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Health economic evaluation of varicella vaccination within the Swedish national vaccination programme for children

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About this publication

The Public Health Agency of Sweden has conducted an evaluation of whether to recommend the Swedish government to introduce varicella vaccination in the national vaccination programme for children in a two-dose schedule. The added impact of a catch-up vaccination of older susceptible children and adolescents up to 18 years of age has also been analysed.

The Swedish Communicable Diseases Act (SFS 2004:168 Section 3 and SFS 2012:452) stipulates three criteria to be assessed and presented in support of a proposal for an introduction of a new vaccine into the national vaccination programme for children (1). One of these criteria is an economic evaluation of the cost-effectiveness of the vaccination programme from a societal perspective. This report presents the methods and results from this economic evaluation.

The main target group for this publication is the government of Sweden (the Ministry of Health and Social Affairs) which decides whether to introduce and fund varicella vaccination as part of the national vaccination programme for children.

The publication may also be of interest to health professionals with responsibility for vaccinating children and adolescents, professional societies and the international community with responsibilities for assessing new vaccines.

The analysis was carried out by Frida Kasteng, health economist in the Unit for Analysis at the Public Health Agency of Sweden, in collaboration with a working group consisting of analysts and experts from the Public Health Agency of Sweden and external experts (see Appendix A).

The Public Health Agency of Sweden

Karin Tegmark Wisell

Director-General

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Abbreviations

EQ-5D	EuroQol five dimensions, instrument used to measure health-related quality of life
HTA	Health technology assessment
HZ	Herpes zoster
ICER	Incremental cost-effectiveness ratio, the difference in costs between two interventions divided by the difference in effect
MMR	Trivalent combination vaccine containing live attenuated measles, mumps and rubella viruses
MMRV	Tetravalent combination vaccine containing live attenuated measles, mumps, rubella, and varicella viruses
PHN	Post-herpetic neuralgia
QALY	Quality-adjusted life year, a measure that combines two dimensions of health: length of life and quality of life
SEK	Swedish currency kronor
USD	United States dollar
VAR	Monovalent varicella vaccine
VZ	Varicella zoster
VZV	Varicella zoster virus

Summary

The Public Health Agency of Sweden has conducted an evaluation of whether to recommend the Swedish government to introduce varicella vaccination in the Swedish national vaccination programme for children in a two-dose schedule complemented by catch-up vaccination of older susceptible children. Our analyses suggest that the inclusion of varicella vaccination in the national vaccination programme for children would be a cost-saving strategy from a societal perspective, which together with a catch-up vaccination offer for susceptible older children would result in a fast decline of varicella in Sweden.

Varicella (chickenpox) is caused by the highly contagious varicella zoster virus. In Sweden, the median incidence of infection is around 4 years, and approximately 95% of 12-year-olds have already been infected with the virus. Most children do not need to seek medical care while infected as the infection is often mild. However, varicella in adolescents and adults usually leads to a higher rate of complications in need of medical attention. Once an individual has been infect78ed with varicella, virus remains latent in the body in the nervous system. The virus can then be reactivated later in life and cause herpes zoster.

In the Nordic countries, national child vaccination programmes against varicella have been in place in Finland since 2017 and in Iceland since 2020. Both Denmark and Norway are together with Sweden considering introduction of varicella vaccination and a joint systematic review of safety and effectiveness of available vaccines has been performed.

We have carried out a health economic analysis to assess the cost-effectiveness of including varicella vaccination in the national vaccination programme for children in Sweden, based on an epidemiological transmission model. In the first scenario, varicella vaccination is provided to young children, dose one at age 18 months and dose two at age 7 years. A second scenario is varicella vaccination at age 18 months and age 7 years, together with a catch-up strategy targeting older children with no known history of varicella infection. The control scenario in the model is a setting without any varicella vaccination in the population. Parameter estimates in the model are based on scientific publications, data from Swedish national and regional registries, and national guidelines.

A national varicella vaccination programme, both with and without catch-up of older susceptible children, would result in economic savings from a societal perspective. The cost-savings are primarily due to a reduction in caregiver productivity loss. From a health system perspective, our analysis estimates a cost per quality-adjusted life year at around SEK 200,000 both with and without catch-up vaccination. The annual cost of a national varicella vaccination programme with a 95% coverage rate, including a catch-up strategy over the first 6 years for all susceptible individuals under age 18 without a history of varicella, would be around SEK 135 million per year, using the 2023 average list price of the two

available monovalent varicella vaccines in the calculation, which would decrease to SEK 113 million per year once the catch-up vaccination is completed.

Sammanfattning

Folkhälsomyndigheten har utvärderat huruvida vattkoppsvaccination bör rekommenderas att bli en del av det svenska barnvaccinationsprogrammet i ett tvådosschema, i kombination med ikappvaccination för äldre icke-immuna barn. Våra analyser visar att ett införande av vattkoppsvaccination som del av barnvaccinationsprogrammet skulle vara kostnadsbesparande från ett samhällsekonomiskt perspektiv, och i kombination med en temporär ikappvaccination av äldre icke-immuna barn resultera i en snabb nedgång av vattkoppsinfektioner i Sverige.

Vattkoppor orsakas av det mycket smittsamma varicella-zosterviruset. Medianåldern för infektion i Sverige är runt 4 år och cirka 95 % av alla 12-åringar har redan haft en vattkoppsinfektion. De flesta barn behöver inte söka medicinsk vård vid en vattkoppsinfektion eftersom infektionen ofta är mild. Ungdomar och vuxna som får vattkoppor drabbas i högre grad av komplikationer som kräver vård. Varicella-zosterviruset kvarstår latent i kroppens nervsystem efter en infektion. Det kan reaktiveras senare i livet och orsaka bältros.

Vattkoppsvaccinationen är en del av barnvaccinationsprogrammen i Finland, sen 2017, och i Island sedan 2020. Danmark och Norge överväger att introducera vattkoppsvaccination i sina nationella barnvaccinationsprogram och har i samarbete med Folkhälsomyndigheten sammanställt en litteraturgenomgång av vaccinernas säkerhet och effektivitet.

Vi har genomfört en hälsoekonomisk analys för att skatta kostnadseffektiviteten av att introducera vattkoppsvaccination i barnvaccinationsprogrammet. Analysen baseras på en epidemiologisk transmissionsmodell. I huvudscenariot ges dos ett vid 18 månaders ålder och dos två vid 7 års ålder. I ett andra scenario, kompletteras detta med en temporär ikappvaccination av äldre barn som inte tros ha haft vattkoppor. I kontrollscenariot har ingen i populationen vaccinerats mot vattkoppor. Modellparametrarna baserades på vetenskapliga publikationer, data från svenska nationella och regionala register, samt nationella behandlingsriktlinjer.

Ett nationellt vattkoppsvaccinationsprogram, både med och utan ikappvaccination av äldre icke-immuna barn, skulle leda till kostnadsbesparingar från ett samhällsekonomiskt perspektiv. Besparingarna består huvudsakligen i en minskad frånvaro för vård av barn. Från ett hälso- och sjukvårdsperspektiv visar våra analyser att programmet skulle kosta runt 200 000 kronor per kvalitetsjusterat levnadsår, både med och utan ikappvaccination. Kostnaden skattas till 135 miljoner kronor per år för vattkoppsvaccination som en del av barnvaccinationsprogrammet, med en antagen täckningsgrad på 95 %, samt ett program för ikappvaccination över en tidsperiod på 6 år för icke-immuna barn upp till 18 års ålder. Denna beräkning baseras på nuvarande genomsnittliga listpris för de två monovalenta vattkoppsvacciner som finns tillgängliga i Sverige. Kostnaden per år skattas till 113 miljoner kronor från år 7 när ikappvaccinationen är avslutad.

Background

Varicella, also referred to as chickenpox, is the primary infection caused by the highly contagious varicella zoster virus (VZV). Besides general symptoms of a virus infection such as fever, headache and fatigue, the virus commonly causes skin lesions that typically last for 5-7 days, after an incubation period of 10-20 days. The number of skin lesions may range from only a few to several hundreds. The virus is transmitted through direct contact with vesicular fluid of the skin lesions or indirect contact through inhalation of aerosols from breath (2, 3). In Sweden, the median incidence of infection is around 4 years (4). Around 92-98% of 12-year-olds have been infected with the virus, based on seroprevalence analyses of blood samples (4, 5). Most children do not need to seek medical care while infected as the infection is often mild. However, around 0.2% of children under 15 years with varicella in Sweden require hospitalisation due to complications, primarily bacterial secondary infections in the skin, pneumonia or pneumonitis, and in rare cases sepsis, cerebellitis, meningitis or encephalitis (6). Furthermore, a fourfold increased risk of stroke has been measured in the time period up to 6 months after an acute primary VZV infection in children (from very low levels, the absolute risk is very small) (7). An average of eight individuals per year in Sweden died with varicella as a contributing factor during the period 2013-22. Of these, on average, one death per year affected a child under the age of 15 while 5 occurred in individuals aged 65 or older (6).

Chickenpox in adolescents and adults usually leads to a higher rate of debilitating symptoms and complications (2), with twice the hospitalisation rate of children under 15 years of age (6). Pregnant women are at a higher risk of complications, and infection during the first 20 weeks of pregnancy may affect the development of the foetus (8). Another concern is if the mother develops a rash between days 4 and 5 antepartum to day 2 postpartum, as the infant may get infected. A serious generalized neonatal varicella may develop which leads to death in up to 20% of affected cases unless promptly treated (9). Individuals aged 13 years and older are generally recommended antiviral treatment upon diagnosis (10).

Once an individual has been infected with VZV, virus remain latent in the body in the nervous system. If the immune system of an infected individual is weakened later in life due to age or suppressed because of disease or medication, the virus can be reactivated and cause herpes zoster (HZ), often referred to as shingles. HZ is characterised by painful rashes or blisters on the skin, often as a band on the trunk on one side of the body. In 10-20% of patients, the ophthalmic division of one of the cranial nerves is affected by the virus reactivation. This condition, HZ ophthalmicus, may result in partial or complete acute or chronic vision loss in the affected eye (11). HZ usually heals after 2-4 weeks, but up to 30% of patients, increasingly so with age, develop post-herpetic neuralgia (PHN), persisting nerve pain which may last for a few months or up to several years in some individuals (12). Subsequent exposure to the VZV in individuals who have already had varicella might reduce susceptibility to HZ, so called exogenous boosting (13).

The first varicella vaccine was developed in Japan in the 1970s (14). The USA was the first country to introduce a universal vaccination programme for varicella in 1995 (15). Other countries have since followed. The first programmes consisted of a single dose, but due to observed breakthrough infections following dose one, as of 2005, the USA has recommended a second dose. Population studies in the USA, now with 25 years of follow-up, have not reported any serious adverse effects of the used monovalent and tetravalent vaccines (16). A first dose provides an estimated 81% (95% CI 78-84) protection with some waning over time while a second dose provides a 92% (95% CI 88-94) protection that remains stable over time, based on available follow-up data on post-licensure estimated of vaccine effectiveness (17).

Two monovalent varicella vaccines (VAR) are licensed in Europe: Varilrix® and Varivax®. Both are live, attenuated vaccines derived from the original Japanese strain. The wild-type VZVs are relatively stable genetically (18). Thus, the initially developed vaccines still provide excellent protection. Tetravalent measles, mumps, rubella and varicella (MMRV) vaccines, Priorix-Tetra® and ProQuad®, are provided by the same two pharmaceutical companies. The tetravalent vaccines are not yet available on the Swedish market.

In the Nordic countries, national child vaccination programmes against chickenpox have been in place since 2017 in Finland and since 2020 in Iceland. In Finland, dose one is given at 18 months (VAR) and dose two at 6 years (MMRV) with catch-up vaccination up to 11 years of age (19). Vaccination coverage rates in Finland have been around 86% for dose one (19). In Iceland, the doses were initially given at 12 and 18 months. This was changed in 2023 to dose one offered at 18 months and dose two at age 2.5 years (both VAR)) (20). Other European countries that recommend varicella vaccination as part of their universal child vaccination programmes include Austria, Germany, Greece, Hungary, Italy Latvia and Spain (21), and since the end of 2023, the UK (22).

The Public Health Agency of Sweden initiated a combined assessment of varicella vaccination for inclusion in the national vaccination programme for children, and HZ vaccination as a national vaccination programme for the elderly in 2018. However, due to the COVID-19 pandemic, the assessment was paused for a couple of years and resumed in late 2022. A previous health economic assessment of a national varicella vaccination programme in Sweden based on the same model used in this analysis was published in the scientific literature in 2021 (23). In that analysis the vaccine doses were offered at 12 and 18 months. No catch-up vaccination of older children was considered. The primary scenario in the present analysis includes a catch-up for older children, motivated by epidemiological and ethical reasons to reduce disease transmission as fast as possible upon the initiation of a vaccination programme. This allows for a later provision of the first dose in the national programme, at age 18 months, which has been shown to lead to a better immune response in combination, and a longer time interval until the second dose so that it can be combined with another child vaccination appointment.

Purpose

The purpose of this evaluation was to assess the cost-effectiveness of including varicella vaccination in the national vaccination programme for children in Sweden and assess its budget impact at national and regional levels.

Methods

We carried out a health economic analysis to assess the cost-effectiveness of including vaccination against varicella in the national vaccination programme for children in Sweden. The cost-effectiveness results are presented in terms of cost per quality-adjusted life year (QALY) gained, also commonly referred to as the incremental cost-effectiveness ratio (ICER) in health economic analyses. The base case analysis was carried out from a societal perspective, as stipulated in the cost-effectiveness criteria of the Swedish Communicable Diseases Act (1).

The analysis compares two intervention scenarios with a control scenario. In the first scenario, varicella vaccination is provided to young children, the first dose at age 18 months and the second dose at age 7 years. As a second scenario, varicella vaccination is provided to young children at the same ages as above, together with a catch-up strategy targeting older children with no known history of varicella infection. The control scenario is a setting without any varicella vaccination in the population.

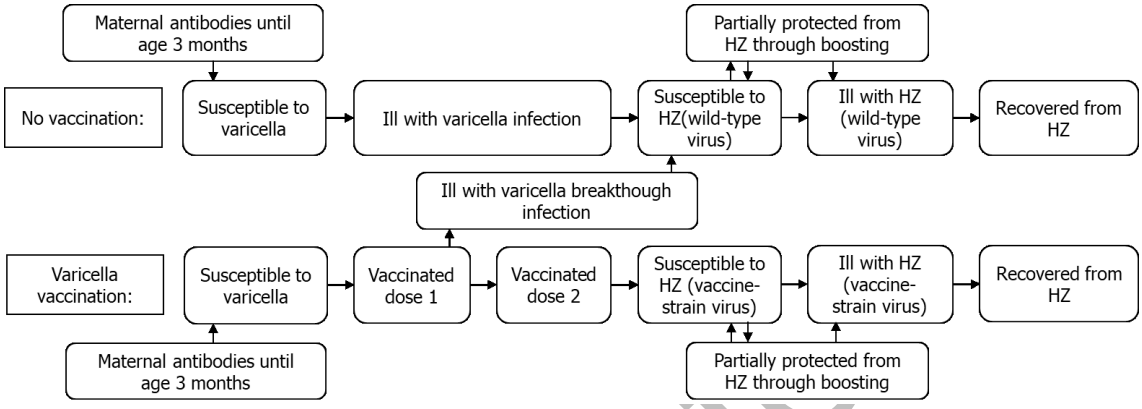
The parameter estimates in the model were based on scientific publications, data from Swedish national and regional registries, and national guidelines for antiviral treatment and prophylaxis for disease (24-26). In cases where published data were missing, assumptions from Swedish clinical expertise have been used (Appendix A).

Epidemiological model

As basis for the health economic analyses, we used an epidemiological model developed in the C programming language (23, 27). The model was a so-called extended age-dependent SIR (susceptible, infected, recovered) model, in which individuals moved between different health states depending on age-specific risk of disease. The flow between health states is illustrated in Figure 1. In each model cycle, individuals could move from one health state to another, stay in the same health state, or die. Movements between health states were defined as differential equations. The cycle length was one day, and the modelled population was assumed to be stable over the modelled time horizon. A constant birth rate of approximately 120,000 children per year was assumed. The main purpose of the model was to study differences between alternative vaccination strategies. This is usually done in population models that are stable, i.e. with constant demography, in order to have a ‘pure comparison’ between the effects of vaccination over time, since demographic variation would affect the spread of disease and the effects of vaccination strategies. Thus, the population used in the model cannot be identical to the actual population in Sweden over the time horizon modelled, although global properties like average life length, total population size and birth cohort size can be approximated. Since many input data such as varicella and HZ incidence and the age dependent contact structure used in the model were from the years 2009-2012, the birth cohort size was set to 120,00 live births per year in order to have a total

population size approximately corresponding to this time period (26). Model outflow was based on natural mortality (28), dependent on age. Quality of life weights and costs of illness were linked to each of the health states and aggregated annually.

Figure 1 Flowchart of the epidemiological model (23, 27)



To include all relevant effects of the vaccination, the time horizon was set at 95 years. This allowed the model to account for the long-term impact of vaccination regarding the health effects that might arise decades after a VZV infection, as the virus remains latent in the body and may cause HZ later in life.

Protection from maternal antibodies was assumed until three months of age, after which susceptibility to VZV was expected. Force of infection and contact rate were calibrated to fit Swedish seroprevalence data for children up to age 12, matched with Finnish data for older age groups (4, 29). Contact patterns were based on a synthetic matrix that described the intensity of total contacts between age groups (30).

VZV incubation time was set at 14 days in the model. The illness and infectious period (at a constant rate) was 7 days. After recovery from infection with VZV, individuals became susceptible to HZ. The reactivation rate of HZ was age-dependent and assumed to occur only once. HZ may recur, most commonly in individuals with haematological malignancies and long-lasting zoster-related pain, but it is relatively rare (12, 31-33). Individuals with HZ transmitted the disease only to a very limited degree in the model. The model allowed for so-called exogenous boosting, i.e. an individual susceptible to HZ who was exposed to the VZV would gain a degree of protection against the incidence of HZ (27).

Vaccinated children received protection against infection corresponding to the effectiveness of the vaccines (17, 34, 35). Varicella vaccination conferred protection against HZ later in life, with the vaccine strain of VZV being less likely to result in HZ later in life compared with the HZ risk from wild-type VZV, as well as leading to a less severe form of HZ (36-39).

Health economic analysis

For the health economic calculation, data from the epidemiological model were extracted to Excel®. The output from the epidemiological model groups the number of individuals in each health state on a yearly basis (0-95) by age group (one-year groups for ages 0-14 years; 10-year groups for ages 15 to 94). To perform the health economic analyses, the data were matched with the corresponding resource use, the unit costs of resources use and the quality-of-life impact. Results were calculated for both a societal and a health system perspective.

The healthcare cost data used in the model were updated to 2023 values using the annual increase in the unit value used to calculate diagnostic-related group weights (40). Both health effects and costs were discounted by 3% annually, according to the Dental and Pharmaceutical Benefits Agency's general advice for health economic evaluations (41). The results were also presented without discounting, as recommended in a proposed European standard for the health economic analysis of vaccination programmes (42). Reporting standards for health economic analyses were used as guidance for the presentation of the results (43). One-way and two-way sensitivity analyses were carried out to assess the sensitivity of results to variations in key input variables.

There is no explicit threshold for when an intervention is considered to be cost-effective in Sweden (44). Priorities in the Swedish healthcare sector are guided by the three main principles of the ethics platform (human dignity, needs and solidarity, and cost-effectiveness) which is part of the Swedish Health and Medical Services Act (45). In general, what is considered to be an acceptable cost of an intervention in relation to its health benefits is a judgement that takes into account also other factors such as the health impact of the intervention and the severity of the condition to be prevented or treated (46). Meanwhile, decisions about national vaccination programmes are based on the three criteria specified in the Swedish Communicable Diseases Act (1).

The cost per QALY framework against which we present our results in this report was based on the methods guidelines from the National Board of Health and Welfare where a cost of SEK 100,000-499,000 is considered a moderate cost per QALY a cost between SEK 500,000-1,000,000 is a high cost per QALY and an cost above SEK 1,000,000 a very high cost per QALY (25).

Parameters and assumptions

Incidence of varicella and HZ

Varicella incidence was based on a study of 957 blood samples from children aged 0-5 years and 12-13 years during the period 2011-2013, this material being the most recent available data for Swedish children (4). The seroprevalence had reached 67% in 5-year-olds and 92% in 12-year-olds. Data from Finland, collected in 1997-1998, were used to estimate seroprevalence in older age groups (29). In this dataset, 93% of 10-14 year-olds and 97% of those aged 15-29 years were

seropositive. It is possible that migration has affected the seroprevalence in later years, however, the number of hospitalisations has remained pretty much the same over time and could serve as a proxy for these seroprevalence data still being valid.

We include HZ incidence in the model due to the impact of varicella vaccination on future HZ susceptibility in vaccinated individuals and the effect of exogenous boosting from VZV on HZ susceptibility. The number of primary care visits due to HZ was used as a proxy for HZ incidence from a study using primary care data for the period 2008-2010, from the Region Västra Götaland (47), one of the larger regions in Sweden population-wise, with nearly one-fifth of the national population (26). We assumed the same age-adjusted incidence rates at national level.

Impact of intervention

Vaccine effectiveness

The effectiveness of varicella vaccination was set at 81% for the first dose with a 2% annual waning rate, and at 92% for the second dose with no waning effect following the second dose (17, 35, 48). We assumed the same effectiveness against varicella for all monovalent and tetravalent vaccines (48-51). Varicella infection following vaccination was referred to as breakthrough infection and assumed to be mild, e.g. not incurring a risk of specialised or inpatient care in the model. We modelled risk of HZ in vaccinated individuals over the 95-year time horizon of the model (52, 53). The HZ reactivation risk with the vaccine strain virus was set at 10% of the risk with wild-type viruses. This figure was derived from follow-up data in varicella-vaccinated children up to the age of 18 years in the USA (36-39). Long-term follow-up in older vaccinated age groups is needed, from different populations.

Vaccination coverage

Vaccination coverage was assumed to be 95% for both the national vaccination programme and the catch-up vaccination (54). This assumption was varied in sensitivity analyses. The same coverage was assumed for dose one and two.

Herd immunity

The model accounted for herd immunity effects of vaccination, since force of infection is proportional to both the number of infected and susceptible individuals. Herd immunity occurs when there are too few susceptible (because of high coverage of vaccination) to sustain disease transmission.

Exogenous boosting

Exogenous boosting refers to protection against HZ due to immune system stimulation after re-exposure to VZV in already infected individuals. In the base case analysis, exogenous boosting is assumed to fully prevent HZ during four years following exposure to VZV among seropositive individuals (27). The impact on the

cost-effectiveness results of alternative impact of boosting are explored in the sensitivity analyses (13, 27).

Resource use and costs

Cost of vaccination

The varicella vaccine is offered in a two-dose schedule. We modelled a national varicella vaccination programme where the first dose is administered at 18 months of age, during an already existing visit to the child health services, and the second dose at age 7 years, by the school health services. The second dose was modelled to be given together with the trivalent measles, mumps and rubella (MMR) vaccine. This vaccine is currently offered during grade 1 or 2, thus, children may be between 6 and 9 years at the time of vaccination. We have chosen the age of 7 years in our model and recommend the varicella vaccination to be given preferably before the end of grade 1. As both visits are already scheduled for vaccine administration in the national vaccination programme for children with another vaccination given at the same time, we assumed that administration costs would encompass only the extra nurse time required for vaccine administration, not the costs of a full visit. Catch-up vaccinations were assumed to occur primarily during already scheduled visits at the child health services and/or the school health services, up to the age of 12 years in the model.

The total vaccination cost included in the cost effective analysis was the average list price per dose of the two monovalent vaccines currently available in Sweden at Apoteket AB (the state-owned pharmaceuticals retailer in Sweden) (Varilrix® at SEK 483,50 and Varivax® at SEK 488,50) (55). Additionally, the labour costs were factored in for an additional 15 minutes of a school nurse's time per administered dose, calculated as SEK 84 (based on the average salary for school nurses in 2022, SEK 41,900 including social fees) (56, 57). The costs did not include the cost for facilities or overheads. Both doses were given as monovalent vaccines in the base case analysis. For the sensitivity analyses, we looked at the second monovalent dose being provided at 5 years of age as well as the use of one of the tetravalent MMRV vaccines for the second dose if administered at age 7 years. Since neither of the two MMRV vaccines are listed in Sweden, we used the average price for the European region from the WHO Mi4A Vaccine Purchase Database (49), approximately SEK 780 (USD 1=SEK 10.6 (average exchange rate 2023 (58))., minus the current list price of the MMR vaccine in Sweden (SEK 124) (55), with no additional administration cost assumed in the analysis since no extra shot was being administered during the visit.

Medical resource use

Healthcare need as a consequence of primary VZV infection was based on a study on the burden of varicella in Sweden published in 2016 where resource use data constituted the average consumption during the period 2007-2012 (59). Although these data are a few years old, we chose to use them as they matched the time

period of the most recent seroprevalence data from Sweden (4). To validate its use in the model, we compared average annual varicella cases (ICD-10 B01) in specialist out-patient and in-patient care for the period 2007-2012 (1,222 specialist out-patient consultations, 236 patients admitted to hospital with varicella as the primary diagnosis, 333 with varicella as primary or secondary diagnosis) with the time period 2014-2019 (1,689 specialist out-patient consultations, 247 patients admitted with varicella as the main diagnosis, 338 with varicella as primary or secondary diagnosis) (6). Admission rates were relatively similar, while specialist consultations were 40% higher during the second time period. The differences may be due to different epidemic profiles during the two time periods, and thus it is arguably more accurate to use resource use data that are closest in time with the available seroprevalence data. Admissions and specialist care visits were approximately halved due to COVID-19 restrictions in the years 2020-2021 and remained at a lower level than before the pandemic in 2022; thus data from the three most recent years were not deemed representative for the long-term perspective of the analysis (6). We included all hospitalisations with varicella as either primary or secondary diagnosis in the analysis, as advised by the external expert group (Appendix A).

Table 1 VZ: Incidence and proportion of patients in need of medical care (4, 6, 59)

Age group	Incidence per 1000 individuals (a)	Primary care VZ, 1 visit per patient	Pharmaceutical need VZ (share of incident cases)	Specialised outpatient care	Hospitalisations (VZ as primary or secondary diagnosis)
0	141.9	4.2%	0%	2.9%	0.4%
1	89.8	13.4%	0%	2.5%	0.5%
2	79.2	16.7%	0%	2.3%	0.4%
3	138.8	8.3%	0%	1.0%	0.2%
4	144.9	6.5%	0%	0.7%	0.1%
5	103.5	6.8%	0%	0.8%	0.2%
6	76.4	6.5%	0%	0.7%	0.1%
7	42.6	7.2%	0%	0.9%	0.2%
8	34.3	5.8%	0%	0.6%	0.1%
9	28.1	4.9%	0%	0.8%	0.2%
10	10.9	6.5%	0%	1.1%	0.2%
11	10.6	6.7%	0%	1.1%	0.2%
12	10.1	7.0%	0%	1.2%	0.3%
13	9.6	7.4%	0%	1.2%	0.3%
14	8.8	8.1%	0%	1.4%	0.3%
15-24	1.9	18.4%	9.2%	4.7%	0.8%
25-34	1.5	19.6%	19.6%	5.8%	1.0%
35-44	1.1	27.1%	27.1%	8.1%	1.4%
45-54	0.4	22.8%	22.8%	4.2%	2.3%
55-64	0.3	29.6%	29.6%	5.5%	2.9%
65-74	0.2	27.8%	27.8%	10.8%	7.6%

Age group	Incidence per 1000 individuals (a)	Primary care VZ, 1 visit per patient	Pharmaceutical need VZ (share of incident cases)	Specialised outpatient care	Hospitalisations (VZ as primary or secondary diagnosis)
74-84	0.2	25.6%	25.6%	9.9%	7.0%
85+	0.1	30.0%	30.0%	11.6%	8.2%

(a) The incidence in the first 3 years in the model does not fully correspond with the incidence data from the seroprevalence study due to the model iteratively fitting the seroprevalence data to the contact matrix

HZ incidence, primary healthcare need, pharmaceutical prescription and risk of PHN and HZ-associated stroke were based on Swedish studies published in 2013 and 2015 using data from 2008-2010 (47, 60). The number of primary care visits for HZ and PHN was based on the estimates used in the two other Swedish economic evaluations for HZ vaccination (23, 61).

In the model, we used in-patient and specialist out-patient care use from the National Patient Register for the corresponding time period (6). In line with the time period selected for varicella, we considered it most relevant to match incidence and resource use data from the same time period in the model. As with varicella, we compared the data we used with more recent data on in-patient and specialist out-patient care. An average annual rate of 3,081 specialist care visits per patient due to HZ in the years 2010-2012 had increased to 3,876 in the period 2017-2019. This corresponds to a more recent analysis of HZ primary care visits which suggests an increase in HZ incidence over the last 15 years (32). Meanwhile, in-patient admission with HZ as the main diagnosis went from an average of 624 in 2008-2010 to 567 in 2017-2019. The COVID-19 pandemic did not cause a change in treatment patterns (3,626 specialist out-patient consultations and 517 in-patient admissions with HZ as the main diagnosis on average per year in 2020-2021) (6). We only included hospitalisation with HZ as the primary diagnosis in the calculations, as advised by the external project reference group (Appendix A).

Table 2 HZ: Incidence and proportion of patients in need of medical care (6, 47, 60)

Age group	Incidence per 1000 individuals	Primary care HZ, 1 visit per patient	Pharma-ceutical need HZ (share of incident cases)	Specia-lised outpatient care HZ	Hospital-isations, HZ as primary diagnosis	HZ-related stroke risk
0-14	1.1	100%	0%	7.1%	1.0%	0.0000%
15-24	1.2	100%	45%	8.2%	0.9%	0.0000%
25-34	1.2	100%	89%	10.3%	1.0%	0.0000%
35-44	1.7	100%	89%	9.6%	1.1%	0.0000%
45-54	2.7	100%	89%	8.7%	1.0%	0.0000%
55-64	4.2	100%	89%	11.9%	1.3%	0.0002%
65-74	6.0	100%	89%	10.7%	1.8%	0.0007%
75-84	7.9	100%	89%	10.9%	3.0%	0.0018%
85+	9.6	100%	89%	10.7%	5.7%	0.0040%

Table 3 PHN: Incidence and proportion of patients in need of medical care (47)

Age group	HZ incidence/ 1000 person-years	Primary care PHN, 5 visits per patient	Pharmaceutical need PHN
0-14	1.1	3.0%	0%
15-24	1.2	3.0%	73%
25-34	1.2	3.0%	73%
35-44	1.7	3.0%	73%
45-54	2.7	4.2%	79%
55-64	4.2	5.8%	84%
65-74	6.0	7.9%	93%
75-84	7.9	12.3%	85%
85+	9.6	13.7%	82%

Cost of care

For both varicella and HZ, the unit costs of primary care visits were provided from the 'Cost-per-patient' database (data shared by the statistics unit of the Swedish Association of Local Authorities and Regions) (62). The unit cost of specialised out-patient care and hospitalisations was extracted directly from the online records of the same database (62). Average costs over the years 2019-2021 were updated to 2023 values, as previously described.

We calculated the total cost for varicella and HZ by multiplying the average cost per visit/admission by the average number of visits/admissions per patient in each group. These data points were extracted from the online database of diagnoses in in-patient and specialised open care provided by the National Board of Health and Welfare (6). Information on pharmaceuticals prescribed was derived from national guidelines (10, 63) and expert advice, with the costs being current list prices (55).

Table 4 VZ: Medical unit costs (SEK) (6, 10, 55, 62)

Age group	Primary care visit	Drugs VZ (valaciclovir 500 mg, 42 pcs)	Specialised out-patient care visit	In-patient admission	Mean days admitted to hospital
0-14	1,280	-	4,839	71,724	3.5
15-64	1,640	123	5,034	60,154	3.3
65+	1,937	123	5,303	192,923	10.7

Table 5 HZ: Medical unit costs (SEK) (6, 55, 62, 63)

Age group	Primary care visit	Drugs HZ (valaciclovir 500 mg, 42 pcs)	Drugs PHN (amitriptylin 10 mg, 100 pcs + 25 mg, 100 pcs times 3) (a)	Specialised out-patient care visit	In-patient admission	Mean days admitted to hospital
0-14	1,779	-	-	5,134	61,382	3.8
15-64	1,843	123	348	5,843	61,382	3.8
65+	1,846	123	348	7,077	75,019	5.6

(a) Alternative treatments include gabapentin and topical treatment with lidocaine or capsaicin

Productivity losses (indirect costs)

Indirect costs were included in the analysis in the form of productivity losses in case of illness. The occupational rates by age group were based on year 2022 statistics (64). The cost of productivity losses was calculated on the basis of an average monthly salary in 2022 of SEK 33,700 (57) and the statutory employers' fee of 31.42% (56). This inferred a productivity loss of SEK 44,289 per month, or SEK 2,109 per working day. The average length of the productivity loss in the model differed among age groups depending on age-specific disease severity states. For varicella, information on caregiver productivity loss was derived from days of caregiver leave reported to the Swedish Social Insurance Agency. We used the average annual rates over the period 2011-2019 (65). A division of this data with the annual number of cases year based on the incidence rates from the epidemiological model indicates that caregiver leave was reported for on average 41% of estimated incident cases in children over the period 2011-2019 (range 31-51%). The proportion of registered cases of caregiver leave per incident case was calculated for 3-year age intervals as it varied year by year, probably due to varying epidemiological patterns (Table 6). For older individuals with varicella and sick leave due to herpes zoster, the days of illness were based on available estimates from the literature paired with expert advice (66).

Table 6 VZ: Indirect costs (57-59, 64)

Age group	Share of registered caregiver leave (VAB) per estimated incident cases	Days caregiver leave per registered (VAB) case	Employment rate (64)	Average illness duration	Average days sick leave	Unit cost per day
0	0%	-	-	-	-	2,109
1	39%	3.5	-	-	-	2,109
2	39%	3.5	-	-	-	2,109
3	39%	3.5	-	-	-	2,109
4	43%	3.4	-	-	-	2,109
5	43%	3.4	-	-	-	2,109
6	43%	3.4	-	-	-	2,109
7	48%	3.4	-	-	-	2,109

Age group	Share of registered caregiver leave (VAB) per estimated incident cases	Days caregiver leave per registered (VAB) case	Employment rate (64)	Average illness duration	Average days sick leave	Unit cost per day
8	48%	3.4	-	-	-	2,109
9	48%	3.4	-	-	-	2,109
10	30%	3.4	-	-	-	2,109
11	30%	3.4	-	-	-	2,109
12	30%	3.4	-	-	-	2,109
13	2%	3.7	-	-	-	2,109
14	2%	3.7	-	-	-	2,109
15-24	-	-	31%	4	1.2	2,109
25-34	-	-	82%	4	3.3	2,109
35-44	-	-	87%	4	3.5	2,109
45-54	-	-	88%	4	3.5	2,109
55-64	-	-	77%	4	3.1	2,109
65-74	-	-	19%	4	0.8	2,109
75-84	-	-	0%	4	-	-
85+	-	-	0%	4	-	-

Table 7 HZ: Indirect costs (57, 58, 64, 66)

Age group	Employment rate	Average illness duration	Average days sick leave	Unit cost per day
0-12	84% (Caregiver)	4	3.4	2,109
13-14	0%	4	0	-
15-24	31%	4	1.2	2,109
25-34	82%	4	3.3	2,109
35-44	87%	4	3.5	2,109
45-54	88%	4	3.5	2,109
55-64	77%	5	3.9	2,109
65-74	19%	5	1.0	2,109
75-84	0%	5	0	2,109
85+	0%	5	0	2,109

Health-related quality of life

Table 8 presents the QALY loss applied in the model for each respective age group and disease. QALY reduction due to varicella was based on estimates from a British study (67). The average duration and proportional utility loss due to different degrees of pain associated with HZ and PHN was derived from the same study (68, 69). This percentile utility loss was multiplied with the age-adjusted utility for the general population in Sweden (70). Furthermore, a UK register study

on the burden of PHN was used to quantify the QALY loss due to HZ and PHN (68).

Table 8 VZ, HZ and PHN: Average annual QALY reductions per episode (47, 67-71)

Age group	QALY loss VZ primary infection	QALY loss VZ breakthrough infection	QALY loss HZ (month 1)	QALY loss PHN	Total QALY loss per HZ case
0-14	0.003	0.001	0.007	0.231	0.011
15-44	0.004	0.002	0.007	0.231	0.011
45-54	0.004	0.002	0.007	0.221	0.017
55-64	0,004	0.002	0.008	0,214	0.027
65-74	0.004	0.002	0.010	0.209	0.035
75-84	0.004	0.002	0.011	0.205	0.042
85+	0.004	0.002	0.011	0.201	0.043

Tables 9 and 10 list the input parameters used to calculate the QALY loss values applied in the model.

Table 9 HZ and PHN: Basis for calculation of QALY loss (67-70)

Age group	Mean utility Swedish population	Utility mild pain	Utility moderate pain	Utility severe pain	Mild HZ pain	Mode-rate HZ pain	Severe HZ pain	Duration pain HZ without persisting pain (months)
0-49	0.88	0.91	0.71	0.32	24%	4%	8%	1
50-59	0.83	0.91	0.71	0.32	24%	4%	8%	1
60-69	0.80	0.91	0.71	0.32	41%	5%	9%	1
70-79	0.79	0.91	0.71	0.32	41%	5%	9%	1
80-89	0.77	0.91	0.71	0.32	41%	5%	9%	1

Table 10 PHN: Basis for calculation of QALY loss (cont.) (67-70)

Age group	Persisting pain following HZ	Mild PHN pain	Moderate PHN pain	Severe PHN pain	Duration mild PHN pain (months)	Duration moderate PHN pain (months)	Duration severe PHN pain (months)
0-49	3%	42%	49%	9%	6.7	10	12.5
50-59	9%	42%	49%	9%	6.7	10	12.5
60-69	12%	42%	49%	9%	6.7	10	12.5
70-79	17%	42%	49%	9%	6.7	10	12.5
80-89	20%	42%	49%	9%	6.7	10	12.5

Sensitivity analyses

In order to investigate the robustness of the results from our analysis, we conducted several sensitivity analyses.

Table 11 Parameters varied in sensitivity analyses

Parameter	Base case	Alternative values in sensitivity analyses
Timing of dose 2	7-year-olds	5-year-olds
Vaccination programme coverage	95% (54)	75%, 85%
Vaccine effectiveness HZ	10% the HZ risk of wild-type VZV (36)	20% the HZ risk of wild-type VZV (39)
Exogenous boosting (protection against HZ after VZV exposure)	100% during 4 years (27)	30% during 20 years (13) 100% during 30 years (27)
Assumed vaccine price following price negotiation	Average of current list prices (SEK 486) (55)	70%, 50%, 30% of current list price average
Type of vaccine	Monovalent VAR (SEK 486) (55)	Tetravalent MMRV (SEK 656 (a)) when dose 2 at age 7 (55, 72)
Vaccine administration cost	SEK 84 (56, 57)	SEK 42, SEK 168
Added cost of information campaign during first 2 years	Not included	SEK 10 million (73)
Cost of care	Unit costs from national/regional cost databases (62)	50%, 200%
Discount rate QALYs	3% (41)	0%, 5% (41)
Discount rate costs	3% (41)	0%, 5% (41)

(a) Average indicative price (SEK 780) (72) minus cost of MMR vaccine (SEK 124) (55) (no vaccine administration cost assumed)

Budget impact analysis

Based on output from the cost-effectiveness model, we present an assessment of costs and potential cost-savings at national and regional levels.

The budget impact of a national varicella vaccination programme is presented as costs during the first 10 years following an introduction of varicella vaccination with dose one at 18 months of age and dose two at 7 years of age, together with catch-up vaccination for older susceptible children and adolescents during already scheduled visits to the child health services or the school nurse. Scheduled vaccinations in the child vaccination programme take place up till the age 16 years. We assumed that only a limited number of adolescents aged 16 and 17 years will need to be vaccinated outside of a scheduled vaccination visit. We have therefore not assumed any additional administration cost for this group of adolescents.

The number of children needed to be vaccinated per year as part of the national vaccination programme was based on (95% of) the 2022 birth cohort. The demand for catch-up vaccination in older children was based on the number of susceptible children in the age groups to be offered catch-up vaccination during already scheduled visits in the model, as well as up to 5% of children aged 13 or older. A 95% coverage was assumed also for this group in combination with 10% extra doses for children who have had asymptomatic or very mild varicella, and therefore may be classified as susceptible by reporting no history of varicella.

The estimation included the cost of administering the vaccine but no other programme implementation costs such as training of healthcare staff or information to the public. In the budget, calculations were based on provision of the monovalent vaccines at all vaccination points since the MMRV vaccines are currently not available on the Swedish market. The budget impact is presented with different vaccine price assumptions (70%, 50% 30% of the current average list prices). The budget impact of future years has not been discounted (74).

Result

Cost-effectiveness

Base case results

In our first scenario, varicella vaccination is provided to young children at the ages 18 months (dose 1) and 7 years (dose 2), without a catch-up strategy for older children. The total discounted cost of a vaccination programme over the 95-year time horizon of the model was estimated at SEK 3.8 billion with the current list price of the vaccine. Total health system costs over the length of the modelled period were estimated at SEK 2.3 billion (the net cost savings due to reduced healthcare costs subtracted from the cost of the vaccination programme). Total societal cost-savings were estimated at SEK 7.5 billion. Nearly 80% of the estimated cost-savings can be attributed to averted caregiver productivity loss, due to a reduced need for parents to be off work to care for children with varicella.

The programme would be cost-saving from a societal perspective due to its large impact on reducing caregiver productivity loss. The cost per QALY gained from a health system perspective was estimated at SEK 203,000 per QALY gained. The total number of QALYs saved over the 95 years modelled was estimated at 11,300 (Table 12).

Table 12 Total programme costs and cost consequences, 95-year time horizon, scenario 2 (vaccination of children at age 18 months and 7 years (SEK million)), Cost/QALY (SEK)

Category	No vaccination	Vaccination	Difference	Cost difference	Share of cost-savings
Vaccination programme		3,837	3,837	+100%	
Direct costs of illness (VZ)	1,164	132	-1,032	-89%	9%
Direct costs of illness (HZ)	4,668	4,169	-499	-11%	4%
Indirect costs of illness (VZ)	10,035	1,007	-9,027	-90%	79%
Indirect costs of illness (HZ)	3,584	2,773	-811	-23%	7%
Total costs (health system)	**5,832**	**8,138**	**2,306**	**+40%**	
Total costs (societal)	**19,451**	**11,919**	**-7,532**	**-39%**	
Total QALYs	**-35,720**	**-24,374**	**11,346**		
Cost/QALY (health system perspective)			**SEK 203,254**		
Cost/QALY (societal perspective)			**Cost-saving (SEK -0.66 million)**		

In scenario two, varicella vaccination is provided to young children, together with a catch-up strategy targeting older children up till age 12 with no known history of varicella infection. In this scenario, the total discounted cost of a vaccination programme over the 95-year time horizon of the model was estimated at SEK 4.2 billion. A programme with catch-up vaccination would result in an estimated 12,400 QALYs saved over the period modelled. It would be cost-saving from a societal perspective, with a cost per QALY gained of SEK 206,000 from a health system perspective (Table 13).

Table 13 Total programme costs and cost consequences, 95-year time horizon, scenario 1 (vaccination of children at age 18 months and 7 years + catch-up vaccination of susceptible children up to 12 years) (SEK million), Cost/QALY (SEK)

Category	No vaccination	Vaccination	Difference	Cost difference	Share of cost-savings
Vaccination programme		4,233	4,233	+100%	
Direct costs of illness (VZ)	1,164	48	-1,116	-96%	9%
Direct costs of illness (HZ)	4,668	4,115	-553	-12%	4%
Indirect costs of illness (VZ)	10,035	221	-9,814	-98%	79%
Indirect costs of illness (HZ)	3,584	2,704	-880	-25%	7%
Total costs (health system)	**5,832**	**8,396**	**2,563**	**+44%**	
Total costs (societal)	**19,451**	**11,320**	**-8,131**	**-42%**	
Total QALYs	**-35,720**	**-23,284**	**12,436**		
Cost/QALY (health system perspective)			**SEK 206,137**		
Cost/QALY (societal perspective)			**Cost-saving (SEK -0.65 million)**		

A catch-up vaccination of children up to age 12 years on top of a vaccination programme is cost-saving per se from a societal perspective. The societal cost-savings of catch-up vaccination were estimated at SEK 600 million (Table 14). The cost per QALY gained of the catch-up vaccination was estimated at SEK 237,000.

Table 14 Total incremental programme costs and cost consequences, 95-year time horizon, catch-up vaccination of susceptible children up to 12 years (SEK million), Cost/QALY (SEK)

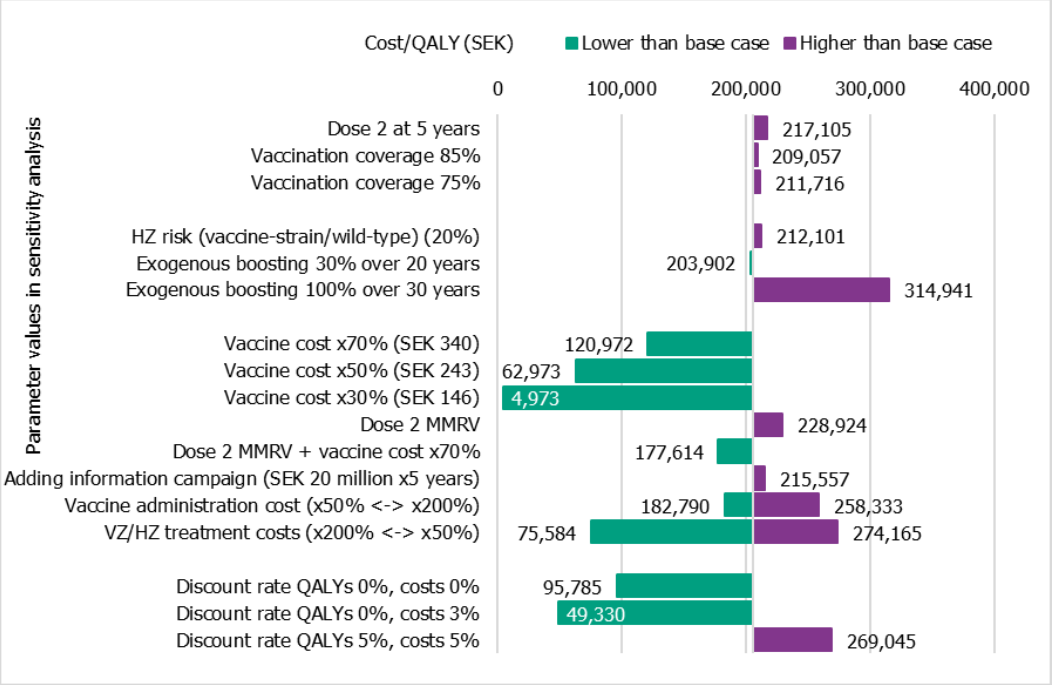
Category	No catch-up (scenario 1)	Catch-up (scenario 2)	Difference
Vaccination programme	3,837	4,233	396
Direct costs of illness (VZ)	132	48	-84
Direct costs of illness (HZ)	4,169	4,115	-54
Indirect costs of illness (VZ)	1,007	221	-786
Indirect costs of illness (HZ)	2,773	2,704	-69
Total costs (health system)	**8,138**	**8,396**	**258**
Total costs (societal)	**11,919**	**11,320**	**-599**
Total QALYs	**-24,374**	**-23,284**	**-1,090**
Cost/QALY (health system perspective)			**SEK 236,697**
Cost/QALY (societal perspective)			**Cost-saving (SEK -0.5 million)**

Sensitivity analyses

From a societal perspective, the vaccination programme remained cost-saving at all changes in key parameters listed in the figure (including an assumption that caregiver time off/sick leave was divided by four). Therefore, sensitivity analyses are not presented for the societal perspective but only from a health system perspective. Figure 2 provides an overview of how the cost per QALY gained from a health system perspective changed with variation of key parameters. The sensitivity analyses were carried out for scenario two, a vaccination programme with a catch-up strategy.

Providing the second dose at age 5 years resulted in a similar cost per QALY. Furthermore, reduced vaccination coverage rates to 85% or 75% did not greatly influence the cost effectiveness results, however, lower coverage rates increase the risk for minor outbreaks should the virus be introduced in a group with many susceptible individuals. A higher impact of exogenous boosting resulted in a higher cost per QALY in our analysis, while different assumption on the vaccine cost, treatment cost and discount rates affected the cost per QALY to different degrees in both directions. Yet, the cost per QALY remained moderate to low with all the variations assessed.

Figure 2 Sensitivity analyses health system perspective, scenario 2 (vaccination at ages 18 months and 7 years with catch-up vaccination up to age 12 years), base case cost per QALY gained (y-axis) SEK 206,137



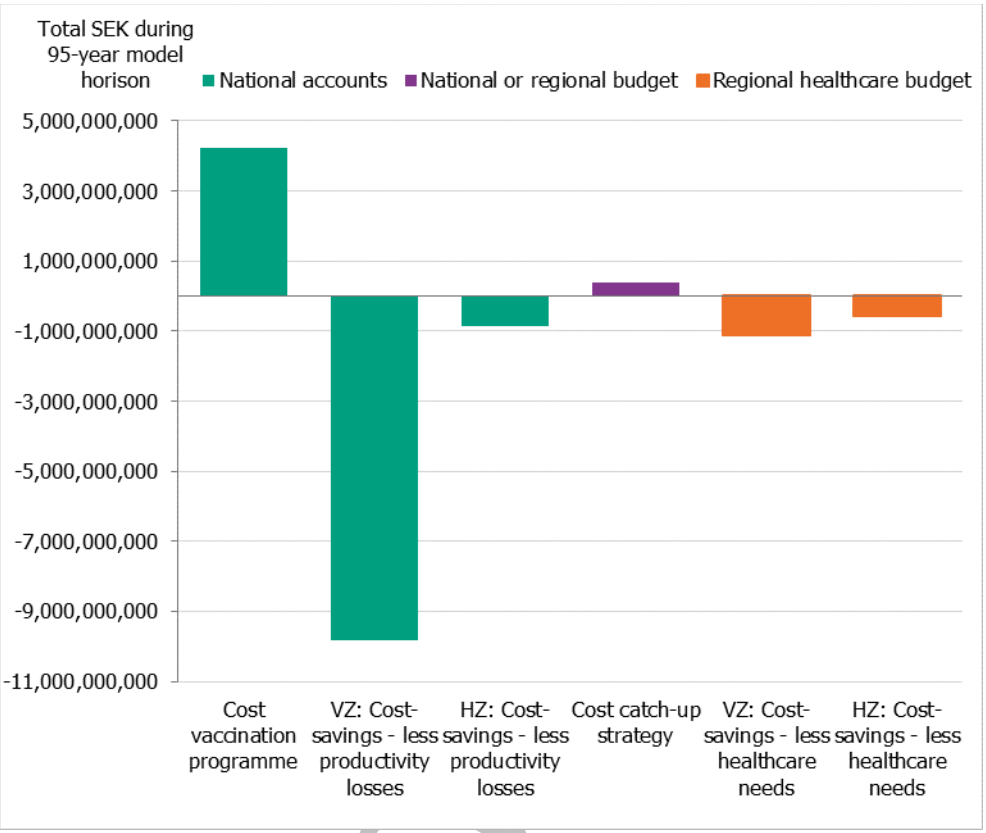
Budget impact

Distribution of cost and cost-savings at national and regional levels

We assume that the cost of vaccination would be funded from the state budget for a national vaccination programme. The increased time use for child health and school nurses due to provision of an additional vaccination in the programme is also included under the national accounts and not the regional healthcare budget, based on the assumption that this cost will be reimbursed by the state as part of the overall programme funding. The cost of a catch-up strategy may be funded either by the national budget or regional healthcare budgets (Figure 3).

The cost-savings due to reduced productivity losses would affect the national accounts and the Swedish social insurance system. From a regional perspective, a varicella vaccination programme would result in a decrease in healthcare resource utilisation due to varicella and HZ and thus long-term net cost-savings at the regional level when the vaccination programme is nationally funded.

Figure 3 Overview of discounted cost and cost-savings as a result of the vaccination programme at national and regional levels, 95-year time horizon, scenario 2 (vaccination of children at age 18 months and 7 years + catch-up vaccination up to age 12 years)



Tables 15 and 16 present the discounted cost and cost consequences extracted from the model at different time periods for the two scenarios with and without catch-up vaccination. Due the discount rate applied in the model, the additional costs and cost-savings per year diminishes over time. The model estimates indicate that a varicella vaccination programme both with and without a catch-up strategy for older susceptible children is cost-saving from a societal perspective already from the initial years due to the foreseen reduction in varicella incidence and consequently in averted production loss for caregivers.

Although the overall averted healthcare costs due to a reduction in varicella incidence with a national varicella vaccination programme would lead to cost-savings in the longer term, financing a temporary catch-up strategy from the regional healthcare budgets would result in a net cost at the regional level during the first six years as the estimated cost of catch-up vaccination would exceed the averted healthcare cost in the short term (Table 16).

Table 15 Discounted cost and cost-savings at national and regional levels from a societal perspective as a result of a vaccination programme (scenario 1, no catch-up) at different time horizons (million SEK)

Cost category	Cumulative year 5	Cumulative year 15	Cumulative year 45	Cumulative year 95
Cost vaccination programme (a)	+307	+1,238	+2,925	+3,837
VZ: Averted productivity losses	-670	-2,834	-6,850	-9,027
HZ: Averted productivity losses	+0	-25	-228	-811
Cost difference national level	**-362**	**-1,621**	**-4,153**	**-6,001**
VZ: Averted healthcare costs	-85	-332	-786	-1,032
HZ: Averted healthcare costs	+4	+12	-87	-499
Cost difference regional level	**-82**	**-321**	**-873**	**-1,531**
Total cost difference	**-444**	**-1,942**	**-5,026**	**-7,532**

(a) Vaccination of children at age 18 months and 7 years, no catch-up

Table 16 Discounted cost and cost-savings at national and regional levels from a societal perspective as a result of a vaccination programme (scenario 2, including catch-up vaccination up to age 12 years) at different time horizons (million SEK)

Cost category	Cumulative year 5	Cumulative year 15	Cumulative year 45	Cumulative year 95
Cost vaccination programme (a)	+307	+1,238	+2,925	+3,837
VZ: Averted productivity losses	-1,265	-3,615	-7,635	-9,814
HZ: Averted productivity losses	+3	-22	-264	-880
Cost difference national level	**-955**	**-2,399**	**-4,974**	**-6,857**
Cost catch-up programme (b)	+345	+395	+395	+395
Cost national or regional level	**+345**	**+396**	**+396**	**+396**
VZ: Averted healthcare costs	-149	-415	-869	-1,116
HZ: Averted healthcare costs	+8	+20	-102	-553
Cost difference regional level	**-141**	**-396**	**-971**	**-1 669**
Total cost difference	**-750**	**-2,399**	**-5,550**	**-8,131**

(a) Vaccination of children at age 18 months and 7 years
(b) catch-up vaccination of susceptible children aged up to 12 years

Vaccination programme budget estimation

The budget impact of the vaccination programme including a catch-up strategy, during its first 10 years was estimated at SEK 135 million annually during the first 6 years and thereafter at SEK 113 million annually (Table 17). This estimation included dose one of the vaccination programme provided to an estimated 98,800 children (95% of 104,000 children born in 2022) and a catch-up vaccination with approximately 140,000 doses given per year in the first four years, decreasing to around 110,000 in year 6. The budget estimate for the catch-up strategy is here based on all susceptible children up to age 18 years.

In year 6, approximately one quarter of the children in the vaccination programme would be given their second dose at the same time as the catch-up vaccination

would be wrapped up. From year 7 and onwards, the budget is estimated based on the two doses given within the vaccination programme only, as all the children in the first age cohort, aged 18 months at programme start, now have reached the age 7 and receive their second dose. The budget calculation is based on the current list prices of the monovalent vaccines (SEK 486 per dose) and an administration cost of SEK 84 per dose.

Table 17 Budget impact model, vaccination of children at age 18 months and 7 years + catch-up vaccination up to age 18 years with monovalent vaccine doses, annual cost (million SEK)

Category	Years 1-5	Year 6	Years 7-10
Vaccination programme dose 1	98,800	98,800	98,800
Vaccination programme dose 2		24,700	98,800
Catch-up doses	138,700	112,500	
Total doses	237,500	236,000	197,600
Cost vaccination programme	**56**	**70**	**113**
Cost catch-up vaccination	**79**	**64**	
Total cost	**135**	**135**	**113**

Table 18 presents the total budget impact under assumptions that the negotiated price of the vaccine is reduced to 70%, 50%, and 30% of the current list price respectively. The assumption of a price at 70% of the list price corresponds with the current average price for the European region in the WHO MI4A vaccine purchase database during the period 2020-2022 of approximately USD 32 (range USD 18-49) (72).

Table 18 Budget impact of a national vaccination programme including a catch-up vaccination up to age 18 years at percentage rates of the current list price of the vaccine, annual cost (million SEK)

Vaccine price (% of list price)	Years 1-5	Year 6	Years 7-10
SEK 340 (70%)	101	100	84
SEK 243 (50%)	78	77	65
SEK 146 (30%)	55	54	45

There is no list price available for the MMRV vaccines in Sweden. The average price of these vaccines in the European region in the WHO MI4A vaccine purchase database during the period 2020-2022 was USD 71 (range USD 62-84) (72). In Table 19, we present a budget alternative where we assumed that the dose given at age 7 years in the vaccination programme as well as 25% of catch-up doses (cases when the second dose can be given at age 7) would be MMRV vaccines. In this budget, since the price estimate of this vaccine was based on average prices from the WHO MI4A database, we used the same price estimate for the monovalent vaccines (70% of the current list price, the approximate average price of the VAR

vaccines in the WHO MI4A database). It is assumed that administration time (and associated costs) can then be disregarded when the combined vaccine is given (MMRV) instead of two separate ones (MMR + VAR). The annual budget impact was estimated at around SEK 110 million.

Table 19 Budget impact of a national programme, together with a catch-up strategy, with dose 2 as part of a MMRV vaccine when the timing of dose 2 is age 7, annual costs (million SEK)

Category	Years 1-5	Year 6	Years 7-10
Cost vaccination programme (dose 1 VAR, dose 2 MMRV)	42	58	107
Cost catch-up vaccination (75% VAR, 25% MMRV)	67	54	
Total cost	**109**	**112**	**107**

Discussion

Our analyses indicates that a national varicella vaccination programme in Sweden, without or with a catch-up vaccination of older susceptible children, is cost-saving from a societal perspective. The cost-savings are primarily due to a reduction in caregiver productivity losses. From a health system perspective, the cost per QALY was estimated at approximately SEK 200,000, classified as a moderate cost per QALY by the National Board of Health and Welfare (25). The additional catch-up strategy is cost-saving in itself from a societal perspective, with a cost per QALY of approximately SEK 240,000 from a health system perspective. Since catch-up vaccination will be offered to susceptible children based on recall, this estimation is contingent on that the children who are indeed susceptible are the ones captured in a catch-up strategy.

We have compared varicella vaccination with a situation with no vaccination. In some parts of Sweden, particularly in the major cities, private vaccination rates have increased in recent years. Sub-optimal vaccine coverage because of this may drive infection to occur at higher ages. The Covid-19 pandemic might further have contributed to a higher degree of school-aged children who have not been infected by VZV during their pre-school years. Both these factors may lead to an increase in more serious cases of varicella as adolescents and adults are at a higher risk of severe disease. A national vaccination programme with sufficiently high coverage in combination with a catch-up strategy would avert this risk.

Models and experience suggest that a vaccine coverage of 80% is necessary to stop endemic infection with varicella (75). Yet, a coverage rate as high as possible is desirable from the perspective of avoiding outbreaks secondary to cases acquired abroad. The model does not account for varicella infections acquired abroad, thus the cost of treating unvaccinated individuals returning with infection after travels abroad is not captured in the analyses. Even among those vaccinated, some individuals will remain susceptible or partially susceptible to infection as they will respond less well to vaccination (17).

It should be kept in mind that a varicella vaccination model is a simplified version of reality. While its quantitative predictions must be considered with caution, the main qualitative conclusions should hold. The main message from several years of modelling is that high coverage universal varicella vaccination will make endemic varicella essentially disappear after a few years. These predictions are upheld by the experience of countries that have initiated such general programmes.

A related, but less documented, question is what will happen to HZ incidence after the initiation of general vaccination. HZ caused by wild-type VZV following varicella infection will broadly disappear as natural varicella infection is prevented through vaccination. This will be noticeable first when vaccinated individuals reach the age when HZ incidence starts to rise, around 50 years and above. However, a limitation of our analyses is that the long-term risk of vaccine-strain HZ in adults who were vaccinated with a live attenuated vaccine as children is not

yet known. In our model, this risk was based on the relative incidence in younger individuals up to 18 years of age in the US routine varicella vaccination programme (36-39). These studies indicate that the incidence will be less than after natural varicella infection, but how much less cannot be predicted. It is also not known how this type of HZ will be affected by HZ vaccination. Therefore modelling becomes quite hypothetical and without real predictive power for HZ prevention in varicella-vaccinated individuals.

Furthermore, one of the main reasons for uncertainty about the introduction of general varicella vaccination has been the possible effect that a decline in circulating VZV in a population would have on HZ incidence due to reduced exogenous boosting. However, recent observational data seem to indicate that these effects are not significant (38, 76).

To date, Finland and Iceland are the only Nordic countries that have introduced varicella vaccination as part of their national child vaccination programmes. A cost-effectiveness analysis conducted by the National Public Health Institute of Finland in 2008 estimated a cost per QALY of EUR 4,900 for a two-dose vaccination programme and of EUR 8,700/QALY for a programme including catch-up vaccination for children up to 12 years (77). The model took a health system perspective and had a 100-year time horizon. In Iceland a varicella vaccination programme was estimated to be cost-saving from a societal perspective (78). Industry-sponsored economic evaluations of universal varicella vaccination in Denmark and Norway - both adopting a 50-year time horizon and comparing different alternatives in terms of age at vaccination and monovalent/tetravalent vaccines - estimated that varicella vaccination would result in a cost per QALY gained between EUR 3,700-5,900 from a societal perspective and EUR 18,000-20,300 from a health system perspective in Denmark (79), and cost-saving from both a societal and health system perspective in Norway (80).

To conclude, our analyses suggest that the inclusion of varicella vaccination in the national vaccination programme for children in Sweden would be a cost-saving strategy from a societal perspective, with a cost per QALY of around SEK 200,000 for a health system perspective, which together with a catch-up vaccination offer for older susceptible children would result in a fast decline in circulating VZV in Sweden.

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Appendix A: Contributing experts

Internal experts from the Public Health Agency of Sweden

2022-2024

- Sören Andersson, professor, head of unit, Unit for vaccine programmes
- Annika Ersson, analyst, infectiologist, previous county officer on disease control, Unit for vaccine programmes
- Kari Johansen, analyst, pediatrician, clinical virologist, previous senior consultant Vaccine Preventable Diseases/Influenza and other Respiratory Diseases, ECDC, former representative EMA Vaccine Working Party, Unit for vaccine programmes
- Frida Kasteng, analyst, health economist, Unit for analysis
- Disa Hansson, analyst, mathematical modeller, Unit for analysis
- Lisa Brouwers, head of unit, Unit for analysis
- Carl Lundberg, analyst, Unit for coordinated public health
- Sofie Larsson, analyst, health economist, Unit for analysis
- Anna Leetma, communicator, Unit for planned communication
- Helene Englund, analyst, epidemiologist, Unit for vaccine programmes
- Ingrid Uhnoo, analyst, infectiologist, previously analyst the Swedish Medicine Agency, former representantive EMA Vaccine Working Party, previously Head of programmes, Unit of vaccine programmes

External consultant modelling

- GianPaolo Scalia Tomba, guest professor, mathematician, Department of mathematical statistics, Stockholm University

2018-2020

- Sören Andersson, analyst, professor, Unit for vaccine programmes
- Ellen Wolff, analyst, health economist, Unit for analysis
- Tiia Lepp, analyst, Unit for vaccine programmes
- Adam Roth, Head of Unit for vaccine programmes
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The Public Health Agency of Sweden is an expert authority with responsibility for public health issues at a national level. The Agency develops and supports activities to promote health, prevent illness and improve preparedness for health threats. Our vision statement: a public health that strengthens the positive development of society.

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