | $\hat{x} = 0.0$ (0.0 - 0.051)                   |
|            |                                      |       | $\hat{q} = 0.15$ (0.0 - 0.19)                   |
|            |                                      |       | $\hat{\rho}_0 = 0.0025$ yr$^{-1}$ (0.0024 - 0.0030) |
|            |                                      |       | $\hat{\theta}_a = 0.053$ yr$^{-1}$ (0.051 - 0.060) |
| M5         | no boosting ($z = 0$)                | -439  | $\hat{\rho}_0 = 0.0021$ yr$^{-1}$ (0.0020 - 0.0022) |
|            |                                      |       | $\hat{\theta}_a = 0.043$ yr$^{-1}$ (0.039 - 0.047) |
|            |                                      |       | $\hat{\theta}_u = 0.0063$ yr$^{-1}$ (0.0043 - 0.0089) |

Table S3. Statistical comparison of pre-vaccination models. A hierarchical estimation procedure is employed which first estimates the basic reproduction number using serological data, and subsequently estimates reactivation parameters using herpes zoster incidence data. Shown are maximum likelihood estimates with corresponding 95% confidence bounds. In all models the basic reproduction number is estimated at $\hat{R}_0 = 8.7$ (95%CI: 8.1 - 9.3). $l^*$ denotes the maximised log-likelihood. See text for details.
Figure S5. Estimate of the age-specific force of infection (black line) with associated 95% confidence bands (blue). Notice the strong peak in young children, and secondary peaks in persons aged 30-40 and 60-70 years. The latter result from high contact rates of persons in these age groups with their children and grandchildren.

Figure S6 gives an overview of the serological and zoster incidence data together with fits of the full model with boosting and the model without immune boosting. Both models seem to describe the data adequately, and in particular are able to quantitatively capture the fast-rising VZV seroprevalence from 0% at 6 months to more than 95% at 10 years and over 99% at 40 years. All models also quantitatively seem to capture the observed zoster incidence data well. In a formal comparison, the model with boosting has substantially higher maximised log-likelihood than the model without boosting (-396 with 5 parameters vs -439 with 3 parameters). This is due to the fact that, for the particular parametric form of the reactivation function chosen here and in earlier work [8], the model with immune boosting fits the data better in the age groups with large number of zoster cases (50-80 years; Figure S6). We do not, however, consider this decisive evidence for immunological boosting, as it is possible to obtain even better model fits (also in the absence of boosting) using more complicated age-dependent reactivation rates than the highly idealised one considered here and in previous work [8](results not shown).

Parameter estimates pertaining to the reactivation rate of the best-fitting model (Table S4) indicate that immune boosting is efficient, with each contact between
Figure S6. Overview of data (dots) and model fits (lines). Dots show VZV prevalence (blue) and zoster incidence (orange) data. The sizes of the dots reflect sample sizes. Total numbers of sera and zoster cases are 6,251 and 7,026, respectively. Lines represent maximum likelihood model fits. Solid and dashed lines through zoster incidence data correspond to the full model with immune boosting (Model M1) and the model without immune boosting, respectively (Model M5).

Reactivation rates increase substantially with age after the age of 45 years ($\hat{\theta}_a = 0.14$ yr$^{-1}$, 95%CI: 0.11 – 0.15), and the reactivation rate is suppressed approximately tenfold with each additional boosting event ($\hat{q} = 0.099$, 95%CI: 0.092 – 0.15). The reactivation rate also increases with time since last boosting event ($\hat{\theta}_u = 0.038$ yr$^{-1}$, 95%CI: 0.035 – 0.042), although the impact of time since boosting is much smaller than the impact of age after 45 years.

3.2 Vaccination scenarios

In the main text we investigate the epidemiological dynamics of various vaccination scenarios using the estimated parameters of the models with full and no boosting (Models M1 and M5 of Table S3). Here we first present detailed epidemiological analyses of the main scenarios, including information with respect to the mean age at infection with VZV and the mean age at development of
Parameter Estimate (95%CI) Explanation
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$R_0$ 8.7 (8.1 − 9.3) basic reproduction number

$z$ 0.51 (0.48 − 0.53) fraction of infectious contacts that lead to boosting

$q$ 0.099 (0.092 − 0.15) reduction of the reactivation rate for each additional boosting event

$\rho_0$ 0.0045 (0.0040 − 0.0047) reactivation rate just after infection or boosting (unit: yr$^{-1}$)

$\theta_a$ 0.14 (0.11 − 0.15) increase of the boosting rate with age (unit: yr$^{-1}$)

$\theta_u$ 0.038 (0.035 − 0.042) increase of the boosting rate with time since infection or boosting (unit: yr$^{-1}$)

Table S4. Parameter estimates of the model with full boosting (cf. Table S3, Model M1). This model has the highest statistical support of the models considered.

HZ by birth cohort and per year, and subsequently analyze a scenario with two vaccinations given around the age of 1 year.

### 3.2.1 Mean age at VZV and HZ by birth cohort

To further our understanding of the ages at infection with VZV and development of HZ we investigate the mean ages at VZV infection and HZ development by birth cohort for scenarios considered in the main text. The results are presented in Figure S7.

It appears that major shifts in the age at VZV infection and HZ development are observed only if the vaccination coverage is high (95%). For high coverage, the mean age at infection with VZV increases in all scenarios in the post-vaccination cohorts. This is caused by a reduced circulation and force of infection post-vaccination, which results in higher ages of infection in persons born in the post-vaccination era but who were left unvaccinated. Interestingly, in some cohorts that experience very low infection pressure when they are young, the mean age at infection is increased to the early twenties, implying a potential health hazard for pregnant women.

At the same time, the mean age at development of HZ decreases substantially in scenarios with immune boosting in the post-vaccination cohorts (Scenarios A, C). This is due to the fact the lack of immune boosting results in an earlier onset of HZ in latently infected persons. Overall, the mean age at HZ decreases from approximately 60 years without vaccination to persons in their early and mid fifties. This has two opposing consequences. On the one hand, HZ is usually
a less severe condition in younger persons than it is in older persons [6]. On the other hand, a decrease in the age at HZ shifts many cases to working ages, which has negative consequences in a cost-effectiveness perspective.

Figure S7. Mean age at VZV infection (solid lines) and HZ development (dotted lines) by birth cohort after the introduction of varicella vaccination in 2020. Black: 95% vaccination coverage. Orange: 50% coverage. Blue: 25% coverage. Yellow: 0% coverage. Scenarios, colours, and lines correspond to Figures 2-3 in the main text. See Figure S4 for model structure.

3.2.2 Mean age at VZV and HZ over time

Figure S8 shows the mean ages at infection with VZV and development of HZ over time for the scenarios presented in the main text. For Scenarios A and B the mean age at VZV infection and herpes zoster is substantially affected only if the vaccination coverage is high (95%). At high coverage, the infection pressure is low and this results in a marked shift of the average age at VZV
infection from very young ages (<5 yr) to approximately 15 yr. At the same time, since less persons are newly infected with VZV after the introduction of vaccination, the average age at herpes zoster shows a substantial transient increase (from ≈60 yr in 2020 to >70 yr for Scenario A in 2090 and to >80 yr for Scenario B). In the long run the mean age at infection decreases in Scenario A (to ≈50 yr, i.e. working ages) by the lack of immune boosting. In Scenarios C and D (reactivation of vaccine virus) the mean age at VZV infection also increases, and in Scenario C the mean age at herpes zoster decreases (to 50–55 yr) because of the decrease in immune boosting.

Figure S8. Mean age at VZV infection (solid lines) and HZ development (dotted lines) by year after the introduction of varicella vaccination in 2020. Black: 95% vaccination coverage. Orange: 50% coverage. Blue: 25% coverage. Yellow: 0% coverage. Scenarios, colours, and lines correspond to Figures 2-3 in the main text. See Figure S4 for model structure.
3.2.3 Two-dose vaccination around the age of 1 year

In the main text we assume a two-dose vaccination regime, with the first dose administered at the age of 1 year, and the second at 4 years. This implies that even with high vaccination coverage a large fraction of the population is only partially protected from 1 to 4 years. Here we explore how the results are affected if the two vaccination doses are given around the age of 1 year. Figure S9 shows the results for scenarios without reactivation of vaccine virus (Scenarios A and B). Overall, the results are only marginally affected, with the exception of the high vaccination coverage scenario (95%, black lines) that results in elimination if the two doses are administered around the age of 1 year but not if the second dose is administered at 4 years.

Figure S9. Impact of vaccination in Scenarios A and B (no reactivation of vaccine virus) if two doses of varicella vaccine are administered around the age of 1 year. Solid lines: varicella incidence. Dashed lines: herpes zoster incidence. Black: 95% vaccination coverage. Orange: 50% coverage. Blue: 25% coverage. Yellow: 0% coverage. Colours and lines correspond to Figure 3 in the main text.

3.3 Cost-effectiveness

In the main text we present a stylised figure of a cost-effectiveness analysis of scenarios with high vaccination coverage (95%, Figure 4). In the next section we present full quantitative cost-effectiveness analyses, including scenarios with lower vaccination coverages (Figures S10-S13). We also consider a suite of analyses that ignore the costs and QALYs lost due to herpes zoster (Figure S14), do not incorporate discounting of costs and effects (Figure S15), assume equal
discounting of costs and effects (Figure S16), assume a lower vaccine price (Figure S17), or use alternative ICER thresholds for cost-effectiveness.

### 3.3.1 Vaccination coverage

Figures S10-S11 show quantitative results for the economic scenarios of the main text with high vaccination coverage (95%, Figure 4). Figure S10 gives the net (i.e. cumulative, see main text) costs (in thousands of euros), the net (i.e. cumulative) Quality-Adjusted Life Years (QALYs), and the Incremental Cost-Effectiveness Ratio (ICER) as a function of time. Figure S11 presents the same analyses differently, i.e. it gives for all years the net costs and net QALYs for all four scenarios. Figures S12 and S13 give additional quantitative results for scenarios with intermediate (50%; Figure S12) and low (25%; Figure S13) vaccination coverages.

![Figure S10. Net costs (in thousands of euros), net QALYs, and ICER by year for Scenarios A-D of the main text. Vaccination coverage is 95%. Figure 4 of the main text is based on the data contained in this figure.](image)

Figure S10. Net costs (in thousands of euros), net QALYs, and ICER by year for Scenarios A-D of the main text. Vaccination coverage is 95%. Figure 4 of the main text is based on the data contained in this figure.
Figure S11. The time trajectories of net costs (in millions of euros) and net QALYs (in thousands of QALYs) for Scenarios A-D of the main text. Vaccination coverage is 95%. Scenarios that run into the lower right quadrant are cost-saving (Scenario B), while scenarios in the upper left quadrant yield net health losses for positive net costs (‘paying for health loss’)(Scenario C and Scenario A on the medium-term). The inset show a magnification of the first decades of the vaccination program. Figure 4 of the main text gives a stylised representation of this figure.

Figure S12 shows results for an intermediate vaccination coverage of 50% (instead of 95%). In comparison with the high vaccination scenario of the main text and Figure S10, the impact of vaccination on net costs and QALYs are smaller. As a consequence, scenario B is no longer cost-saving. Scenario B remains cost-effective.

Figure S13 shows results for a low vaccination coverage of 25% (instead of 95%). In comparison with the high vaccination scenario (Figure S10) and intermediate vaccination scenario (Figure S12), the net costs and net QALYs are even lower. Scenario B is not cost-saving (as in the main text), but remains cost-effective.

3.3.2 Ignoring herpes zoster

Figure S14 shows results for a scenario that ignores costs and QALYs of herpes zoster. In this case, the results are identical for all scenarios A-D and varicella vaccination is cost-effective from five years into the vaccination program onward.
3.3.3 No discounting of costs and effects

Dutch guidelines advise discounting of costs at a rate of 4% and life-years gained at a rate of 1.5%. Figure S15 shows results for a scenario with no discounting of costs and effects. In comparison with the main analyses (Figure S10), scenarios that are cost-effective with discounting are now cost-effective 10 – 30 years earlier.

3.3.4 Equal discounting of costs and effects (4%)

To further our understanding of the impact of discounting rates, Figure S16 shows results for a scenario with equal discounting of costs and effects, at a rate of 4%. In comparison with the main analyses (Figure S10), Scenario A is not cost-effective anymore, not even on very long time scales of > 150 years.
Figure S13. Net costs (in thousands of euros), net QALYs, and ICER by year for Scenario A-D with 25% vaccination coverage.

### 3.3.5 Reduced vaccine price (50%)

Figure S17 shows results of cost-effectiveness analyses if the vaccine price is €21.95 (instead of €43.90 in the main text). As expected, this has positive impact on cost-effectiveness as measured by ICER.

### 3.3.6 Alternative thresholds for cost-effectiveness

In all above analyses, we have used an ICER threshold for cost-effectiveness of €20,000. This value, albeit not official, is often used in the Netherlands [19]. We have investigated the impact of alternative ICER thresholds of €50,000-€200,000. In all cases, such strong increases in the ICER threshold lead to marginal widening of the period in which varicella vaccination is cost-effective. Graphically this can be understood by inspection of the ICER in Figures S10-S17 (the black dashed lines). In all figures and scenarios, the ICER decreases strongly in the first few years after start of the vaccination campaign when the
Figure S14. Net value costs (in thousands of euros), net value QALYs, and ICER by year for Scenario A-D with 95% vaccination coverage for varicella only, i.e. all costs and QALYs related to herpes zoster are ignored.

upfront costs of the vaccination campaign are offset by strong health gains due to reduced VZV circulation. In scenarios with immune boosting (Scenario A and Scenario C), there is a similarly strong increase in the ICER after approximately 20 years when the health benefits caused by reduced VZV circulation are nullified by even stronger negative health effects caused by increasing HZ incidence. Altogether, we conclude that the cost-effectiveness of varicella vaccination is dominated by the epidemiological impact of vaccination, and the decision whether vaccination is cost-effective is hardly affected by the specific threshold for cost-effectiveness.
Figure S15. Net costs (in tens of thousands of euros), net QALYs, and ICER by year for Scenario A-D with 95% vaccination coverage without discounting.
Figure S16. Net costs (in thousands of euros), net QALYs, and ICER by year for Scenario A-D with 95% vaccination coverage and equal discounting of costs and effects, at a rate of 4%.
Figure S17. Net costs (in thousands of euros), net QALYs, and ICER by year for Scenario A-D with 95% vaccination coverage (discounted) and vaccine price of €21.95 (i.e. halved compared to main analyses).
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