Folkhälsomyndigheten
PUBLIC HEALTH AGENCY OF SWEDEN

Evaluation of an introduction of vaccination against varicella in the Swedish national vaccination programme for children

Summary of evidence

This title can be downloaded from: www.folkhalsomyndigheten.se/publications.
Some titles may be ordered as printed.

Article number: 24216

About this publication

The Public Health Agency of Sweden (PHAS) has conducted an evaluation of the prerequisites and conditions for the possible inclusion of vaccination against varicella (chickenpox) for children in a national vaccination program. This report describes the current knowledge, conditions, and assessments that will form the basis for making a policy decision on whether to introduce varicella vaccines in the national vaccination program for children.

The Public Health Agency of Sweden is required by law to evaluate thirteen factors when proposing changes to the national vaccination programme. This report summarizes the current evidence for these thirteen criteria regarding vaccination against varicella. A summary of a modelling assessment of the potential impacts of varicella vaccines based on the Swedish context and a cost-effectiveness analysis of the vaccination and the expenses and savings for the state, the regions and the municipalities is included. The medical ethics and humanitarian considerations (criteria 13) are analysed and published separately by the Swedish National Council on Medical Ethics (SMER).

The main target group for this publication is the government of Sweden (the Ministry of Health and Social Affairs). It could also be of interest for health professionals in Sweden and elsewhere, as well as ministries of health and public health institutions in other countries considering vaccination against varicella zoster virus-induced infections. This report will serve as the summary of evidence as reference to a proposal to the Swedish government regarding a national vaccination programme against varicella. The report was composed by a working group comprised of analysts from the Public Health Agency of Sweden and external experts (see Appendix A).

This report was initiated in June 2018 but was halted due to the COVID-19 pandemic. The work was restarted and has since then been updated with new data between October 2022 and September 2023. A round of referral was performed in June 2024. After considering input from referral, the final work was handed in to the government by October 2024.

The Public Health Agency of Sweden

Olivia Wigsell
General Director

Innehåll

Abbreviations

ACIP	Advisory Committee on Immunisation Practices (USA)
ALL	Acute lymphatic leukaemia
BOI	Burden of illness
BV	Breakthrough (varicella) infection
BVC	Barnavårdscentral (child health centre)
HE	Health economy
HZ	Herpes zoster
MMRV	Combined measles, mumps, rubella and varicella vaccine (an example of one vaccine including a combination of four vaccines)
NIP	National immunisation programme
OR	Odds ratio
PHN	Post-herpetic neuralgia
PY	Person year
QALY	Quality adjusted life year
RCT	Randomised controlled trial
SAGE	Strategic Advisory Group of Experts on Immunisation (WHO)
SCB	Statistics Sweden (Statistiska Centralbyrån)
SEK	Swedish currency (krona). In June 2023 the exchange rate was 11.7 SEK to one EUR and 10.8 SEK to one USD.
SMER	The Swedish National Council on Medical Ethics (Statens medicinsk-etiska råd).
SPC	Summary of product characteristics
TIA	Transient ischemic attack
VE	Vaccine effectiveness
VZIG	Varicella zoster immunoglobulin
VZV	Varicella zoster virus
WHO	World Health Organisation

Summary

Purpose of the evaluation

The national immunisation programmes (NIPs) are regulated by the Communicable Diseases Act (SFS 2004:168). This act stipulates that a communicable disease shall be covered by a national vaccination programme if the vaccination against the disease is expected to:

- Effectively prevent communicable diseases from spreading in the population
- Be socioeconomically cost effective
- Be sustainable from an ethical and humanitarian point of view.

At the advice of the national reference group for vaccinations, convened under the auspices of the Public Health Agency of Sweden (PHAS), and an internal decision at the PHAS, varicella vaccinations were prioritised for review.

Burden of varicella-zoster virus (VZV)-caused disease in Sweden

In principle the whole population in Sweden is exposed to and infected with VZV at a young age. In Swedish seroprevalence studies it has been shown that by the age of twelve years approximately 92-98% have been infected. For most children varicella is a mild disease, but around 300 children and adults per year are admitted to hospital, with an average stay of 3-4 days. About five times as many children and adults seek medical evaluation in the primary health care system due to varicella and its complications. Risk factors for complications include malignancies, immunosuppression, neurological disabilities, and respiratory disease. Complications include secondary skin infections and neurological symptoms, e.g. cerebellitis. Infection late in pregnancy or at the time of delivery may lead to infection of the unborn or the newborn child. These infections can become very severe and needs to be treated promptly. About one third of the hospitalised cases are in need of antibiotic treatment. The infection affects society in terms of parents being absent from work to care for their sick children and production loss at work places.

A late complication of the acute varicella infection is herpes zoster (HZ). HZ can occur any time during life after a varicella infection, but is most commonly seen after 65 years of age. The burden of HZ in terms of clinical disease requiring treatment and hospitalisation is high. The lifetime risk of developing HZ is around 30 percent, and in Sweden approximately 34 000 cases are evaluated in the health care system per year. Of them, approximately 1200 require hospitalisation yearly.

Vaccines against varicella

There are four different vaccine products available for protection against varicella, two monovalent against varicella only and two tetravalent in combination with vaccines against measles, mumps, and rubella (MMRV). These are all live

attenuated vaccines, and in terms of effectiveness and side effects the vaccines can be considered similar although there is more scientific data available regarding the two vaccine products Varivax and ProQuad compared to Varilrix and Priorix-Tetra.

Impact of varicella vaccination

Post-licensure studies, including systematic reviews, consistently show very high estimates of vaccine effectiveness (VE) in the prevention of severe illness from one dose, about 95–98 percent, as well as in the prevention of all grades of any varicella illness from two doses, almost 100%. The VE against all varicella from one-dose programmes is somewhat lower at 81–85 percent.

Two main concerns regarding the introduction of varicella vaccines in national programmes have been the risk of causing an upward shift in age for varicella infections to older children, teenagers and adults and the impact on HZ rates. By reaching a vaccine coverage high enough to interrupt virus circulation in the population, the risk of an upward shift in age will be diminished; however, unvaccinated individuals will remain susceptible to infection should they be exposed to VZV later in life. The impact of varicella vaccination on HZ rates in individuals that acquired wild-type VZV in a natural infection is still debated including the role of exogenous boosting.

Recurrent exposure to VZV has been believed to improve the immune response to the VZV and provide protection against HZ, so-called exogenous boosting. However, an increasing body of evidence indicates that varicella vaccinations do not have a substantial impact on the incidence of HZ by reducing circulating VZV. There has been an increase of HZ in the elderly in Western countries, but this trend started many years before varicella vaccinations were introduced and has been attributed to more aggressive treatments of cancer and autoimmune diseases causing immunosuppression. A number of follow-up studies indicate that the possible role of vaccines against varicella on herpes zoster incidence is, if any, quite limited. However, the varicella vaccine virus itself has been shown to be less prone to reactivation later in life and may this way be protective against herpes zoster in a life perspective although the observation period so far is up to 18 years of age.

Expected impact of vaccinations on burden of disease in the Swedish context (modelling studies)

We modelled the impact of varicella and/or HZ vaccination on VZV transmission in Sweden with an assumed moderate impact from exogenous boosting. The model suggests that vaccinating against varicella with a two-dose programme in young children will considerably decrease disease caused by VZV. After 8 years there will only by a few hundred cases of varicella per year and the number of HZ cases will be prevented more effectively in the long run (after about 40 years) than from the HZ vaccine. If catch-up vaccination of older susceptible children and teenagers

up to 18 years also takes place at the start of a vaccination programme, the circulation of varicella will be interrupted after only two to three years.

Number of doses needed

Based on experiences from national immunization programmes (NIPs) in countries such as Germany and United States where varicella vaccines were first introduced, it is evident that a two-dose schedule is more efficient in terms of control of all varicella-induced morbidity and transmission.

Target groups for vaccination

The varicella vaccines are approved from the age of 9 months, and there are several programme design options. One or two doses could be given to young children either independently or in combination with MMR, i.e. as a monovalent varicella vaccine or as a tetravalent MMRV vaccine. The various scenarios, of whether to start vaccination at 12 or 18 months and whether to offer the second dose at 18 months, 5 years or 7 years, are taken into consideration in the modelling and health economic evaluations.

Vaccine safety

Safety data from clinical trials and worldwide post-marketing for the available vaccines against varicella include hundreds of millions of doses. The vaccines are generally safe to administer and are well tolerated. In population studies after authorisation of ProQuad and Priorix-Tetra febrile seizures have been observed 5-12 days after MMRV offered as first dose and has been estimated to 1 child per 2 000 – 3 000 vaccinated, which is about double the frequency compared to when monovalent varicella vaccine is used. Both monovalent and tetravalent vaccines are being used for dose 1 in national programmes.

Impact of varicella vaccinations on health care providers

The impact on the health services depends largely on the age groups that are vaccinated and to some extent which vaccines are used. For children, if varicella vaccinations are coordinated with existing visits to child health or school health care, the extra workload is less than if additional visits are required. The aim is to develop a strategy where both the routine programme and the catch-up vaccination may be offered during already existing visits.

Attitudes and acceptance for vaccination

Parents in Sweden have a strong intention to vaccinate their children. One study conducted by the Public Health Agency of Sweden suggests that the vast majority of parents would choose to vaccinate their children against varicella should it be offered as part of the NIP.

Nurses within the child health system execute the vaccination programmes in Sweden and are therefore important for the parental attitudes to varicella vaccination. During the evaluation nurses have been represented in the external expert group and have expressed a preference for offering dose 1 at 18 months rather than 12 months of age to avoid three needle sticks at any vaccination time-point. The need for sufficient resources upon a possible implementation was emphasized.

Other preventive measures

Strategies available for the treatment and prevention of VZV-associated disease and its complications include antiviral treatment, varicella-specific immunoglobulins for the exposed neonates, vaccinations of those close to individuals at risk of developing severe varicella infection (cocooning), and isolation of at-risk patients. However, no preventive measures can effectively replace vaccinations.

Monitoring the impact of vaccinations

The main objective of monitoring vaccination programmes is to ensure that the set goals will be achieved regarding the implementation and impact of the vaccination on disease burden and the expected risk-benefit profile. Monitoring consists of follow up of obtained vaccination coverage by dose, disease surveillance by age group, virological surveillance, seroepidemiology, and routine safety monitoring.

Communication activities

Several actors, such as the regional child health and the school health care, are involved in supporting a successful NIP through their communication activities. The PHAS will provide key actors with overall messages and basic information material for vaccinators and care-takers of children to be invited for vaccination. Communication strategies for HZ vaccinations will be designed and developed in similar ways as for varicella, but directed to the recommended target groups, i.e. immunocompromised, elderly people and health care staff planned to be involved in vaccinations of those target groups.

Sammanfattning

Syfte och anledning till utredningen

De nationella vaccinationsprogrammen regleras i smittskyddslagen (SFS 2004: 168). Enligt lagen ska en smittsam sjukdom omfattas av programmet om vaccination mot sjukdomen förväntas

- effektivt förhindra spridning av smittsamma sjukdomar i befolkningen,
- vara samhällsekonomiskt kostnadseffektiv och
- vara hållbart från etiska och humanitära utgångspunkter.

På inrådan av referensgruppen för nationella vaccinationsprogram och efter ett internt beslut har Folkhälsomyndigheten utrett om vaccination mot vattkoppor och bältros bör ingå i ett nationellt vaccinationsprogram.

Sjukdomsbörda orsakad av VZV i Sverige

I princip exponeras hela befolkningen för och smittas av varicella-zoster-viruset (VZV) i ung ålder. Årligen läggs ca 300 barn och vuxna in på sjukhus med en medelvårdtid på 3-4 dygn. Ungefär en tredjedel av dessa har komplikationer i form av bakteriell infektion och behöver behandling med antibiotika. Cirka 1500 personer årligen söker vård inom primärvården. Riskfaktorer för svår sjukdom är immunbrist efter behandling för tumörsjukdom, annan immunosuppression, neurologiska funktionsnedsättningar och lungsjukdomar. Sekundära hudinfektioner och neurologiska tillstånd, som cerebellit, är vanligaste komplikationerna. Infektionen påverkar samhället genom att föräldrar är frånvarande från sitt arbete för att ta hand om sina sjuka barn och med produktionsförlust som följd för arbetsgivaren.

En sen komplikation till vattkoppor är bältros. Bältros kan uppkomma när som helst i tiden efter en vattkoppsinfektion men är vanligast efter 65 års ålder. Bördan av bältros är hög när det gäller klinisk sjukdom som kräver behandling och sjukhusvistelse. Risken för att utveckla bältros under en livstid är cirka 30 procent och ökar med åldern. I Sverige bedöms ungefär 34000 personer per år inom sjukvården, varav uppskattningsvis 1200 personer kräver sjukhusvård.

Vacciner mot vattkoppor

Det finns fyra olika vacciner tillgängliga mot vattkoppor, varav två är monovalenta (Varivax och Varilrix) och två är tetravalenta (ProQuad och Priorix-Tetra) i kombination med vacciner mot mässling, påssjuka och röda hund. Alla fyra är levande försvagade vacciner. När det gäller effektivitet och biverkningar kan vaccinerna anses vara likvärdiga, även om det finns mer data för Varivax och ProQuad.

Vaccineffektivitet

Studier visar genomgående mycket hög skyddseffekt för vacciner mot vattkoppor. En dos ger 95-98 procentigt skydd mot allvarlig sjukdom, och två doser har skyddseffekt på 100 procent mot all sjukdom. Vaccinens skyddseffekt mot all sjukdom efter en dos är något lägre, 81-85 procent. På befolkningsnivå är en dos tillräcklig för att minska dödligheten och svår sjukdom orsakad av vattkoppor även bland ovaccinerade kohorter, men inte för att förhindra spridning och mindre utbrott.

Vaccinationens förväntade påverkan på sjukdomsbördan

Exponering för VZV har länge förmodats förstärka immunförsvaret mot viruset och därmed förstärka skyddet mot bältros hos sedan tidigare vattkoppsexponerade personer, så kallad exogen boostring. Det kommer dock fler och fler studier som talar för att vattkoppsvaccination inte har någon betydande påverkan på bältrosincidensen. Man ser en ökande incidens i västländer, men denna ökning startade redan innan man började vaccinera i många länder.

Vi modellerade påverkan av vaccination på epidemiologin av vattkoppor och bältros i Sverige och antog en moderat betydelse av exogen boostring jämfört med tidigare modelleringar. Modellen visar att vaccination mot vattkoppor i tvådos-schema minskar förekomst av sjukdom orsakad av VZV avsevärt och att genomförande av ikapp-vaccination vid programstart har större betydelse för epidemiologin än valet av ålder för dos 1 respektive dos 2. Om ikapp-vaccination av äldre mottagliga barn och ungdomar genomförs under programmets första år, skulle efter 2-3 år endast några hundra fall av vattkoppor förekomma per år. Utan ikapp-vaccination skulle det ta 6-8 år att uppnå samma resultat. Antalet fall av bältros minskar dessutom mer effektivt på lång sikt (> 40 år) med vaccination mot varicella än genom vaccination mot bältros.

Antal doser som behövs

Vaccinationsprogram mot vattkoppor med en dos skulle minska allvarlig sjukdom medan för att minska den allmänna spridningen av viruset, d.v.s. totalt antal fall och utbrott behövs två doser.

Målgrupper för vaccination

Vaccinerna mot vattkoppor är godkända för att användas från 9 månaders ålder. Det finns flera alternativ för ett program. En eller två doser kan ges till små barn antingen enskilt eller i kombination med vacciner mot mässling, påssjuka och röda hund (MPRV).

Vaccinsäkerhet

Säkerhetsdata för de tillgängliga vaccinerna mot vattkoppor inkluderar hundratals miljoner doser. Vaccinerna är i allmänhet säkra och tolereras väl. I studier har

feberkramper observerats efter att MPRV har givits som en första dos till barn < 2 år med en frekvens av 1 fall per 2-3000 vaccinerade barn. Detta har varit ett skäl för vissa länder att erbjuda monovalent vattkoppsvaccin som dos 1.

Vaccinationens påverkan på verksamheter

Påverkan på hälso- och sjukvården beror till stor del på vilka åldersgrupper som vaccinationer införs för och även till viss del vilka vacciner som används. Den extra arbetsbelastningen är mindre om vaccination mot vattkoppor sker i samband med befintliga besök inom barnhälsovård eller elevhälsan än om ytterligare besök krävs.

Attityder och acceptans för vaccination

Sköterskor inom barnhälsovården och elevhälsan kommer att ha en viktig roll när det gäller att stödja attityder för vaccination mot vattkoppor. Behovet av tilldelning av tillräckliga resurser vid eventuellt införande betonades.

Föräldrar i Sverige har en stark avsikt att vaccinera. Enligt en studie från Folkhäsomnyndigheten skulle majoriteten av föräldrarna välja att vaccinera sina barn mot vattkoppor om vaccinet erbjuds som en del av ett nationellt program.

Andra förebyggande åtgärder

Tillgängliga strategier för behandling och förebyggande av sjukdom och komplikationer inkluderar antiviral behandling, vattkoppsspecifika immunglobuliner för exponerade nyfödda, vaccination kring individer som riskerar att utveckla allvarlig sjukdom och isolering av riskpatienter. Inga förebyggande åtgärder kan ersätta vaccinationer.

Uppföljning av vaccinationernas effekter

Huvudsyftet med uppföljning av vaccinationsprogram är att utvärdera om uppsatta mål angående genomförande, vaccinationens påverkan på sjukdomsbördan och en förväntad risk-nyttaprofil blir uppfyllda. Uppföljningen kommer att omfatta uppföljning av vaccinationstäckning, övervakning av sjukdomar, virologisk övervakning, seroepidemiologi och säkerhetsövervakning.

Kommunikationsinsatser

Flera aktörer, exempelvis barn- och skolhälsovården, deltar med kommunikationsinsatser för att stödja ett framgångsrikt vaccinationsprogram. Folkhälsomyndigheten ger nyckelaktörer övergripande budskap och grundläggande informationsmaterial.

Background

Varicella zoster virus (VZV) infections

VZV is a highly contagious herpes virus that only affects humans and can cause both varicella (chickenpox) and herpes zoster (HZ, shingles). Varicella is the presentation of primary infection occurring after the first-time successful exposure to VZV from someone with varicella (common) or with HZ (rare). Viral spread from someone with varicella is very high, mainly through air and droplets. Varicella is a disease normally occurring only once in a lifetime, i.e. it induces life-long immunity, and after the primary infection VZV will remain in the body in a dormant state.

This latent infection in which the virus is located in nerve cells of the posterior root of spinal nerves can reactivate weeks to decades later leading to virus replication and zoster blisters in the area of the affected nerve. The risk increases with age and/or certain illnesses and treatments. This secondary VZV infection is not a separate infectious disease, but rather a late complication of the previous varicella infection. Viral spread from zoster blisters can occur and may cause a case of varicella. The HZ can in turn also have subsequent complications, of which persistent pain after resolution of the zoster rash is the most common, so-called post-herpetic neuralgia (PHN). Further reactivations to more episodes of HZ can occur.

Varicella commonly affects children of pre-school age, and in non-tropical countries where vaccinations against varicella are not used virtually all children are exposed and become infected. Thus, in principle the whole population will also become carriers of the virus (1).

Vaccines against varicella

In Europe four different vaccines are available against varicella, including two monovalent vaccines against varicella only (Varilrix® manufactured by GlaxoSmithKline (GSK) and Varivax® manufactured by Merck) and two tetravalent vaccines in combination with vaccines against measles, mumps, and rubella (MMRV; Priorix-Tetra®, GSK, and ProQuad®, Merck). These are all live attenuated vaccines based on the same strain of VZV (the Oka strain, originally from Japan) (2).

VZV vaccination in NIPs

Varicella vaccination

The first countries to introduce one-dose programmes were the US (1995), Canada (1999), and Uruguay (1999). A second dose was added in the US (2006), in Canada with variation by province (from 2011 onwards), and in Uruguay (2014). One-dose programmes were also introduced in Australia (2004) and in some

countries in Central and South America, whereas others initiated two-dose dose schedules from the start. This included Japan, the origin of the Oka strain vaccine, where a two-dose programme was introduced in 2014 (2-10).

Germany was the first European country to implement varicella vaccination in an NIP. Initially one dose was recommended (2004) with later addition of a second dose (2009). Some autonomous regions in Italy and Spain preceded or followed with one-dose programmes, whereas other regions in these countries chose two-dose programmes from the start (11, 12)). In Finland and Iceland, being the first Nordic countries with a varicella vaccination programme, a two-dose programme was initiated in 2017 and 2020 respectively (13-15).

Globally, 43 countries had introduced varicella vaccination in their routine programmes by January 2023, and another 8 had programmes for at-risk groups.

Of the 14 countries in the European Union that introduced varicella vaccination to children by 2023, 12 have a general recommendation of two doses. In five of these countries the second dose is given before 2 years of age, in three countries it is given at age 2–4 years and in five countries it is given at 4–7 years. Two countries (Czech Republic and Poland) use risk-group strategies that may include children, for instance, in the households of immunocompromised patients. Five countries (Finland, Germany, Greece, Lichtenstein and Spain,) have implemented catch-up/complementary vaccination of adolescents, or other specific groups, without a history of varicella or who are seronegative. The use of monovalent and/or tetravalent vaccines in these programmes varies (11).

In November 2023, the Joint Committee on Vaccination and Immunisation (JCVI) has recommended that varicella vaccine should be added to the UK's routine childhood immunisation programme, using the tetravalent MMRV vaccine (16).

Some European countries have considered but decided against general varicella vaccination programmes, including the Netherlands and France (3, 5, 9-11).

Evaluation

Legal framework

Swedish NIPs are regulated by the Communicable Diseases Act (SFS 2004:168 and SFS 2012:453), which stipulates that a communicable disease shall be covered by an NIP if the vaccination against the disease is expected to:

- Effectively prevent communicable diseases from spreading among the population
- Be socioeconomically cost effective
- Be sustainable from an ethical and humanitarian point of view

The corresponding ordinance (SFS 2004:255) regulates the following 13 criteria that the PHAS must evaluate when proposing changes in the NIP to the Government:

1. The burden of the disease on society, the healthcare sector, and individuals.
2. The expected impact of vaccinations on the burden and epidemiology of the disease.
3. The number of doses that are required to achieve the desired effect.
4. The target groups who will be offered the vaccination.
5. The safety of the vaccine.
6. The effect of vaccinations on the activities of county councils, municipalities, and private healthcare providers.
7. The suitability of combining the vaccine with other vaccines in the NIP.
8. The general public's ability to accept the vaccine, and the effect of the vaccination on attitudes towards vaccinations in general.
9. Other accessible preventive measures or treatments that might be alternatives to an NIP.
10. An assessment of the cost-effectiveness of the vaccination and of the expenses and incomes for the state, municipalities, and county councils.
11. The opportunities to monitor the effect of the vaccination in the ten above-stated factors and the estimated costs to the state for follow-up.
12. The need and cost for information initiatives for the population and healthcare providers.
13. Medical ethics and humanitarian considerations.

The PHAS is mandated to define the target groups, number of doses, timing, etc., of vaccinations within NIPs. The vaccination programme for children has been specified through regulations (HSLF-FS 2016:51).

Vaccinations included in NIPs shall be offered by regions or municipalities free of charge and be registered in the National Vaccination Register in accordance with the corresponding legal act (SFS 2012:453).

Rationale behind the appraisal

The national reference group for NIPs is convened under the auspices of the PHAS and is made up of representatives of government agencies, child and school health care, and medical professional organisations. It is the Swedish form of a National Immunization Technical Advisory Group (NITAG), and its role is to discuss and prioritise any needed changes to the Swedish NIP. At the advice of the reference group and after internal decision at the PHAS, varicella and zoster vaccinations were prioritised for review.

Methods

The PHAS started the work on the appraisal in 2018, and the appraisal has been carried out in accordance with the general process for proposing changes to NIPs (17). An external expert group (see Appendix A) consisting of experts in different fields was appointed to describe the evidence outlined in the Communicable Diseases Act. The work was paused in 2020 due to the COVID-19 pandemic and restarted in October 2022.

Guidance documents from the WHO and ECDC based on their work from expert groups, including systematic reviews (5, 6, 18), were reviewed in a Swedish context and also updated by subsequent international reviews and other studies that were considered relevant by the expert group.

Disease burden and current treatment possibilities were described primarily using Swedish register data from the National Board of Health and Welfare and national care programmes for the main diseases and their complications. Scientific publications were used to further update and complement this information.

When the work restarted in 2022, the modelling and the health economic analysis was updated with new data. A new expert group was established for reference and an update of the literature review was initiated in collaboration with Norway. The updated systematic literature review (PROSPERO ID: CRD42023416345 *Clinical efficacy, effectiveness, and safety of varicella and zoster vaccines, possible vaccination strategies including timing of the two doses of varicella vaccines and catch-up vaccination of susceptible individuals*) was conducted concerning efficacy, effectiveness and safety of the available varicella and zoster vaccines. The types of studies addressed were randomised clinical trials (RCTs) and other intervention studies, including pivotal efficacy studies before licensure as well as intervention studies after licensure, observational studies, systematic reviews of effectiveness, and other follow-up reports including grey literature through February 2023 from countries using varicella vaccines within NIPs and publications addressing protective effects in groups other than healthy children.

After a review of previous modelling studies and the assumptions made in these studies, as well as the evidence behind them, we conducted a modelling study on the possible impacts on varicella vaccination in the Swedish context. The results of this model served as a basis for the health economic analysis.

Vaccine safety, the number of doses recommended, and the suitability of simultaneous administration were described mainly using European Public Assessment Reports and summaries of product characteristics.

Attitudes towards varicella vaccinations were described by experts in the area, supported by the results of i) a literature review of scientific articles related to attitudes, perceptions, acceptance, and willingness concerning these vaccinations among parents and health care professionals, ii) a web-based survey among Swedish parents, and iii) a web-based survey among child health nurses and school nurses.

The expected impacts on the child and school health care services, including the effects on the implementation of the current NIP, were described in interviews with representatives of the health care services performing the childhood vaccinations in Sweden. The required monitoring and communication activities by Swedish agencies were outlined by specialists at the PHAS and discussed in the expert group.

This summary of evidence was presented to the Swedish National Council on Medical Ethics for their analysis and conclusion, which will be published separately.

Summary of evidence

Burden of VZV-induced disease in Sweden

Varicella

Clinical picture and epidemiology

Varicella is the clinical presentation of primary infection with VZV. The symptoms include fever and malaise, followed or combined with an itching, vesicular rash over the head and upper body that can spread all over the skin as well as the mucosa. The disease is generally mild in children and symptoms recede without complication within a week.

Due to the high contagiousness of varicella, nearly everyone will contract the disease early in life. In a study using blood samples collected in 1997, the seroprevalence of VZV antibodies was 98% among Swedish 12 year olds, i.e. almost all of them had had varicella at some time before that age (19). In a seroprevalence study analysing residual blood samples from diagnostic laboratories collected in 2011–2013 nationally in Sweden, the seroprevalence at 5 years of age was 66% and 92% at 12 years of age, with a suggested median age of infection around 4 years (20). This immunity level has been corroborated by other studies looking at the same age group (21, 22). In an adult cohort (mean age 60 years) followed with regards to their immune memory function and health across the lifetime (the Betula study) the VZV seroprevalence was 97.9% (23).

Since age of infection and seroprevalence in the adult population vary greatly between countries and regions, primarily between temperate and tropical climates, migrants from low-endemic countries could potentially be seronegative and thus be at risk of contracting varicella upon arrival to Sweden and hence be at risk of severe disease.

Complications and risk factors for severe disease

Complications occur in a minority of varicella cases, and these include secondary bacterial infections of the vesicles with, for example, *Staphylococcus aureus* or S*treptococcus pyogenes*, which can lead to abscesses, cellulitis, sepsis, or, in rare cases, necrotising fasciitis. Skin complications are seen in 15–25% of hospitalised paediatric chickenpox cases (24).

There are also neurological complications, and in children this mainly concerns acute cerebellar ataxia, which generally has a benign prognosis with full recovery (2). In the Netherlands, 1 in 20,000 varicella cases in children below 5 years of age are admitted to hospital due to acute cerebellar ataxia (25). Furthermore, meningitis/meningoencephalitis/encephalitis can affect both children and adults (26). It is likely that the pathogenesis of neurological complications is partly explained by VZV-caused vasculitis, and it has been shown that the risk of stroke is elevated in the months after an episode of varicella (27, 28). VZV can also cause

viral hepatitis or pneumonitis, the latter sometimes complicated by a secondary bacterial infection (2).

In a Swedish study, data were compiled on all hospitalised patients in Stockholm and Gothenburg between 2012 and 2014 with a varicella diagnosis (ICD-10 B01) at discharge. Of 273 patients, 76% had one or more complications (excluding dehydration), with 26% having secondary bacterial infection of vesicles, 19% having neurological complications, and 13% having pneumonia or bronchitis. Dehydration was very common and was seen in 29% of patients, either alone or in combination with other complications (20).

The risk of severe disease is higher in adults and in the immunocompromised. Newborn infants, particularly if infected by their mother in the perinatal period, run a significant risk of severe disease because they are not protected by maternal antibodies. Pregnant women themselves risk a more severe disease, mainly in late pregnancy, whereas varicella in early pregnancy (before the third trimester) can give rise to birth defects, so-called congenital varicella syndrome. It can also lead to benign HZ in the child within the first 2 years of life. The clinical features of congenital varicella syndrome are multi-system with skin lesions, limb hypoplasia, neurological abnormalities, eye disorders, and malformations of the cardiovascular system, the gastrointestinal and the genitourinary tracts. The syndrome is associated with a 30% mortality rate; however, it is quite rare and as of 2013 only about 130 cases had been described in the literature (2, 29).

Concerning hospitalisations, the most recent Swedish nationwide study found an overall hospitalisation rate of 3.6/100,000 person-years (PY) and 19.8-41.0/100,000 PY in the age groups between 0 and 5 years of age. This means an average of 333 hospitalised varicella cases of all ages per year nationally (including 239 children <15 years of age). There was a slight male predominance, and the peak admission incidence was found in 1 year olds (30). According to data from the Swedish National Board of Health and Welfare, the average duration of hospital stay due to, or with varicella, is 3-5 days. These figures are in line with data from other European countries, including those that are not vaccinating or pre-vaccination in countries that now vaccinate, e.g. the Netherlands, Belgium, Italy, and Spain.

A previous nationwide Swedish register-based study from 1993 found that 322 children and 154 adults were hospitalised with chickenpox as the primary or secondary diagnosis during that year (31). In addition, Astrid Lindgren's Children Hospital in Stockholm has published several studies on the incidence of common vaccine-preventable diseases. Their uptake area covers 10% of all Swedish children, and in 1998–2005 the hospitalisation rate in children (below 18 years of age) was estimated to be 1.6 per 1,000 varicella cases. Risk factors for severe disease, such as malignancies, immunosuppression, neurological disabilities, and respiratory disease, were seen in 28% of children (32). In the same hospital the hospitalisation rate for chickenpox in children 5 years of age and younger was 30/100,000 PY in 2003–2008 and 21/100,000 PY in 2008–2013 (33, 34).

The overall consultation rate in specialist and primary care due to varicella was 20.1 and 109/100,000 PY, respectively, which approximates 2% and 10% of all cases. The peak ages for consultations were <1 year for specialists care and 2 years for primary care (30).

Data from the Swedish Social Insurance Agency showed that nearly 25% of children had parents staying home from work to care for them when sick with varicella at some time during their childhood. The mean duration of absence from work was 3.5 gross days per child (30).

Very few people die from varicella, and the disease is mentioned as an underlying or contributing cause of death in an average of only 3.2 deaths per year in Sweden (30).

Neither varicella nor herpes zoster are notifiable diseases in Sweden. However, when VZV is the cause of disease in the central nervous system, e.g. meningitis, encephalitis, or meningoencephalitis, and is verified by PCR or serology of cerebrospinal fluid, it falls under mandatory reporting. According to the Communicable Disease Control Act, notifications are needed from both the diagnosing laboratory and from the treating physician. Notifications from 2007 to 2013 were examined in the study by Widgren et al., and the incidence of reported VZV-related meningoencephalitis was 0.3–1.8/100,000 PY over the age groups, with the highest incidence in the elderly. Data on clinical presentation were limited in about 90% of reports, and thus it is unknown whether the complications were connected to primary infection or to reactivation of a dormant VZV infection (30).

Primary VZV infection in the immunocompromised host

Primary VZV infection in the immunocompromised host is a predominantly paediatric condition that reflects the fact that the majority of varicella cases occur in children below 5 years of age. In this context, it is also important to know that the peak for the most common paediatric malignancy, acute lymphoblastic leukaemia, occurs in pre-school age. In the immunocompromised child, severe illness with pneumonia, hepatitis, and encephalitis may occur as a consequence of varicella. Before the introduction of antiviral therapy, the case fatality rate for primary VZV infection was 7%–10% for children with cancer undergoing chemotherapy (35). Children with leukaemia were most at risk, and there were few or no deaths caused by VZV in children treated for solid tumours. Thus, immunocompromised children, and particularly those with impairment of cell-mediated immunity, are at high risk for severe varicella. Unfortunately, available data in the literature are sparse and are often limited to case reports regarding primary VZV infection in these patients. In the immunocompromised child, it is important to remember that varicella infection may present with unusual symptoms or with a prolonged clinical course.

The use of immunosuppressive chemotherapy is increasing, and new immunosuppressants are regularly being introduced, including biological therapy,

and this suggests new indications of the potential risks for varicella infections. There are, however, limited data on biological therapies and varicella infection in children and adolscents.

Herpes zoster

The life-time risk of developing HZ after primary VZV infection is about 30% and in Sweden approximately 34 000 cases per year are treated. Details about HZ, or shingles, and its implications are to be found in ”Kunskapsunderlag om vaccination för skydd mot bältros till vuxna med ökad risk för sjukdom orsakat av stigande ålder (från 50 år), sjukdom och/eller behandling (från 18 år)”. Although HZ is less contagious than varicella, cases of HZ may be important sources of varicella (36). The varicella vaccine virus has been shown to be less prone to reactivation later in life and may this way be protective against HZ in a life perspective although the observation period so far is up to 18 years of age (37).

Summary – burden of VZV-caused disease in Sweden

In principle, the whole population in Sweden is infected by VZV at a young age. However, the burden of severe disease is relatively low, with around 300 persons (all ages) per year admitted to hospital and about five times as many seeking health care. Risk factors for complications include age at infection (adolescence or adulthood), malignancies, immunosuppression, neurological disabilities, and respiratory disease. Deaths are rarely seen. These infections affect society in terms of parents being absent from work in order to care for their sick children and in terms of production loss in the work-place.

The burden of HZ in terms of clinical disease requiring treatment and hospitalisation is much higher, and the situation in Sweden is similar to other comparable countries.

Vaccine-induced protection

Immune responses

A combination of humoral and cellular immune responses is essential for protection against VZV disease, but with differences in the responses to primary disease, latent infection, and secondary disease. These differences are of importance in vaccine evaluation. Antibodies play an important role in the immune response to the primary infection. VZV immunoglobulin (VZIG, containing a concentrate of VZV antibodies) can prevent or modify varicella if administered during the first days of infection, probably by neutralising extracellular viruses and thereby lowering the viral load. However, the cell-mediated immune response is critical in defence against intracellular forms of VZV, which is the major means by which the virus spreads in the body during acute illness. It is also the cellular immunity that is fundamental in maintaining control of the latent infection and preventing reactivation leading to HZ (38, 39).

Immunogenicity studies of the initial vaccine response (”vaccine take”) are inevitably necessary in the prelicensure documentation and are also useful when comparing products, but further documentation of the protective effect of VZV vaccines will require clinical trials and long-term cohorts or other types of follow-up, preferably in combination with immunogenicity studies.

Varicella vaccine effectiveness (VE)

In this section follows a review of the available relevant data from trials, reviews, and follow-up studies through 2023 on the VE of the four different varicella vaccines available in Europe as of the second quarter of 2019.

Randomised controlled trials (RCTs)

There were two pivotal double-blind and placebo-controlled efficacy studies of the two monovalent vaccines before licensure, one in the US (40, 41) and the other in Finland (42). In the US, Varivax (17,000 PFU) protected 100% of vaccinated children aged 1–14 years against varicella during the initial 9-month follow-up (41), 98% after an extended follow-up at 2 years, and 95% after 7 years (40). In Finland, three candidate versions of the GSK vaccine Varilrix (high-dose 10,000 or 15,850 PFU, low-dose 630 or 1,260 PFU) administered to children at age 10–30 months protected 88% of high-dose and 55% of low-dose vaccinees during an average follow-up of 29 months (42). Following these RCTs the authorised vaccine products Varivax and Varilrix contains 17,000 PFU and 1,995 PFU, respectively.

In the US, about 2,000 children aged 4–12 years were followed for up to 10 years after another pre-licensure RCT of one or two doses of Varivax. The overall one and two dose efficacy estimates for the 10-year period were 94% and 98%, respectively (43).

To our knowledge there is only one phase 2 study including both monovalent vaccines Varivax and Varilrix side-by-side, and this was a three-armed immunogenicity study in about 600 children aged 11–20 months. The two candidate lots of the Varivax vaccine performed similarly in spite of different PFU contents, and they induced higher seroconversion rates (95–97%) compared to a licensed lot of Varilrix (86%). Also, the geometric mean titres were somewhat higher for Varivax when tested in the same assay (44).

There is one RCT comparing two doses of tetravalent vaccine (MMRV, PriorixTetra) with one dose of monovalent vaccine Varilrix (plus separate MMR,) from the same producer, including long-term follow up. The trial was conducted in 10 countries with endemic varicella and with no recommendation for general vaccination of children at the study start in 2005. Most participants were from Eastern Europe and Russia (82%), some were from Sweden and Norway (8%), and the remainder were from Spain and Italy. Two tetravalent doses provided better protection than one monovalent dose during the initial efficacy follow-up of about 3 years, with 65% vs. 95% protection against all varicella after one vs. two doses,

and 99.5 vs. 91% against moderate to severe varicella, respectively (45). Six years after administration, the one-dose protection against all varicella was slightly higher (67%), but the efficacy against moderate to severe varicella as well as results after two doses remained virtually the same (46, 47). The final follow-up over 10 years confirmed the 6-year results, with an overall vaccine efficacy against all varicella of 95% from two (tetravalent) doses compared to 67% from one (monovalent) dose, with 99% vs. 90% VE against moderate and severe varicella. Overall, VZV antibodies increased gradually from 1 to 10 years of follow-up, indicating natural boosting (45).

Reviews on VE and breakthrough varicella (BV)

BV is defined as varicella in a person who received at least one dose of varicella vaccine at least 42 days before the onset of symptoms. Early BV cases represent primary failures (non-response to vaccination) whereas later BV cases can occur due to primary failure as well as to waning immunity, i.e. because of secondary vaccine failure (an initial response but loss of protection over time). The definition of BV does not include vaccine-virus-induced rash, which is typically seen around 21 days post-vaccination.

The update of the WHO position paper on varicella and HZ in 2014 was preceded by a systematic review of studies addressing the VE of one or two doses in children aged 9 months to 12 years. One dose protected a median of 83% against all varicella, 95% against moderate or severe disease, and 100% against severe disease. Overall, two doses provided better protection against all grades of severity (median 95%) (18).

Another systematic review, including a meta-analysis of publications through December 2014, found a pooled one-dose VE of 81% (95% CI: 78–84) against all varicella, 98% against moderate/severe disease, and 100% against severe disease, with no significant association with vaccine type or study design. The pooled two-dose VE against all varicella was 92% (95% CI: 88–95) (48).

There is also a literature review from 2017 on the effectiveness and epidemiological impact of vaccination, further supporting that both one- and two-dose schedules are highly effective against varicella, with widely reported large reductions in disease incidence, particularly moderate to severe disease. In addition, this review concluded that there is currently no evidence that the introduction of varicella vaccination results in a shift of varicella burden to older age groups (49).

A meta-analysis from 2017 identified 27 studies and found a pooled average of 8.5 BV cases per 1,000 PY in children vaccinated with one dose compared to 2.2 cases per 1,000 PY in those vaccinated with two doses. High heterogeneity was observed in the average BV incidence rate after one dose. Sources of heterogeneity identified in a meta-regression included study design and vaccine type. The pooled trend of annual BV after one dose fluctuated from the first to the eighth year, with a peak of

35.3 cases per 1,000 PY in the fourth year. One conclusion was that an interval of 3–4 years between the first and second vaccination might achieve higher efficacy (50).

A recently published overview of reviews in 2023 on the efficacy and effectiveness of different varicella vaccination strategies included 20 reviews, with 17 assessing the efficacy/effectiveness of one-dose strategies and 10 assessing the efficacy/effectiveness of two-dose strategies (51). The evidence suggests that one-dose and two-dose strategies have similar high efficacy/effectiveness when it comes to preventing moderate or severe varicella. Up to 14 years post-vaccination with one dose, the average pooled incidence of breakthrough infection of any severity was 8.5 cases per 1000 PY.

Fortunately, BV cases of varicella have usually proven to be mild, although a few cases of severe disease have been reported (18, 40, 48, 52). A systematic review of severe BV concluded that it appears to be a rare phenomenon after two doses given to healthy individuals (52).

Follow-up studies of one-dose programmes

A literature review of studies from the US from 1995 to 2006 found one dose to be 84.5% effective in preventing all varicella and 100% effective in preventing severe varicella (53). The programme during this period included one dose to children 12–18 months of age and a catch-up dose to susceptible children aged 19 months–12 years, and from 1999 there were also national recommendations to implement childcare and school entry requirements. The MSD monovalent vaccine (Varivax) was used almost exclusively. Three US surveillance sites were assigned an enhanced follow-up of varicella-related illness and outbreaks, including Antelope Valley (California), West Philadelphia (Pennsylvania), and Travis County (Texas). Long-term data, available from the first two of these, indicated an overall 90% reduction in incidence of varicella over the years 1995–2005. Coverage rates in the two states rose during this time period from 40–41% to 92–94% among children aged 19–35 months (54, 55).

In Uruguay, there was an 81% reduction in the proportion of hospitalisations over the years 1999–2005, with a 94% reduction in the 1–4 year age group, and there was also an 87% overall reduction in out-patient visits due to varicella in the country. Vaccination was recommended at 12 months of age, and coverage was estimated to be over 90%. The GSK monovalent vaccine (Varilrix) was used (56).

In Canada, the single dose was recommended at 12–18 months of age with catch-up for susceptible older children, but implementation varied between provinces and territories over the years 2000 to 2007. A study from 12 hospitals across the country demonstrated a gradual decline of varicella-related hospitalisations over the years 2000–2008, with a 90% overall reduction in the 1–4 year age group, a 78% reduction in the 5–9 year age group, and a 76% reduction in infants (57). In Alberta, the reported cases of varicella decreased from around 240 to less than 30

per 100,000 persons during the period 2000–2011 (58). Both available EU authorised monovalent vaccines were used.

In Australia in 2005, a single dose was recommended at 18 months, with a catch-up in the school-based programme at 12–13 years. Varicella notification rates from Southern Australia were reduced by 63% in children aged 0–4 years over the 9-year period of 2007–2015. There was also, similar to in the US and Canada, a decline in varicella hospitalisation rates, and this was most noticeable in the youngest children and during the first part of the surveillance period (9). In a case-control study from Queensland, the one-dose programme was found to be 82% effective in preventing hospitalisation among children aged 1,5–6 years (59). Both available EU-authorised monovalent vaccines were used until 2012, and from then the tetravalent vaccine has been used.

In Europe, the German one-dose VE during the four years of 2005–2008 was estimated at 83% in the 1–2 year age group (60). Both EU-authorised available monovalent vaccines were available in Germany at the time, and the recommended age of vaccination was 11-14 months. In Italy, Sicily was the first region to offer one dose of varicella vaccine to all children in 2003, with the addition of a second dose from 2010. The first dose was recommended at 13–15 months of age, with catch-up offered to susceptible adolescents at 12 years of age. During the years 2003–2012, the annual notification rate of varicella decreased by more than 95%, from 5290 cases in 2003 to 207 cases in 2012. The median age of hospitalised varicella patients increased from 5 to 20 years (61). There is no information on product use.

Follow-up studies of two-dose or mixed programmes

In the US, the reduction in varicella incidence at the national level was 85% when comparing the period 2005–2006 (before two doses) with 2013–2014 (two doses implemented), and of this the largest decline was reported in children aged 5–9 years (89%) (3). During the 25 years of programme implementation, the varicella incidence has declined by more than 97% based on data from the four states that have continued reporting (62). In Antelope Valley, the decline in the number of outbreaks was 95% when comparing the two periods 1995–1998 and 2007–2010. The outbreaks also decreased in size (the number of varicella cases per outbreak) and duration (63). The same trend with fewer and smaller outbreaks could be seen as the data was reviewed and updated with data from 2016 to 2019. During 2016–2019, 79% of outbreak cases occurred among unvaccinated or one-dose vaccinated individuals (64). Enhanced follow-up revealed a 76% decline in varicella incidence in Antelope Valley, a 67% decline in West Philadelphia from 2006 to 2010, and a combined decline in varicella-related hospitalisations of over 40% (65). A case-control study from these states, comparing 125 clinically diagnosed varicella cases with 408 matched controls, found a 75.6% one-dose VE for the prevention of varicella of any severity and a 78.1% VE for the prevention of moderate or severe disease. Among subjects over 4 years old, the two-dose VE was 93.6% against any

varicella and 97.9% against moderate or severe varicella (66). Either the monovalent (Varivax) or tetravalent (ProQuad) MSD vaccine was used.

A Canadian follow-up from Ontario in 2010–2013 covered the first years after adding the second dose at 4–6 years of age, together with a second dose catch-up to children born from 2000. In this province, the first dose was with either the GSK (Varilrix) or MSD (Varivax) monovalent vaccine and the second dose was the GSK (Priorix-Tetra) tetravalent vaccine. By 2011, the incidence rate had already decreased from 181 to 51 cases per 100,000 population after the introduction of the first dose, and it continued to decrease slightly after the introduction of the second dose to around 30/100,000 in 2013 (67). Another region, Alberta, saw a more modest decrease during the first 2 years after introducing the second dose in 2012 (no catch-up offered) (58).

In a large follow-up from Germany, 29,400 cases of varicella were identified among 1.4 million children over a period of 8 years. The one-dose and two-dose VE estimates were 81.9% and 94.4%, respectively. There was no association with age at vaccination with first dose (11–14 months vs. ≥15 months), time since vaccination, or vaccine type (mono vs. tetravalent), but the VE was significantly lower after the first dose if given 1–27 days after a measles-containing vaccine. The tetravalent (Priorix-Tetra) GSK vaccine was used in 2009–2010, with a change to the monovalent (Varilrix) GSK or MSD (Varivax) vaccine in 2011 (68).

The region of Navarra in Spain introduced a two-dose programme in 2007, implemented by cohort to children born from 2006 and onwards. The first dose was given at 15 months of age, and the second dose was given at 3 years of age. Vaccination of susceptible children had started already before this programme and continued as catch-up vaccination to 10 year olds. Monovalent (Varivax) MSD vaccine was used. During the first 6 years of the programme, the incidence of varicella in children 0–14 years of age decreased by 98% from 50 cases to 1 case per 1000 inhabitants, and the hospitalisations for varicella declined by 95% in this age group (69).

Studies addressing the duration of protection after one dose

A meta-analysis of vaccine effectiveness in varicella outbreaks found an overall one-dose VE of 72.5% (95% CI: 68.5–760) derived from 3,157 children in 14 publications, where waning immunity was addressed in nine studies. Two of these reported no relation between VE and time since vaccination, but without specifying how this had been assessed. The other seven all calculated relative risks for BV, reporting an increased relative risk with time since immunization. Four publications provided enough data to plot the dependence of VE on time since immunisation, indicating a substantial waning immunity over the time covered within the studies, which was up to 6 years. The number of available data points did not, however allow the authors to distinguish whether the decrease was linear or not. The meta-analysis also states that the true VE might be higher since "vaccine-prevented outbreaks" will not be reported (70). There is also a small

German study from outbreaks in day-care, which was published after that review. The non-brand-specific VE after one dose was calculated to 62%, where the VE after Varilrix (GSK) was 77%, although the numbers are too small to provide statistically significant results on VE (71).

Three case-control studies indicate some waning protection over 3 to 10 years of follow up. A Spanish study (Navarra) showed a VE of one dose of 93% in the first year, declining to 61% after the third year (72). An American study performed in West Virginia public schools found a slower decrease of one-dose VE with time since vaccination and reported VEs of 93%, 88%, and 82% at less than 5 years, 5–9 years, and 10 years or more, respectively, since vaccination. Breakthrough cases had milder rash than unvaccinated cases (73). Another study from Spain (Madrid) demonstrated a more modest decline of VE from 98.2% in the first year after vaccination to 93.1% after 9 years of follow-up (74).

There is to our knowledge only one study that did not indicate any waning of protection. A long-term clinical cohort study from northern California in 1995 included 7,585 children after routine vaccination in the second year of life, with follow-up by phone calls to the parents. There were no signs of waning protection over the 14 years of 1995–2009. In all there were 1,505 BV cases, with about 26 cases per 1,000 PY in the first 4 years after vaccination, decreasing to <20 thereafter and further to 2 per 1,000 PY in 2009. About a third of the children later received a second dose, and no child developed varicella after the second dose (75).

Protection in immunocompromised children

Despite our current knowledge about varicella vaccination in the general healthy population, less is known about the efficacy and safety of the vaccine in an immunocompromised child. In theory, severely immunocompromised patients might be unable to limit the replication of live-attenuated vaccine viruses, resulting in severe vaccine virus disease. Therefore live vaccines are generally contraindicated for use in patients with significant immunosuppression. However, the contraindication to using live VZV vaccines is relative rather than absolute and depends on the type and state of immunosuppression in each patient.

The live varicella vaccine was actually developed in the 1970s for protection of children with leukaemia against varicella, provided that the patient was in remission or that chemotherapy was suspended around the time of vaccination (Chiu Exp Rev Vacc 2005). The usefulness turned out to be limited, however, and the vaccine was redeveloped for protection of healthy children and adults – thereby contributing to reduced viral circulation in the close proximity of vulnerable patients. As of today, the varicella vaccine has again been evaluated in some of these patient groups and might actually provide direct protection (2).

A recent review of such studies concluded that the varicella vaccine is safe and induces high seroconversion rates in immunocompromised children with a history

of bone marrow transplant, solid organ transplant, or immune-mediated inflammatory disease (76). Vaccine strain-related infections were rare in all groups, and no severe infections were seen.

Another obstacle regarding varicella vaccination in immunocompromised patients, mainly young children, is timing. Varicella vaccination prior to immunosuppressive therapies may be recommended, but it is not always prioritised. However, a few studies on varicella vaccination during ongoing chemotherapy or immunosuppressive treatment indicate that this might be feasible. This includes a Swedish study of renal transplant recipient children. Antiviral prophylaxis is also an option to prevent the spread of vaccine-VZV to other children in, for example, oncology wards (77, 78).

Summary – vaccine impact on varicella

There are currently a large number of studies consistently showing high VE from the varicella vaccines. The introduction of one-dose programmes has substantially reduced the general disease burden but has not prevented limited virus circulation or outbreaks. Two-dose programmes have virtually eliminated acute primary varicella infections. Catch-up programmes have been effective in eliminating virus circulation and, consequently, the incidence of BV. The available monovalent and tetravalent vaccines from two manufacturers appear similar in terms of their effectiveness. For the immunocompromised children with hiv clinical trials are on-going with an inactivated vaccine and may become an option in the future.

Number of doses needed

Varicella vaccines

The conclusion drawn from follow up of NIPs where varicella vaccines were introduced first, e.g. the US, Canada, and Germany, was that one-dose schedules had a high impact with reductions in morbidity and mortality. However, these countries continued to have outbreaks, even among vaccinated children. The studies also produced evidence that a one-dose regimen would not provide sufficient stimulation of the immune system to induce long-lasting memory and protection. Following the introduction of two-dose schedules, the incidence rates were further reduced across the whole spectrum of varicella disease and complications. Nowadays there is consensus that two doses should be recommended if the goal is to further reduce varicella (all cases) and to control outbreaks (5, 6, 79). To individuals from 12 months of age, the doses should be given at least 6 weeks apart, while in infants from 9 to 11 months of age, the interval between the 2 doses should be at least 3 months (summary of product characteristics, SPC).

For further details, see the section above on vaccine impact.

Target groups for vaccination

Varicella vaccines

The varicella vaccines are approved from the age of 9 months (summary of product characteristics, SPC) and the primary target groups are children – including toddlers, preschool, and school children. A two-dose schedule will both provide direct protection and reduce the overall risk of exposure in unvaccinated or for other reasons non-immune persons of various ages. These groups are secondary target groups for indirect protection by vaccination of children by means of a high-coverage NIP. Most countries with national varicella vaccination programmes administer the vaccine at an early age in order to decrease the overall chickenpox incidence and disease burden (e.g. Germany, Finland, and the US). A few countries have also opted for vaccination of children and/or adolescents who have not yet had varicella, in Finland and Spain assessed by clinical history only (15). There are two main reasons for the latter strategy. First, the risk of severe disease increases with age at varicella infection, and late-onset cases will be prevented this way. Second, the circulation of wild-type virus in society will be eliminated rapidly and thereby provide protection to vulnerable individuals, e.g. those undergoing immunocompromising treatment (5, 6).

The varicella vaccine could be given to young children either independently or in combination with MMR, i.e. as a monovalent varicella vaccine or as a tetravalent MMRV vaccine.

The priming effect of the first immunisation dose is significantly dependent on the age at which it is given according to studies on measles vaccination. The first dose given at 12 months is expected to result in inferior priming compared to when it is given at 18 months. The increased response to the first dose administered at 18 months is expected to persist also after the second dose (80-82).

In Sweden, a campaign for vaccinating seronegative children and adolescents up to the age of 18 years could be considered in order not to leave any age cohort unprotected, with the risk of getting infected at an older age and thereby being at risk to develop a more serious disease. In addition, such a campaign would eliminate the probability of a rebound effect of varicella infection with an NIP without a catch-up.

Most relevant scenarios included in the modelling work

- First dose at 18 months as MMR + V and second dose at 7–8 years, either as MMRV or MMR+V.
- First dose at 18 months as MMR + V and second dose at 5 years, either as MMRV or MMR+V.
- First dose as monovalent (V) at 12 months and second dose as MMRV at 18 months.

- All of the above scenarios with and without vaccination of older children <18 years of age.

Safety of vaccines against varicella and the suitability of simultaneous administration with other vaccines

Monovalent vaccines against varicella

The two monovalent vaccines against varicella that are licensed in Sweden, Varilrix (GSK) and Varivax (MSD), have been marketed in their current forms since 1994 and 2004, respectively. Globally, a previous version of Varilrix was registered in Europe in the 1980s, while Varivax was first registered in the US in 1995. Both are live attenuated vaccines and have some differences in composition and attenuated virus titre, but for the vaccination programme purposes they are considered similar.

The adverse events that have been reported in clinical studies and after licensing are described in detail in the product information for the respective vaccine and in the published literature (83, 84). The reported adverse events are similar for the two monovalent vaccines. This also includes the reported adverse events after the introduction of the vaccines for clinical use. Among the most common reactions are mostly mild general symptoms or reactions at the site of injection, e.g. fever, erythema, and pain and swelling at the injection site, and these appear in 1–10% of the vaccinees. A skin rash appearing as a mild form of the varicella infection is also fairly common. No serious adverse events have been reported from monovalent vaccines used for immunocompetent individuals (1, 3, 4, 174, 176, 177). A recent overview of 17 reviews, comprising 34 RCTs and 62 other primary studies, found evidence that varicella vaccination is safe. Febrile seizures were found to be possible adverse effects of both monovalent varicella and quadrivalent MMRV vaccine, but serious adverse reactions were found to be rare. Several reviews estimated febrile seizures to be twice as common when MMRV was given to a child younger than 24 months, compared to giving the MMR-vaccine alone (85).

Active surveillance of children for >10 years after vaccination did not show any increased incidence of HZ compared to children who previously had suffered from wild-type varicella infection (before the introduction of the vaccine). The varicella vaccine virus may cause HZ, but this seems to be a rare phenomenon and usually occurs within a few years after vaccination (86-88). More long-term the varicella vaccines may prevent against HZ shown up to 18 years following the use of Varivax (37).

For Varilrix, HZ has been reported to be a rare adverse event (summary of product characteristics, SPC).

Both Varilrix and Varivax are possible to administer simultaneously with other vaccines, either live attenuated or inactivated. However, they should never be mixed and should be given at different sites of the body. If a varicella vaccine is

not given at the same time as MMR, at least a month should separate the vaccinations. There are examples of studies where subjects receiving varicella vaccine 30 days or less before MMR vaccine had a 2.5 times higher risk of vaccine failure of the second vaccine compared to longer vaccine intervals. The mechanism is postulated to be the production of interferon in response to the first attenuated vaccination, which inhibits the second live vaccine. There are, however, no reasons to believe that this should be product dependent because it is supported by general knowledge about vaccines (see also ref 4).

Combination vaccines against measles, mumps, rubella, and varicella (MMRV)

There are currently two vaccines licensed in Sweden where varicella is included as a component in a combined, quadrivalent vaccine against MMR, namely Priorix Tetra and ProQuad. We consider the vaccine efficacy to be equivalent for both available vaccine products. None of the quadrivalent vaccines are currently marketed in Sweden. In general, the two MMRV and MMR vaccines share many of the more common side effects. However, differences have been reported concerning measles-like rash, fever, and febrile seizures. Serious adverse effects following vaccination with MMRV are very uncommon, but include febrile convulsions, urticarial allergic reactions, fever, cough, and bronchiolitis (89-91). All subjects have recovered without sequelae.

In population studies after authorisation of ProQuad and Priorix-Tetra febrile seizures have been observed 5- 12 days after MMRV offered as first dose and has been estimated to 1 child per 2 300 – 2 600 vaccinated why most, but not all countries have opted for offering monovalent varicella vaccine for dose 1 (84, 92-95). This risk is about double, but from a low level, compared to when administering MMR and monovalent varicella vaccine.

In Germany, both the first and the second dose were given with a quadrivalent vaccine in 2009–2010, but from 2011 the monovalent vaccine has been preferred as the first dose due to higher rates of febrile seizures from the combined MMRV vaccine (68). In November 2023, the Joint Committee on Vaccination and Immunisation (JCVI) has recommended that the tetravalent MMRV vaccine should be used for dose 1, given that the very small increased risk was not of clinical concern and that there was a considerable benefit from giving fewer injections across all eligible children (16).

Both ProQuad and Priorix Tetra can be administered simultaneously with inactivated vaccines offered as part of the Swedish childhood vaccination programme, i.e. vaccines against diphtheria, tetanus, pertussis (acellular), *Haemophilus influenzae type B*, poliomyelitis, hepatitis B (HBsAg-based), and pneumococcal infections. In addition, both vaccines have been administered simultaneously with vaccine against hepatitis A.

Summary of the expected impact of vaccinations on the burden of disease and epidemiology, including health economic evaluation

Vaccination campaign of older susceptible children

A catch-up campaign to offer vaccine to varicella-susceptible children who are older than the age for vaccination within the NIP has been implemented in some countries at the start of varicella vaccination in NIPs. For example, Finland offered VZV vaccine to all susceptible children under 12 years of age as the VZV vaccine was implemented in the NIP. The campaign was successful, with less than 1000 confirmed varicella cases nationwide within 3 years from implementation (15).

The exogenous booster discussion

The possibility of the effect of reduced circulation of VZV on the incidence of HZ due to reduced exogenous boosting of VZV-specific immunity has been an area of much discussion and of some worry when considering the potential effects of vaccination programmes. The first observation of this came in the 1960s by Hope-Simpson who introduced the concept of exogenous, as well as endogenous, boosting (96). Hope-Simpson postulated that regular contacts with VZV would stimulate VZV-specific immune responses and maintain control of the virus. Likewise, subclinical reactivation of the virus could also give an endogenous boost. Since then, a number of studies have confirmed that there is probably a boosting effect of exposure to VZV throughout life. This might be of some importance especially for older people with otherwise waning immunity. Forbes et al concluded that up to 20 years after household exposure to a child with varicella, adults were about 30% less likely to develop HZ (97). Thus, a possible reduction of this exogenous boosting effect could then lead to an increase in HZ infections if the circulation of VZV is diminished by a national varicella vaccination programme. Indeed, the incidence of HZ infections has gradually increased in countries where varicella vaccinations have been introduced, e.g. the US, but this increase started already before the varicella vaccination programmes were launched (the first was in the US in 1995). A number of follow-up studies in the US and other countries (e.g. Canada, Australia, Taiwan, Spain, and Germany) have addressed this issue, but none of them have been able to provide clear evidence for the reduced circulation of VZV as the cause for the increase of HZ. Other factors, such as changing demographic patterns, an increasingly ageing population, and the increased use of immunosuppressive therapies, are important for this trend. In addition, it is not clear if a single and larger VZV dose provides a more efficient booster of VZV immunity than smaller but repeated exposures. Changing contact patterns among people could also have an impact. Another aspect further complicating the discussion on external boosting is the effect of internal boosting due to reactivation of the virus harboured in the nerve cells. This has been less studied, but some evidence exists from VZV as well as from other herpes viruses

Above all, real-life studies cannot tell if HZ epidemiology will be affected until after a very long time (5, 6, 98-102).

Vaccine coverage and the risk for an upward shift in age for varicella infections

The WHO states in their position paper that vaccine coverage less than 80% is expected to shift varicella infection to older ages, which would increase the risk for complication among those who do get infected (6). With a high vaccine coverage, the circulation of virus will be interrupted quickly, diminishing the risk for susceptible individuals to contract varicella in that setting. However, unvaccinated individuals with no history of varicella infection will remain susceptible to infection should they be exposed to VZV later in life. By offering vaccination also to older susceptible children, the number of individuals at risk of contracting varicella late in life will be smaller. The section below, on the epidemiological model and health economics, describes how a temporary vaccination campaign for older children is expected to eliminate the risk of "rebound", i.e. an increasing number of infections a few years after the vaccination programme is initiated.

Epidemiological model and health economics

We developed an epidemiological transmission model to explore the transmission of VZV in Sweden in order to assess the impact of a set of vaccination programmes targeting varicella and subsequently HZ through vaccination against varicella. The model was developed in the programming language C. A health economic model was developed in Excel using data output from the transmission model to assess the health economic consequences of the different vaccination programmes. The epidemiological effect of administering dose one and dose two at different ages was modelled, then the effect when adding a catch-up vaccination of susceptible children, older than the age for dose one. As it turned out, the catch-up vaccination had more impact on the epidemiology than the different ages for dose one and two, hence we chose to continue with health economic modelling on scenarios that offer dose one at 18 months of age. Four main scenarios were investigated with slight variations regarding ages, see table 1.

Table 1. Description of modelled scenarios for vaccination.

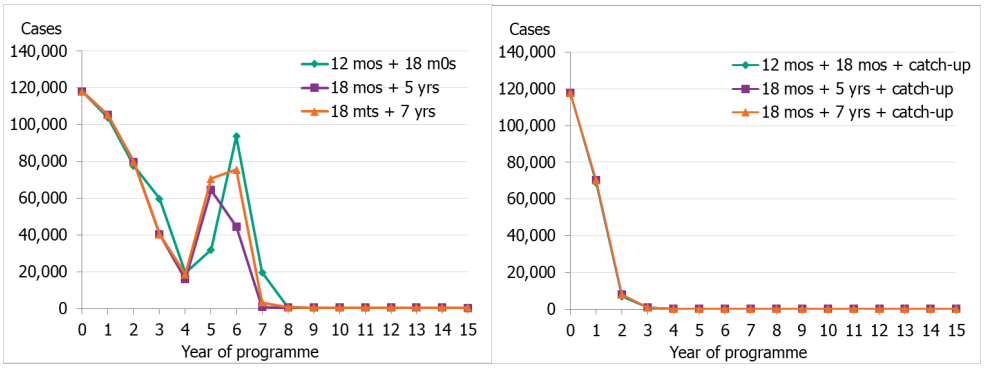
Modelled scenarios	**No catch-up vaccination of older naïve children/ adolescents**	**Catch-up (cu) vaccination offered at ages 5+7 years, 7+11 years and 11+13 years (95% coverage)**
Age at vaccination: 18 months + 5 years	Scenario: 18m5y	Scenario 18m5y+cu 5+7,7+11,11+13y
Age at vaccination: 18 months + 7 years	Scenario: 18m7y	Scenario 18m7y+cu 5+7,7+11,11+13y

The transmission model is a deterministic, compartmental, age-structured, dynamic model. A review of the literature was conducted prior to this work, focusing on the

methods in previous modelling studies as well as the assumptions made in these studies and any changes in the evidence base behind them.

In the transmission model, a two-dose varicella vaccination programme, with the first dose given at 12 or 18 months, will considerably diminish virus circulation after 7 years. From over 100,000 varicella cases per year, only a few hundred will be seen, see figure 1. A *rebound* period with a higher number of cases is expected to be seen after approximately 5 years, possibly due to many children still being susceptible as they reach school age. By performing a vaccination campaign for susceptible older children as the programme is initiated ("catch-up" vaccination), the virus circulation will diminish even faster, with fewer than 1000 cases/year within 3 years from the implementation. Furthermore, no rebound period was seen in the models vaccinating susceptible older children. A 95% coverage rate of vaccination was assumed both for the vaccination starting at 12 or 18 month of age and for catch-up vaccination. Varicella vaccination also has a great impact on the number of HZ cases in the long-term.

Figure 1. The annual number of varicella cases after introducing varicella vaccination in a national immunisation programme, without (left) and with (right) a vaccination campaign targeting susceptible older children.



Health economic analyses

In the health economic analyses, we compared the costs and health effects of the four vaccination scenarios to no vaccination over their respective time horizons and discounted both costs and health outcomes by 3% annually. The analyses were conducted from both a societal and a health systems perspective. The results were not sensitive to the differences in the four varicella vaccination strategies presented above (Table 1). Our analyses suggest that scenarios without catch-up would lead to approximately 11,300 QALYs gained during the 95-year time horizon of the model versus approximately 12,400 QALYs with catch-up, all in comparison with no vaccination. The scenarios would lead to a decrease in costs associated with varicella of roughly 7.5 billion SEK (no catch-up) versus 8.1 billion SEK (with catch-up) from a societal perspective. Cost-savings were dominated by averted child caregiver productivity losses. This implies that VZV vaccination is a 'dominant' health intervention, i.e. it improves health outcomes at a lower cost to society than no vaccination programme. From a health systems perspective (with

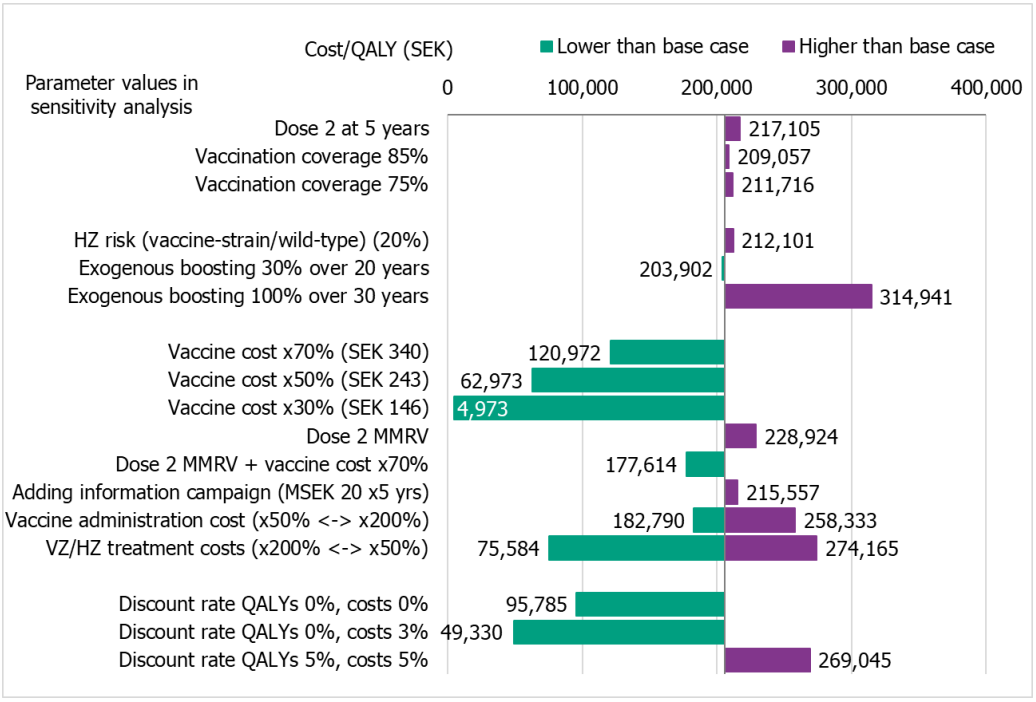
production losses excluded from the analysis) the cost per gained QALY would be slightly above SEK 200,000 for all scenarios.

Table 2. Cost-effectiveness results

Scenario	Total QALY gain, 95-year time horizon	Total cost savings (societal perspective), 95-year time horizon	Cost per QALY gained (societal perspective)	Cost per QALY gained (health system perspective)
Scenario 18m5y	11,500 QALYs	SEK 7.5 billion	Cost saving	SEK 209,000/QALY
Scenario 18m7y	11.300 QALYs	SEK 7.5 billion	Cost saving	SEK 203,000/QALY
Scenario 18m5y+cu 5+7,7+11,11+13y	12,400 QALYs	SEK 8.0 billion	Cost saving	SEK 215,000/QALY
Scenario 18m7y+cu 5+7,7+11,11+13y	12,400 QALYs	SEK 8.1 billion	Cost saving	SEK 206,000/QALY

In order to investigate the robustness of the results of our analysis, we conducted several sensitivity analyses. Since the vaccination was cost-saving from a societal perspective with any variation in key input parameters these analyses are only presented from a health systems perspective. Variations in the vaccine price, exogenous boosting assumption, healthcare cost and discount rates applied had the highest impact on the results (see Figure 2).

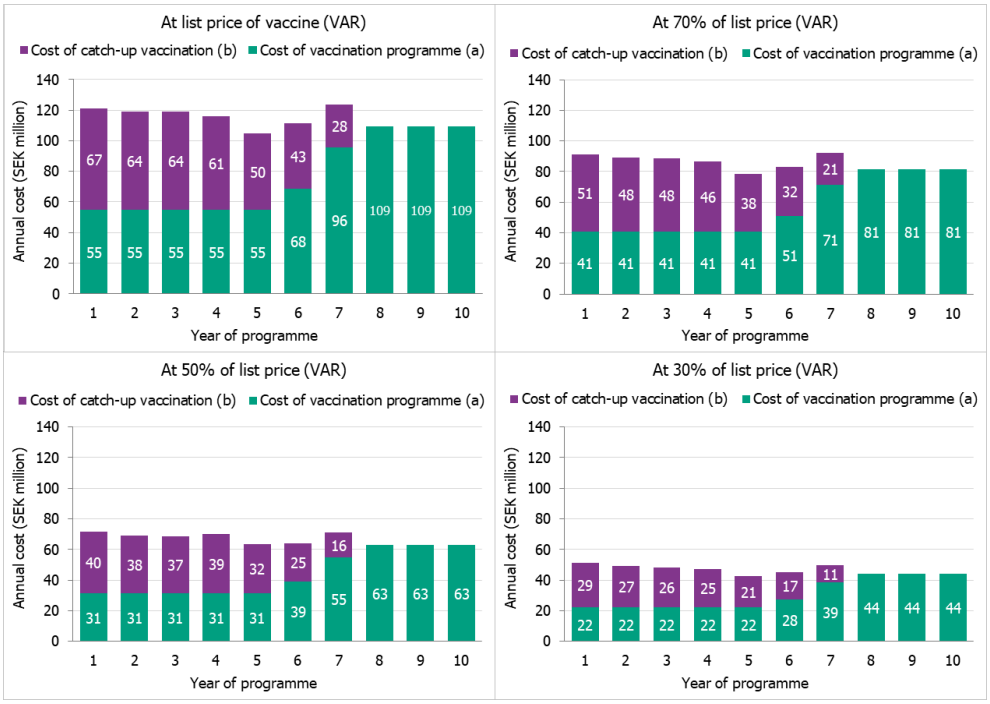
Figure 2. Sensitivity analyses provider perspective (vaccination at age 18 months and 7 years with catch-up (base case cost per QALY gained (y-axis) SEK 206,137)



Budget impact

Figure 3 gives an overview of annual programme costs over the first 10 years of the programme with different assumptions of vaccine price. The estimation includes the administration cost of giving the vaccine but no other programme implementation costs such as training of health care staff and providing information to the public. A coverage rate of 95% is assumed for both the vaccination programme and the catch-up. The cost of providing dose 1 is assumed to be SEK 55 million/year 1 with the current list prices for the vaccines, and SEK 31 million/year assuming a vaccine cost at 50% of the current list prices (both calculations include vaccine administration costs, estimated at SEK 84 per dose (15 minutes nurse time) given as part of an already scheduled vaccine visit and SEK 180 when given as a separate visit (for children aged 15 year or older in the catch-up programme). The annual cost of the catch-up vaccination over the first 4 years (where after it gradually decreases) is estimated to around SEK 64 million with the current list price of the monovalent vaccines and to SEK 38 million per year assuming a cost of 50% of the list prices. In the health economic evaluation are also presented budget calculations where MMRV is used for administering dose 2 or both doses.

Figure 3. 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 (VAR), annual cost (million SEK)



(a) The calculation is based on a cohort of 101,000 children in the programme (the number of children born in Sweden in 2023 (103))

(b) Annual cost of the cost of the catch-up programme are spread over 7 years in order for both dose 1 and 2 to be administered to eligible children in combination with other vaccine visits with other already scheduled vaccination visits.

Impact of varicella vaccinations on health care providers work situation

Regional level – Child health services

Background

The chickenpox vaccine, as part of the NIP, will be administered at the Swedish child health units (BVCs) as part of the national child health programme when doses are given before the age of 6 years. The child health programme includes health visits at certain ages, and additional visits are offered when concerns about the child's physical, social, or mental health status arise (104).

At 12 months of age the child will be offered two vaccine injections: one combined vaccine against diphtheria, tetanus, pertussis, polio, haemophilus type B, and hepatitis B and a separate vaccine against invasive pneumococcal disease. At 18 months of age, immunisation against measles, mumps, and rubella is due, and the final immunisation within the child health programme before school entry is at age 5 with the boosting of diphtheria, tetanus, pertussis, and polio.

Time and timing

The process of immunising a child against varicella within the NIP needs to include the following steps: preparation of the vaccine and syringe, thorough vaccine information about effects and side-effects, addressing parents' questions, pain-reduction, and the subsequent documentation in the child's record. The estimated time for this process is approximately 15 minutes on average, but when interpreter services are needed at least 10 more minutes should be added to the process. Extra time is needed for ordering the interpreter services, co-ordinating the visit, and performing the vaccination. Children who migrate to Sweden from countries with different NIPs have to be smoothly transitioned to the Swedish schedule. With one more vaccine to be considered, this work will gain complexity, and some concerns have been raised about the additional workload if varicella vaccination is added to the NIP.

Based on the Swedish birth cohort of 2022, this would translate to a total of 49400 extra working hours per year (based on an assumed 15 minutes per vaccination). If tetravalent MPRV is used for the second dose, that dose is assumed not to need any extra time and the two doses would then demand to 24700 extra working hours in total. If varicella vaccination is introduced in the NIP, extra resources may be needed for the prolonged time in already existing health visits or for additional health visits.

The short-term effects of the introduction of varicella vaccination in the NIP are expected to decrease the number of children contracting and spreading VZV. In 2022, 51% of children aged 12 months and 91% of children aged 24 months had started in day-care (105). Protection against varicella would assumingly have a larger impact in preventing the disease when the first dose is given before 24

months of age. The impact in disease prevention is assumed to be even greater if a temporary stake vaccination (catch-up) of susceptible older children is implemented as varicella vaccine is included in the NIP. Presumably, this would have a positive impact on child health services because fewer appointments are going to be cancelled due to varicella disease, although the number of cancelled appointments due to varicella in Sweden today is unknown. In addition, it would lead to fewer contacts with the health care system, thus saving resources at that end (further elaborated on in the modelling and health economic sections).

The expected impact on health care services from vaccine doses planned at different ages is presented in table 6.

Monovalent vs. tetravalent vaccines

Depending on whether the vaccine is offered separately or in combination with the MMR vaccine, the impact on services will differ. Administering monovalent varicella vaccine will require more time for another visit or will lengthen the visit due to several injections. In case of choosing the monovalent varicella vaccine, this vaccine has to be ordered separately compared to choosing the tetravalent vaccine where just one order has to be processed. In addition, there is a risk of mixing up vaccines when dealing with multiple syringes. Finally, administering monovalent varicella vaccine concomitantly with other vaccines would challenge injection techniques and pain-reducing procedures (106). Independent of the child's age, fewer shots implies less stress and pain for the child.

The MMRV combination vaccines, i.e. including varicella, have been shown to increase the risk for febrile seizures in children 12–23 months of age after the first vaccination, which requires thorough information from the nurse. Caregivers might worry and more frequently seek BVC services after immunisation. Potentially, the higher risk for febrile seizures could increase the number of caregivers declining immunisation or choosing MMR only or MMR and varicella vaccines separately (107). It is crucial to maintain trust among caregivers in order for the NIP to continuously reach high coverage even for the already established vaccines. The increased risk for febrile seizures after combined MMRV vaccine is not evident at age 4–6 years (95). See also the section on Safety.

Community level – School Health Care Services

Background

Scenarios for varicella vaccination as part of the NIP that include children older than 5 years of age would affect the school health organisation. The school health care programme includes health visits, at least four times during primary school (school year 0–9) and most often offered in grade 1-2, 4, and 7 and in the first year of high school. Today, immunisation is offered and carried out by school nurses. In grade 1 or 2 MMR vaccinations are offered, in grade 5 or 6 two doses of HPV vaccine are offered, and in grade 8 or 9 vaccination against DTP (booster) is

offered. Moreover, school nurses provide complementary vaccines prescribed by the school physician or designated school health nurses until 18 years of age. Usually, two school nurses work together when performing the vaccinations in order to maintain a high level of quality and safety. The municipalities and independent schools determine what vaccination routines should apply in their district or school. The circumstances for the school nurses can differ between various municipalities and independent elementary schools, but also between schools within the same municipality or independent school group. The capacity for imposing additional duties on a school differs within the country. However, more statutory tasks risk pushing aside non-statutory work such as open reception for students, health education, etc.

A survey was conducted in 2017 to determine the impact on school health care regarding the extra time needed for HPV vaccination of boys. School nurses in 15 municipalities and some independent schools were asked about their estimated time for the different parts of the vaccination procedure with regards to HPV vaccination of girls. Around 235 school nurses responded to the questionnaire. The first parts of the immunisation process, e.g. ordering vaccine, providing information in the classroom, and scheduling vaccination together with the teacher, are estimated to take an average of 30 minutes for each round of vaccinations. Additional time for vaccination procedures on an individual level is estimated to be an average of 15–20 minutes per child and dose. The time required for documentation of vaccinations depends on various factors. Documentation in digital health records with access to templates requires less time than the documentation on paper-based records. Caregivers with digital records have the option of transferring vaccination data from the records, either directly or via Svevac, to the National Vaccination Register. More time is required in the case of manual online reporting to the National Vaccination Register by caregivers with paper-based records and caregivers without automatic transfer (similar as for the BVCs).

It is important to note that the different parts of the immunisation process are spread out over a period of time that can range from a few weeks to several months. Obtaining consent from the caregiver is a time-consuming process both in terms of minutes per child and regarding the period of time from handing out the forms to getting all of them back.

In Sweden 113,000 to 117,700 children were born each year in the 2013–2021, followed by a dip in 2022 (104,000 children born). Due to immigration and the fact that all children living in Sweden have the right to go to school and thereby also have access to school health care, the number of children in each age group is somewhat higher.

The expected impact on health care services from vaccine doses planned at different ages, is presented in table 6.

Table 3. Expected impact on health care services from vaccine doses planned at different ages.

Alt	Age for vaccination	Child health services	School health services
A	12 months, monovalent varicella vaccine given as first dose	There is an existing health visit scheduled at 12 months in the national child health programme. Adding one dose of monovalent varicella vaccine implies one extra shot, resulting in three injections at a single health visit. This increases discomfort for the child and could cause hesitancy among parents and staff (i.e. a potential trust issue). An average 15–20 minutes extra time has to be calculated for information about and preparation of the vaccine. When an interpreter is needed, the amount of time should be increased.	No impact on school health services.
B	18 months, monovalent varicella vaccine or combined tetravalent MMRV vaccine given as first or second dose	There is an existing health visit scheduled at 18 months in the national child health programme. Given as the first dose, the vaccine could be given as MMRV or as monovalent V concomitantly with the MMR dose. If the first dose is given as monovalent V it would result in two injections instead of one at this health visit. This implies greater discomfort for the child. The first dose instead given as a tetravalent MMRV vaccine has a higher risk for febrile seizures. This implies discomfort for the child and caregivers and might lead to increased contact with health care services. Febrile seizures as a side-effect might have a negative impact on trust in the NIP. Given as the second dose, MMRV could be used. Combined chickenpox vaccine has not shown any increased risk for febrile seizures when given as a second dose.	No impact on school health services.
C	5 years, monovalent varicella vaccine given as a second dose	The second dose could preferably be given concomitantly with the tetravalent booster dose at 5 years of age, resulting in two injections instead of one at this health visit. This implies greater discomfort for the child. An average of 15–20 minutes extra time has been calculated for information about and preparation of the vaccine. When an interpreter is needed, the amount of time should be increased.	No impact on school health services.

Alt	Age for vaccination	Child health services	School health services
D	7-8 years, monovalent varicella vaccine or combined tetravalent MMRV vaccine given as a second dose	No impact on child health services.	Information for caregivers and the child on why varicella was added to the NIP. Combined chickenpox vaccine has not shown any increased risk for febrile seizures when given as a second dose. If the dose is given as a monovalent varicella vaccine, there will be two injections instead of one at this health visit. See alternative C. Convenient to vaccinate at an age already established in the programme.
E	Catch-up vaccination of susceptible children, older than age for first dose	Vaccine could be given concomitantly with the tetravalent booster dose at 5 years of age. See alternative C.	Vaccine could be given concomitantly with MMR at 6–8 years of age, both doses of HPV at 11 years of age, or DTP booster at 14 years of age, resulting in two injections instead of one at these health visits. See alternative C. Convenient to vaccinate at ages already established in the programme.

Attitudes and acceptance towards varicella vaccinations

Varicella vaccination

Attitudes and acceptance among parents

Parental attitudes and acceptance of childhood vaccinations are complex and are influenced by numerous factors. Factors influencing parental decision-making regarding vaccinations range from individual determinants to social norms and contextual factors as well as vaccination services and political policies (108). In particular, having health care professionals as well as national guidelines advise or recommend childhood vaccinations has been identified as a key factor for promoting vaccinations (109). Moreover, the importance of trust in health care providers has also been identified as an essential factor for vaccine uptake and the acceptance of childhood vaccines (108, 110) as well as trusting the information provided to the parents by the physician or nurse (111).

Several countries have already implemented varicella vaccination, and factors for vaccine uptake and acceptance have been assessed. Routine varicella vaccination has been offered in Germany since 2004, and therefore vaccination acceptance and coverage has been assessed in several studies, mainly performed in the early years after the introduction of the vaccine. The general picture was an increasing acceptance and coverage (112-114). Access to information was a key factor as well as having had the vaccine recommended by a paediatrician. Similarly, positive attitudes among parents towards varicella vaccinations have been reported from

studies in Hong Kong and New Zealand (115, 116). In contrast, only 28% of parents with children aged 0–4 years in the Netherlands had a positive intention to accept universal varicella vaccination for their child, whereas 21% were indecisive (117). If the vaccine would not be offered free of charge, the positive intention was even lower (20%). In relation to other diseases vaccinated against in the Netherlands, parents ranked varicella as the mildest, and the majority believed that it is a disease that "one is better off having been through". No association was found between parents' knowledge scores for VZV and intention for universal vaccination. An important predictor for positive intention was agreeing with the belief that "varicella is a disease serious enough to vaccinate against".

Finland introduced varicella vaccination in the child immunisation programme in 2017. A separate appointment was introduced at 18 months of age to receive the first dose (118). Among children born from 2015, vaccination coverage did not reach 80% by 2018, which is considered too low to interrupt virus circulating in society. As varicella vaccine was introduced, a campaign to vaccinate children up to 11 years without any history of varicella infection was also rolled out, which was expected to have been effective in interrupting the circulation of varicella virus in society. Vaccination coverage among children born in 2020 has by 2023 been stabilized at 86%, which is lower than for other vaccines in the Finnish child immunisation programme that for the same age cohort range between 93% and 97% (119).

In 2018, a survey regarding attitudes towards varicella and varicella vaccination was sent to Swedish parents participating in the web-panel "Hälsorapport" run by the PHAS (unpublished). In total, 1,056 parents to children aged 0–15 years (75%) responded. Data were weighted based on background variables in order to achieve representativeness of the Swedish population. Parents reported that 70% of the children had had a VZV infection, and only a few (6%) had been admitted to hospital due to the infection. A minority (9%) of the parents had vaccinated their child against varicella at their own initiative and payment. Overall, most parents responded that they had either a positive (46%) or neutral (39%) attitude towards varicella vaccination for children. When asked about VZV infection being a mild disease for children, about one quarter (27%) of the parents agreed to a great extent, 48% somewhat agreed, and close to a fifth (18%) did not agree at all. Only a few parents (13%) either agreed or agreed to a great extent that they were worried about adverse events from the varicella vaccine. If the vaccine were to be included in the NIP and offered to children under the age of 2 years, a striking majority of the parents to children 0–5 years (86%) said they intended to have their children vaccinated. Similarly, 79% and 87% of parents to children 6–10 and 11–15 years of age, respectively, had a positive intention for vaccination of younger children. The positive intention among parents was even higher (96%) if the vaccine were to be offered to teenagers who have not yet had varicella infection.

One possible scenario is that the varicella vaccination is given during the routine 12-month visit as part of the national child health programme. In this case, three

vaccinations will be given to the child during the same visit. Another survey focusing on MMR vaccination for children was conducted through the web-panel "Hälsorapport" of parents with children aged 0–15 years in November 2017. The survey assessed parental acceptance of giving three injections of vaccination (combination against measles, mumps and rubella; combination against diphtheria, tetanus, pertussis, polio, haemophilus type B, hepatitis B; and a separate vaccine against invasive pneumococcal disease) during the 12-month routine visit at the BVC. A majority of the parents (76%) felt comfortable with having their child receiving three injections, and 24% were not comfortable. However, the acceptance was lower (a 12% reduction) compared to the current national immunisation programme of two shots. If there was a possibility to postpone one of the three vaccinations, 47% would not want to postpone whereas 20% would definitely or most likely postpone.

A literature review suggests that reluctance among parents increases with the number of injections given at the same visit (120). The main reasons being concerns about the child's pain, adverse events, and stress on the immune system. However, parents who accepted multiple injections had performed a risk-benefit analysis with the positive aspects outweighing the risks. Recommendations from the provider, disease severity, and VE were important factors for accepting vaccinations.

Attitudes and acceptance among child health nurses

In Sweden, if the varicella vaccination is introduced to the NIP it might be offered and administered by nurses specialising in child health at national BVCs. To our knowledge, there are no scientific studies that have been conducted earlier on attitudes and acceptance among nurses for varicella vaccination in Sweden. Therefore, surveys were conducted to get a sense of the attitudes among child health nurses in Skåne and Stockholm, Sweden. One survey included 118 nurses from the Region of Skåne, and 58 nurses (49%) were in favour of varicella vaccination while 39 nurses (33%) were against the introduction of varicella vaccination to the Swedish NIP. A total of 21 nurses (18%) were undecided. Regardless of their responses, nurses in all three categories expressed a desire for improved knowledge about the vaccine.

Among nurses in support of the vaccine, frequent comments were that the vaccine has already been introduced in many other countries and that even in Sweden there is also an increasing demand for the varicella vaccine among parents coming to the BVC. A potential inclusion of the varicella vaccine in the NIP was also seen as an opportunity to offer equal health services to all children, including families with several children and/or families who do not have the means to pay for the vaccine themselves. Some nurses emphasised that especially children at risk should be offered the vaccine. If introduced to the NIP, the combined vaccine including MMRV was preferred. The nurses participating in the survey considered it impossible to introduce another health visit to the BVC. Crucially, all nurses

emphasised that additional time is needed for the procedure of immunising against varicella, which has to be funded and allocated accordingly.

On the one hand, among nurses who were indecisive regarding the varicella vaccine many expressed ambivalence and the need for more information. On the other hand, nurses doubting or disagreeing with the introduction of a varicella vaccine in the NIP expressed that varicella is a harmless disease and that only teenagers and adults who have not yet had the disease would need protection by the vaccine. A similar rationale was seen in a study from the Netherlands (117). Hesitant nurses suggested that the HZ vaccine for adults should be introduced nationally before varicella vaccine for children. Also see the Impact on health care providers section for more details. Reluctance among providers has also been seen to increase with the number of injections given at the same visit. Among providers, reluctance was due to a number of reasons such as concerns of giving too many injections, safety, risk of adverse events, and pain for the child, as well as questioning the need for newly introduced vaccines (120).

A small sample of specialist nurses (40 nurses) working in the south-west region of Stockholm were also asked about the potential inclusion of the varicella vaccine in the NIP. The results were similar to the above-mentioned survey conducted among nurses in Skåne.

Furthermore, the same survey was administered to 14 managers responsible for various BVCs in Skåne, as well as to a group of 14 managers in charge of either antenatal care units, delivery room units, postnatal care units, or neonatal intensive care units. The vast majority of the managers were in favour of the introduction of varicella vaccine (13 and 11 persons, respectively).

Importance of trust and knowledge

BVC nurses in Sweden are subspecialised and experienced nurses in health promotion as well as disease prevention and interventions. Parents seek advice for their child from their BVC nurse for a broad range of health-related issues, and they trust their medical judgement. Therefore, parental trust in the BVC nurse is essential when they make the decision regarding childhood vaccinations (121). The vaccination coverage for current vaccinations included in the NIP has been high and stable in Sweden for many years. This successful vaccination coverage is primarily built on strong parental trust of the nurses at BVCs. Parents also trust the health care system recommending and delivering the vaccinations included in the NIP.

Nurses' knowledge is not only needed regarding the vaccine, but also concerning both varicella and shingles and the complexity and the interplay of the diseases. Being able to respond to questions posed by parents is crucial because nurses have the opportunity to provide parents with trustworthy information and knowledge for making informed decisions. Nowadays parents are frequently overwhelmed by complex and often conflicting information available from different sources.

Perceiving varicella as a harmless disease and therefore believing it not necessary to vaccinate against might be a risk for low acceptance of the vaccine if introduced in the NIP. A German study showed that professionals and parents who perceived varicella as a serious disease and necessary to vaccinate against had a positive attitude or intention to vaccinate (117).

Nurses have to be thoroughly educated in order to address various parental questions and concerns. Therefore, there is a need for a well-designed educational programme that can provide the nurses with up-to-date knowledge regarding varicella and the vaccine. Such an intervention is also key for the successful implementation of the varicella vaccine in the NIP and for enhancing parental acceptance and confidence for the vaccination.

Attitudes and acceptance among school health care nurses

There are different scenarios to examine when considering the inclusion of varicella vaccine in the NIP. One of the scenarios is to offer and administer varicella vaccine by specialised school health care nurses at schools. In order to get a sense of the actual attitudes of these school health care nurses, a small survey was conducted among specialised school nurses from the Region of Örebro, Sweden. The survey (4 questions) was sent to 58 nurses, of which 24 responded (43%). Nearly all nurses, 92%, were in favour of the introduction of a varicella vaccine. About one third of these nurses were positive even if the vaccine was not being offered and administered by the school health care nurses. These nurses believed it is better for the children and the effect of the programme if the vaccine is given early in the child's life. They pointed out that the workload for the school nurses might be a problem, but despite this 15 nurses (63%) were positive to the introduction of varicella vaccine. However, they emphasised that it is necessary to allocate additional resources specifically to the school health care nurses in order to compensate for the extra workload. Along with the survey, the nurses also received brief information about VZV, severe complications of the disease, the burden of disease, and why the varicella vaccine is being considered to be included in the NIP. This information might have influenced the answers towards a more positive attitude. A positive attitude among school health care nurses was previously seen in a Canadian study on attitudes towards both current and proposed vaccines to be included in the NIP (122). The results of that survey showed that nurses had a more positive attitude to combined vaccines and to vaccines that they had received more information about. Similar results were also found by Dubé et al. in Canada (123). A more negative attitude towards the varicella vaccine was seen in a study conducted among nurses and parents in the Netherlands (117), and the authors concluded that a negative attitude towards the vaccine was more common among those perceiving varicella to be a mild disease.

Summary

Health care staff, and in Sweden especially child and school health care nurses, have a central role in promoting and supporting attitudes towards varicella and other vaccines, and recent surveys have found that they have varying views on the potential introduction of a varicella vaccine in the NIP. Nurses not only need more information and better knowledge about the vaccine, but also about the disease and its complications. The introduction of any vaccine in the NIP must be preceded by thorough educational efforts in order to facilitate successful implementation.

The school health nurses had positive attitudes towards a potential introduction of the varicella vaccine in the NIP when given brief background information about both the disease and the vaccine, and they emphasised the need for allocation of sufficient resources. The most convenient alternative, and probably the most accepted among health care staff, would be to offer the first dose as monovalent varicella vaccine at 18 months of age and the second dose as a combined vaccine (MMRV) at the age for the second dose of MMR, which is currently given in school. With this strategy, the workload for school health nurses would only be expanded to respond to parents' questions regarding the vaccine and the disease once the catch-up vaccination of older children is finished (approximately 3-4 years).

Although the intention to vaccinate might differ from actual behaviour, the strong intention reported by Swedish parents indicates that a majority of parents would accept vaccinating their children against varicella if the vaccine were to be offered as part of the NIP. To complement the survey performed among Swedish parents and to get a deeper understanding of parental attitudes and acceptance of varicella vaccination, a qualitative study would be needed. Having nurses and health care professionals recommending the vaccine as well as providing satisfactory information materials would be key factors for successful implementation and for reaching a high vaccine uptake.

Other preventive measures or treatments

Treatment of varicella in the immunocompetent host

Varicella

Antiviral treatment is not indicated in the healthy child with varicella, but symptomatic treatment is recommended, e.g. over-the-counter drugs against fever and itching. Adults with primary varicella are recommended antiviral treatment, generally acyclovir or valacyclovir tablets, if treatment can be initiated early in the course of disease, preferably within 24 hours of onset but no later than 72 hours.

Varicella with complications

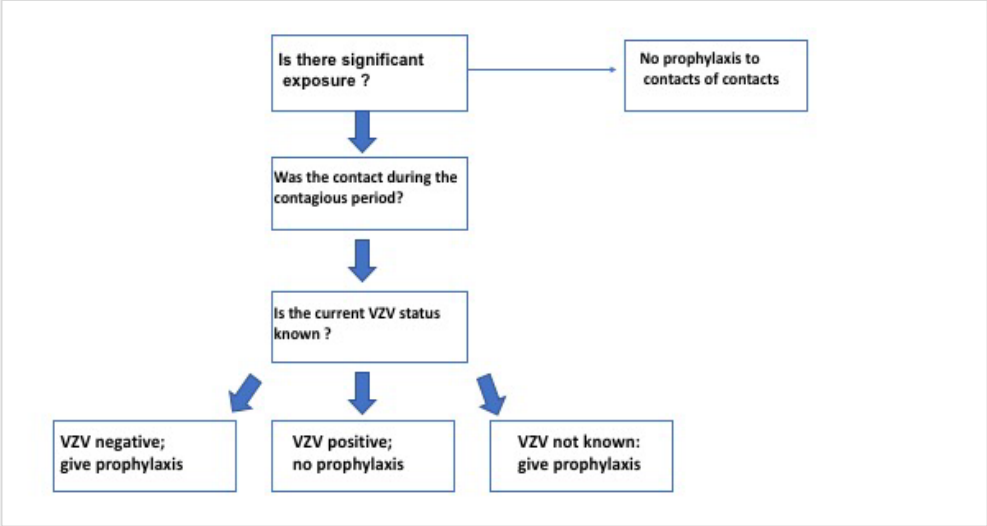
Anyone with VZV disease with complications, e.g. pneumonitis or hepatitis, should receive treatment with intravenous acyclovir.

In severe cases of cerebellitis, antiviral treatment should be considered. Other VZV-related complications affecting the CNS, such as encephalitis, meningitis, myelitis, and stroke, should be treated with 7–14 days of intravenous acyclovir. In the case of myelitis, there should be the addition of a short course of high-dose glucocorticoids. Cranial nerve engagements should also be treated with antivirals and glucocorticoids, but not all cases will need parenteral treatment (124).

Post-exposure prophylaxis and treatment of varicella infection in the immunocompromised patient

Significant exposure to VZV with a risk for contracting the virus has been defined as household contact, face-to-face conversation, and being in the same room for at least 15 min (125). Contact with a healthy person who develops chickenpox within 2 days should also be considered a significant exposure. According to the UK guidelines, if a patient has pre-existing immunity no further actions are needed (Fig 2). However, in the Swedish guidelines for children with cancer, prophylaxis is given to all children during high-dose intensive chemotherapy (126).

Figure 4. Flow chart for varicella prophylaxis. Modified from the Green Book (UK) (125).



Once significant VZV exposure is established, prophylaxis can be offered in two forms – antiviral agents (acyclovir or valacyclovir) or VZIG. VZIG is prepared from pooled plasma from donors with high VZV antibody titres and has been shown to prevent varicella in healthy children provided that VZIG is given within 72 hours of exposure (127). In immunocompromised children, VZIG also reduces the incidence of varicella and reduces disease severity. The effective duration of VZIG is not known but is most likely 3–4 weeks as for other immunoglobulins. VZIG has been used to prevent varicella in immunocompromised children for at least 40 years, but the supply of VZIG is limited and should be restricted to those at greatest risk (125).

Prophylaxis with antiviral agents is commonly used for immunocompromised patients. Prophylaxis with acyclovir should start within 7 days after exposure at a dose of 20 mg/kg four times a day (maximum 800 mg × 4) and continue for 14 days (128).

Treatment of varicella in immunocompromised patients should always be done in close contact with a specialist. In Sweden, guidelines issued by the Swedish MPA (Läkemedelsverket) should be followed (128).

It should be noted that the monovalent vaccines (Varivax and Varilrix) are also licensed as post-exposure prophylaxis to non-immune individuals if administered no later than 72 hours after exposure. The protective efficacy was for Varivax reported to be ≥90%, and there are limited data indicating that severity may be somewhat reduced if administered after day 3 but within 5 days from exposure (129). The protective efficacy for Varilrix was reported to be 80% against moderate/severe illness (130).

Summary – other preventive measures and treatment

Strategies available for the treatment and prevention of VZV-associated disease and complications include antiviral treatment, varicella-specific immunoglobulins, vaccinations around individuals at risk of developing severe varicella infection or HZ (cocooning), and isolation of at-risk patients. The use of these different strategies depends on individual clinical situations and decisions made by medical specialists.

Monitoring the impact of vaccinations

The main objective of monitoring vaccination programmes is to ensure that set goals are achieved regarding the implementation of vaccination, the impact of the vaccination on disease burden, and the expected risk-benefit profile. The results of monitoring can indicate if the programme needs to be changed, e.g. the scheduled age or the need for booster doses.

The monitoring of the effects of vaccinations in the NIP consists of:

- Vaccination coverage
- Disease surveillance
- Microbiological surveillance
- Seroepidemiological investigations of immunity in the population
- Safety monitoring

Monitoring of the varicella vaccination programme

Vaccination coverage

High vaccination coverage is required for a successful vaccination programme. For varicella vaccination, achieving a high coverage for two doses is crucial. At low coverage, the programme may have undesirable effects on disease burden because it might shift onset towards older age groups who are at risk of more severe disease. According to the WHO, reaching a coverage of at least 80% must be ensured before considering the introduction of varicella vaccination in the NIP (6). The goal for achieving two-dose coverage in Sweden would be 95%, equal to the coverage for MMR vaccine.

The national vaccination register is used to monitor vaccination coverage, and all vaccinations included in the NIP should be reported to the National Vaccination Register maintained by the PHAS. The data in the National Vaccination Register can be used to calculate vaccination coverage per dose, age group, county, and municipality. The analysis of vaccination coverage through the National Vaccination Register is currently done yearly by the PHAS. When introducing new vaccines, the coverage can be followed more frequently from the beginning.

Disease surveillance

The aim of disease surveillance is to monitor the impact of vaccination on VZV disease burden and epidemiology. The indicators that are followed include hospitalisations and age-specific varicella and HZ incidence. In order to monitor outbreaks after the disease is no longer endemic, a system for active outbreak reporting should be considered 5–7 years after the introduction of vaccination.

Varicella, except for its complication meningoencephalitis, is not a notifiable disease according to the Communicable Diseases Act. Most varicella cases do not seek medical care, and even if the disease were to become notifiable underreporting is expected to be considerable if attempting to include all varicella. Laboratory reporting of VZV-positive samples can be used to follow age-specific incidence of severe cases, but microbiological samples are rarely collected in varicella cases and routines vary between clinics. To monitor changes in disease burden, the National Patient Register data on varicella-related hospitalisations and the Cause of Death Register data on mortality can be analysed retrospectively. A better monitoring would likely be obtained by also making varicella cases admitted to hospital notifiable according to the Communicable Disease Act. Data from the studies on disease burden performed in the pre-vaccination period will be used as a baseline (30).

The National Patient Register maintained by the National Board of Health and Welfare (NBHW) contains data on all inpatient care and outpatient specialist health care and visits to specialist medical clinics and emergency departments. Reporting is mandatory by law, and the register has a good completeness (131). There is, however, some delay in registering and updating the database. ICD-10 codes at hospital discharge could be used to identify varicella-related cases, and overall and age-specific varicella incidence for hospitalised cases can be analysed using data from the National Patient Register.

Varicella vaccination will provide indirect protection to people who are not eligible for vaccination. For example, varicella incidence among infants is expected to decrease after the introduction of varicella vaccination into the NIP. Data on hospitalisations and consultations in specialist care among infants in the baseline study could be compared to data from the patient register after vaccine introduction. Age-specific case-based data from registers allow for the analysis of potential changes in median age among hospitalised cases.

Cases of viral meningoencephalitis caused by VZV are reported to Sminet, a database for notifiable diseases at the PHAS. Although meningoencephalitis can be a complication of both varicella and HZ, it is mostly caused by reactivation of the latent virus. Clinical data, such as symptoms or primary diagnosis, are usually not provided on the clinical reporting form. Diagnosis could be confirmed by register studies where data from Sminet and the patient register are co-processed.

Although varicella-related mortality is low, the impact of the vaccinations on mortality could be monitored and evaluated by analysing data for the pre- and post-

introduction periods within a later impact study. Relevant records of varicella-related deaths in the Cause of Death Register can be identified using ICD-10 codes.

Data on the cause and length of parents' absence from work to care for sick children are available from the Swedish Social Insurance Agency. Parents need to report care for a sick child to the Social Insurance Agency on the first day of their absence from work in order to receive the temporary benefit. Such data could be used to evaluate changes in overall varicella disease burden in children and the health economic benefit of the vaccination programme. A system for using social insurance data in monitoring the impact of health interventions needs to be further developed.

HZ surveillance is important in order to assess the impact of varicella vaccination on HZ epidemiology. Long-term follow up of HZ cases in vaccinated and unvaccinated cohorts is needed.

Microbiological surveillance

Virus identification from clinical specimens in order to differentiate wild-type VZV from vaccine-type VZV should be considered in case of severe varicella in a recently vaccinated child or if secondary cases caused by the vaccine strain are suspected. Viral strain identification should also be considered when HZ occurs in a previously vaccinated person.

Polymerase chain reaction testing to differentiate vaccine type from wild-type VZV is performed by the PHAS.

Seroepidemiological investigations

Antibody levels in the population and changes in age-specific seroprofiles can be studied through serological surveys, as is done for other vaccine-preventable diseases in approximately 10-year intervals,

Safety monitoring

The safety of any varicella vaccine will be followed by the MPA. All adverse events (AEs) or suspected AEs should be reported to the MPA. Even BV cases should be reported. The MPA's routine monitoring of vaccine safety is based on data from AE reports from health care personnel and consumers and other safety information (e.g. the European database for AEs and the mandatory periodic safety reports from the companies), as well as data from epidemiological studies and the scientific literature.

The safety monitoring is product oriented, i.e. it is dependent on the safety profile of each vaccine, and it is carried out by several parties. The producer of the vaccine has the main responsibility for the product, including safety monitoring. The Swedish MPA together with agencies in other EU countries, the EU commission, and the European Medicines Agency (EMA) are responsible for the approval, safety monitoring, and supervision of medical drugs, including vaccines, in Europe.

A safety signal is information on a new or known AE that might be caused by a medicine and requires further investigation. The EMA, together with the regulatory authorities in the EU Member States and marketing authorisation holders, is responsible for detecting and managing safety signals. Safety signals can be detected from a wide range of sources, such as spontaneous reports, clinical studies, and the scientific literature. The presence of a safety signal does not mean that a medicine has directly caused the reported AE, and an illness or another medicine taken by the patient could also be the cause. The assessment of safety signals establishes whether or not there is a causal relationship between the medicine and the reported AE. The evaluation of safety signals is part of routine pharmacovigilance and is essential to ensuring that regulatory authorities have the most up-to-date information on a medicine's benefits and risks.

Associated costs

The cost will be influenced by the number of register studies planned because these are labour intense and require the purchase of data from other agencies (such as the NBHW and Statistics Sweden). The costs are estimated to be 30,000 SEK yearly. These costs do not include overhead costs or funds to maintain the National Vaccination Register.

Summary – monitoring

The main objective of monitoring of vaccination programmes is to ensure that set goals are achieved regarding the implementation, the impact of the vaccination on disease burden, and the expected risk-benefit profile. The results will indicate if the programme needs to be changed, e.g. the scheduled age or the need for booster doses. Monitoring will be carried out through disease surveillance and virological surveillance and follow up of data concerning coverage, seroepidemiology, and safety. The monitoring activities will involve external partners such as the MPA, the NBHW, and the Swedish Social Insurance Agency.

Communication activities

In relation to the public and health care providers and associated costs.

Varicella vaccination

Communication activities to support the implementation of a national varicella vaccination programme are related to a large number of aspects, for example, the knowledge level and attitudes among child health and school health personnel, children (depending on age of vaccinations), and parents. The communication should mainly support action, such as parents' and children's informed decision-making and nurses' information about the vaccines and diseases as well as administering and registering of the vaccinations. As described in earlier sections about attitudes and impacts on health care, knowledge about varicella and the vaccinations likely varies among children and their parents.

Considering the important role of the nurses in child health and in schools in communicating with parents and children, the planned national communication activities should aim at supporting nurses with facts, hands-on tools for dialogue, and guidance for registering the vaccinations. Additionally, national activities should seek to clear up any misunderstandings or lack of knowledge that might hinder parents' and children's individual and informed decision making.

Objectives

During the introduction and further on, the communication activities should aim at:

- empowering health care professionals and relevant key actors in their task of offering and administering the vaccination
- facilitating children's and guardians' informed decision-making
- supporting equivalent communication and awareness in all units in all parts of the country.

Methods and activities

Several actors are involved in supporting a successful NIP through their communication. The most effective face-to-face communication will take place in, or in relation to, the local setting (child and school health care). This will be supported by national communication activities mainly through broader, non-personal communication channels and the various channels of the health care sector, such as 1177 Vårdguiden.

The PHAS will provide key actors with overall messages and basic information material. The agency will also collaborate with, for example, 1177 Vårdguiden, Rikshandboken för barnhälsovård, and digital communication channels to coordinate the dissemination of information to the public. Content, such as Questions and Answers, will be available on national websites, as well as relevant texts and graphic material. The national resources will aim at filling the gaps related to varying resources and at offering a variety of communication tools. Web-based questionnaires, education, and webinars as well as communication through social media will allow needs to be identified and information to be disseminated. The extension of the programme will also be an opportunity to strengthen the national communication supporting registration of administrated doses in the National Vaccination Register. County councils, municipalities, and child health and school health care units can build on the national material to develop their own activities that are tailored and supplemented according to the needs of the local target groups.

To support communication in the local setting, national printed material to hand out to parents and children and material to support dialogue and reflection would be a priority. When needed, timely support and updates through established networks would aim at preventing rumours and misunderstandings that might

prevent parents from accepting the vaccination. Because fear and rumours (often facilitated by media and social media) might occasionally affect the public perception of a vaccination, clear and timely support for communication by the well-trusted child health and school health care system aimed at maintaining confidence in the vaccination programme is important.

Time is a scarce resource already in these settings. This was shown in the previously mentioned survey among nurses in child health and school health care (see Impact of vaccinations on health care providers and Attitudes towards vaccinations). If issues with time negatively affect the nurses' ability to acquire knowledge and to communicate and to have an active dialogue with parents and children, this can become a problem for the extension of the vaccination programme. This cannot be solved by national communication and has to be planned for in the local setting.

References

1. Whitely R. Principles and Practice of Infectious Diseases. Ninth ed. Bennett JD, R; Blaser, M, editor: Elsevier.
2. Gershon A, Marin M, Seward JF. Varicella Vaccines. In: Plotkin SA, Orenstein WA, Offit PA, editors. Vaccines. 7th ed. Philadelphia, PA, USA: ELSEVIER; 2018. p. 1145-80.
3. Lopez AS, Zhang J, Marin M. Epidemiology of Varicella During the 2-Dose Varicella Vaccination Program - United States, 2005-2014. MMWR Morb Mortal Wkly Rep. 2016;65(34):902-5.
4. Campbell A, Ismail S, Tan B, approved by N. Literature Review on One-Dose and Two-Dose Varicella Vaccination: An Advisory Committee Statement (ACS) National Advisory Committee on Immunization (NACI)(dagger). Can Commun Dis Rep. 2010;36(ACS-10):1-24.
5. European Centre for Disease Prevention and Control. Varicella vaccination in the European Union: European Centre for Disease Prevention and Control; 2014 [Available from: https://ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/Varicella-Guidance-2015.pdf.
6. World Health Organization. Varicella and herpes zoster vaccines: WHO position paper, June 2014. Wkly Epidemiol Rec. 2014;89(25):265-87.
7. World Health Organization. Vaccines in National Immunization Programme. Update February 2019. Vaccine introduction slides. 2019. Contract No.: 2019-11-22.
8. Campbell A, Ismail S, Tan B, approved by N. Literature Review on One-Dose and Two-Dose Varicella Vaccination: An Advisory Committee Statement (ACS) National Advisory Committee on Immunization (NACI). Can Commun Dis Rep. 2010;36(ACS-10):1-24.
9. Sheel M, Beard F, Quinn H, Dey A, Kirk M, Koehler A, et al. Australian vaccine preventable disease epidemiological review series: varicella-zoster virus infections, 1998-2015. Commun Dis Intell (2018). 2018;42.
10. Varela FH, Pinto LA, Scotta MC. Global impact of varicella vaccination programs. Hum Vaccin Immunother. 2019;15(3):645-57.
11. European Centre for Disease Prevention and Control. Vaccine scheduler: ECDC; [Available from: https://vaccine-schedule.ecdc.europa.eu/.
12. VENICE. Varicella and herpes zoster surveillance and vaccination recommendations. 2011.
13. Finnish Institute for Health and Welfare (THL). Infectious diseases and vaccination. Varicella vaccine: THL Finland; [Available from: https://thl.fi/en/web/infectious-diseases-and-vaccinations/vaccines-a-to-z/varicella-vaccine.
14. Directorate of Health I. National Childhood Vaccination Program in Iceland as of July 2023. 2023.
15. Salo H, Perala J, Hannila-Handelberg T, Sarvikivi E, Luomala O, Ollgren J, et al. Decline in varicella cases contacting primary health care after introduction of varicella vaccination in Finland - A population-based register study. Vaccine. 2023.
16. JCVI statement on a childhood varicella (chickenpox) vaccination programme. Joint committee on vaccination and immunisation; 2023 14 november 2023.
17. Folkhälsomyndigheten [the Public Health Agency of Sweden}. Arbetsmodell för ändringar av nationella vaccinationsprogram [Model description for changes to the national vaccination programme]. 2015.
18. SAGE working group. Background paper on Varicella vaccines. SAGE working group; 2014.
19. Svahn A, Berggren J, Parke A, Storsaeter J, Thorstensson R, Linde A. Changes in seroprevalence to four herpesviruses over 30 years in Swedish children aged 9-12 years. J Clin Virol. 2006;37(2):118-23.

20. Widgren K, Persson Berg L, Morner A, Lindquist L, Tegnell A, Giesecke J, et al. Severe chickenpox disease and seroprevalence in Sweden - implications for general vaccination. Int J Infect Dis. 2021;111:92-8.

21. Parment PA, Svahn A, Ruden U, Brakenhielm G, Storsaeter J, Akesson L, et al. Immunogenicity and reactogenicity of a single dose of live attenuated varicella vaccine and a booster dose of measles-mumps-rubella vaccine given concomitantly at 12 years of age. Scand J Infect Dis. 2003;35(10):736-42.

22. Smittskyddsinstitutet [The Swedish Institute for Communicable Disease Control]. Barnvaccinationsprogrammet når även du utlandsfödda barnen [The Childhood vaccination programme reaches also the foreign-born children]. Smittskyddsinstitutet; 2012.

23. Olsson J, Kok E, Adolfsson R, Lovheim H, Elgh F. Herpes virus seroepidemiology in the adult Swedish population. Immun Ageing. 2017;14:10.

24. Bozzola E, Bozzola M, Krzysztofiak A, Tozzi AE, El Hachem M, Villani A. Varicella Skin Complications in Childhood: A Case Series and a Systematic Review of the Literature. Int J Mol Sci. 2016;17(5).

25. van der Maas NA, Bondt PE, de Melker H, Kemmeren JM. Acute cerebellar ataxia in the Netherlands: a study on the association with vaccinations and varicella zoster infection. Vaccine. 2009;27(13):1970-3.

26. Grahn A, Studahl M. Varicella-zoster virus infections of the central nervous system - Prognosis, diagnostics and treatment. J Infect. 2015;71(3):281-93.

27. Amlie-Lefond C, Gilden D. Varicella Zoster Virus: A Common Cause of Stroke in Children and Adults. J Stroke Cerebrovasc Dis. 2016;25(7):1561-9.

28. Thomas SL, Minassian C, Ganesan V, Langan SM, Smeeth L. Chickenpox and risk of stroke: a self-controlled case series analysis. Clin Infect Dis. 2014;58(1):61-8.

29. Lamont RF, Sobel JD, Carrington D, Mazaki-Tovi S, Kusanovic JP, Vaisbuch E, et al. Varicella-zoster virus (chickenpox) infection in pregnancy. BJOG. 2011;118(10):1155-62.

30. Widgren K, Giesecke J, Lindquist L, Tegnell A. The burden of chickenpox disease in Sweden. BMC Infect Dis. 2016;16(1):666.

31. Linde A, Lindberg A. [Should more people be vaccinated against varicella? Time to decide!]. Lakartidningen. 1997;94(14):1296, 9-301.

32. Grimheden P, Bennet R, Hjern A, Nilsson A, Eriksson M. [Chickenpox not always a harmless child disease. General vaccination in Sweden can prevent significant morbidity]. Lakartidningen. 2009;106(9):580-2.

33. Bennet R, Bogdanovic G, Giske CG, Eriksson M. [More severe bacterial infections could be prevented with vaccine. Rotavirus, influenza and varicella cause thousands of hospital admissions]. Lakartidningen. 2010;107(48):3040-3.

34. Laestadius A, Nilsson A, Bennet R, Bogdanovic G, Eriksson M. [The child immunisation programme--effective but insufficient. Experiences from the Astrid Lindgren pediatric hospital, 2008-2013]. Lakartidningen. 2017;114.

35. Feldman S, Hughes WT, Daniel CB. Varicella in children with cancer: Seventy-seven cases. Pediatrics. 1975;56(3):388-97.

36. Saidel-Odes L, Borer A, Riesenberg K, Frenkel A, Sherlis R, Bouhnick L, et al. An outbreak of varicella in staff nurses exposed to a patient with localized herpes zoster. Scand J Infect Dis. 2010;42(8):620-2.

37. Weinmann S, Naleway AL, Koppolu P, Baxter R, Belongia EA, Hambidge SJ, et al. Incidence of Herpes Zoster Among Children: 2003-2014. Pediatrics. 2019;144(1).

38. World Health Organization. The immunological basis for immunization series : Module 10: Varicella-zoster virus. Geneva: World Health Organization; 2008.

39. Laing KJ, Ouwendijk WJD, Koelle DM, Verjans G. Immunobiology of Varicella-Zoster Virus Infection. J Infect Dis. 2018;218(suppl_2):S68-S74.

40. Kuter BJ, Weibel RE, Guess HA, Matthews H, Morton DH, Neff BJ, et al. Oka/Merck varicella vaccine in healthy children: final report of a 2-year efficacy study and 7-year follow-up studies. Vaccine. 1991;9(9):643-7.

41. Weibel RE, Neff BJ, Kuter BJ, Guess HA, Rothenberger CA, Fitzgerald AJ, et al. Live attenuated varicella virus vaccine. Efficacy trial in healthy children. N Engl J Med. 1984;310(22):1409-15.

42. Varis T, Vesikari T. Efficacy of high-titer live attenuated varicella vaccine in healthy young children. J Infect Dis. 1996;174 Suppl 3:S330-4.

43. Kuter B, Matthews H, Shinefield H, Black S, Dennehy P, Watson B, et al. Ten year follow-up of healthy children who received one or two injections of varicella vaccine. Pediatr Infect Dis J. 2004;23(2):132-7.

44. Lau YL, Vessey SJ, Chan IS, Lee TL, Huang LM, Lee CY, et al. A comparison of safety, tolerability and immunogenicity of Oka/Merck varicella vaccine and VARILRIX in healthy children. Vaccine. 2002;20(23-24):2942-9.

45. Povey M, Henry O, Riise Bergsaker MA, Chlibek R, Esposito S, Flodmark CE, et al. Protection against varicella with two doses of combined measles-mumps-rubella-varicella vaccine or one dose of monovalent varicella vaccine: 10-year follow-up of a phase 3 multicentre, observer-blind, randomised, controlled trial. Lancet Infect Dis. 2019;19(3):287-97.

46. Henry O, Brzostek J, Czajka H, Leviniene G, Reshetko O, Gasparini R, et al. One or two doses of live varicella virus-containing vaccines: Efficacy, persistence of immune responses, and safety six years after administration in healthy children during their second year of life. Vaccine. 2018;36(3):381-7.

47. Henry O, Brzostek J, Czajka H, Leviniene G, Reshetko O, Gasparini R, et al. Corrigendum to "One or two doses of live varicella virus-containing vaccines: Efficacy, persistence of immune responses, and safety six years after administration in healthy children during their second year of life" [Vaccine 36 (2018) 381-387]. Vaccine. 2018;36(45):6894.

48. Marin M, Marti M, Kambhampati A, Jeram SM, Seward JF. Global Varicella Vaccine Effectiveness: A Meta-analysis. Pediatrics. 2016;137(3):e20153741.

49. Wutzler P, Bonanni P, Burgess M, Gershon A, Safadi MA, Casabona G. Varicella vaccination - the global experience. Expert Rev Vaccines. 2017;16(8):833-43.

50. Zhu S, Zeng F, Xia L, He H, Zhang J. Incidence rate of breakthrough varicella observed in healthy children after 1 or 2 doses of varicella vaccine: Results from a meta-analysis. Am J Infect Control. 2018;46(1):e1-e7.

51. Ahern S, Walsh KA, Paone S, Browne J, Carrigan M, Harrington P, et al. Clinical efficacy and effectiveness of alternative varicella vaccination strategies: An overview of reviews. Rev Med Virol. 2023;33(1):e2407.

52. Leung J, Broder KR, Marin M. Severe varicella in persons vaccinated with varicella vaccine (breakthrough varicella): a systematic literature review. Expert Rev Vaccines. 2017;16(4):391-400.

53. Seward JF, Marin M, Vazquez M. Varicella vaccine effectiveness in the US vaccination program: a review. J Infect Dis. 2008;197 Suppl 2:S82-9.

54. Guris D, Jumaan AO, Mascola L, Watson BM, Zhang JX, Chaves SS, et al. Changing varicella epidemiology in active surveillance sites--United States, 1995-2005. J Infect Dis. 2008;197 Suppl 2:S71-5.

55. Centers for Disease Control and Prevention (CDC). Monitoring the Impact of varicella Vaccination. 2018.

56. Quian J, Ruttimann R, Romero C, Dall'Orso P, Cerisola A, Breuer T, et al. Impact of universal varicella vaccination on 1-year-olds in Uruguay: 1997-2005. Arch Dis Child. 2008;93(10):845-50.

57. Tan B, Bettinger J, McConnell A, Scheifele D, Halperin S, Vaudry W, et al. The effect of funded varicella immunization programs on varicella-related hospitalizations in IMPACT centers, Canada, 2000-2008. Pediatr Infect Dis J. 2012;31(9):956-63.

58. Alberta Go. Incidence of chickenpox in Alberta. [uppdaterad 2015-06-16; citerad 2018-10-07]. 2015.

59. Sheridan SL, Quinn HE, Hull BP, Ware RS, Grimwood K, Lambert SB. Impact and effectiveness of childhood varicella vaccine program in Queensland, Australia. Vaccine. 2017;35(27):3490-7.

60. Hohle M, Siedler A, Bader HM, Ludwig M, Heininger U, Von Kries R. Assessment of varicella vaccine effectiveness in Germany: a time-series approach. Epidemiol Infect. 2011;139(11):1710-9.

61. Amodio E, Tramuto F, Cracchiolo M, Sciuto V, De Donno A, Guido M, et al. The impact of ten years of infant universal Varicella vaccination in Sicily, Italy (2003-2012). Hum Vaccin Immunother. 2015;11(1):236-9.

62. Marin M, Leung J, Anderson TC, Lopez AS. Monitoring Varicella Vaccine Impact on Varicella Incidence in the United States: Surveillance Challenges and Changing Epidemiology, 1995-2019. J Infect Dis. 2022;226(Suppl 4):S392-S9.

63. Leung J, Lopez AS, Blostein J, Thayer N, Zipprich J, Clayton A, et al. Impact of the US Two-dose Varicella Vaccination Program on the Epidemiology of Varicella Outbreaks: Data from Nine States, 2005-2012. Pediatr Infect Dis J. 2015;34(10):1105-9.

64. Leung J, Lopez AS, Marin M. Changing Epidemiology of Varicella Outbreaks in the United States During the Varicella Vaccination Program, 1995-2019. J Infect Dis. 2022;226(Suppl 4):S400-S6.

65. Bialek SR, Perella D, Zhang J, Mascola L, Viner K, Jackson C, et al. Impact of a routine two-dose varicella vaccination program on varicella epidemiology. Pediatrics. 2013;132(5):e1134-40.

66. Perella D, Wang C, Civen R, Viner K, Kuguru K, Daskalaki I, et al. Varicella Vaccine Effectiveness in Preventing Community Transmission in the 2-Dose Era. Pediatrics. 2016;137(4).

67. Harris T, Seo CY, Shing E, Wong K, Fediurek J, Deeks SL. A spot of bother: Why varicella vaccine programs matter. Can Commun Dis Rep. 2015;41(10):241-9.

68. Rieck T, Feig M, An der Heiden M, Siedler A, Wichmann O. Assessing varicella vaccine effectiveness and its influencing factors using health insurance claims data, Germany, 2006 to 2015. Euro Surveill. 2017;22(17).

69. Garcia Cenoz M, Castilla J, Chamorro J, Martinez-Baz I, Martinez-Artola V, Irisarri F, et al. Impact of universal two-dose vaccination on varicella epidemiology in Navarre, Spain, 2006 to 2012. Euro Surveill. 2013;18(32):20552.

70. Bayer O, Heininger U, Heiligensetzer C, von Kries R. Metaanalysis of vaccine effectiveness in varicella outbreaks. Vaccine. 2007;25(37-38):6655-60.

71. Spackova M, Wiese-Posselt M, Dehnert M, Matysiak-Klose D, Heininger U, Siedler A. Comparative varicella vaccine effectiveness during outbreaks in day-care centres. Vaccine. 2010;28(3):686-91.

72. Cenoz MG, Martinez-Artola V, Guevara M, Ezpeleta C, Barricarte A, Castilla J. Effectiveness of one and two doses of varicella vaccine in preventing laboratory-confirmed cases in children in Navarre, Spain. Hum Vaccin Immunother. 2013;9(5):1172-6.

73. Thomas CA, Shwe T, Bixler D, del Rosario M, Grytdal S, Wang C, et al. Two-dose varicella vaccine effectiveness and rash severity in outbreaks of varicella among public school students. Pediatr Infect Dis J. 2014;33(11):1164-8.

74. Latasa P, Gil de Miguel A, Barranco Ordonez MD, Rodero Garduno I, Sanz Moreno JC, Ordobas Gavin M, et al. Effectiveness and impact of a single-dose vaccine against chickenpox in the community of Madrid between 2001 and 2015. Hum Vaccin Immunother. 2018;14(9):2274-80.

75. Baxter R, Ray P, Tran TN, Black S, Shinefield HR, Coplan PM, et al. Long-term effectiveness of varicella vaccine: a 14-Year, prospective cohort study. Pediatrics. 2013;131(5):e1389-96.

76. Croce E, Hatz C, Jonker EF, Visser LG, Jaeger VK, Buhler S. Safety of live vaccinations on immunosuppressive therapy in patients with immune-mediated inflammatory diseases, solid organ transplantation or after bone-marrow transplantation - A systematic review of randomized trials, observational studies and case reports. Vaccine. 2017;35(9):1216-26.

77. Lindahl JK, Friman V, Ladfors SW, Hansson S, Andersson R, Jertborn M, et al. Long-term study showed that vaccination protected paediatric renal transplant recipients from life-threatening varicella zoster virus. Acta Paediatr. 2018;107(12):2185-92.

78. Smedegaard LM, Poulsen A, Kristensen IA, Rosthoj S, Schmiegelow K, Nygaard U. Varicella Vaccination of Children With Leukemia Without Interruption of Maintenance Therapy: A Danish Experience. Pediatr Infect Dis J. 2016;35(11):e348-e52.

79. Ngai AL, Staehle BO, Kuter BJ, Cyanovich NM, Cho I, Matthews H, et al. Safety and immunogenicity of one vs. two injections of Oka/Merck varicella vaccine in healthy children. Pediatr Infect Dis J. 1996;15(1):49-54.

80. De Serres G, Boulianne N, Defay F, Brousseau N, Benoit M, Lacoursiere S, et al. Higher risk of measles when the first dose of a 2-dose schedule of measles vaccine is given at 12-14 months versus 15 months of age. Clin Infect Dis. 2012;55(3):394-402.

81. Carazo Perez S, De Serres G, Bureau A, Skowronski DM. Reduced Antibody Response to Infant Measles Vaccination: Effects Based on Type and Timing of the First Vaccine Dose Persist After the Second Dose. Clin Infect Dis. 2017;65(7):1094-102.

82. Defay F, De Serres G, Skowronski DM, Boulianne N, Ouakki M, Landry M, et al. Measles in children vaccinated with 2 doses of MMR. Pediatrics. 2013;132(5):e1126-33.

83. Galea SA, Sweet A, Beninger P, Steinberg SP, Larussa PS, Gershon AA, et al. The safety profile of varicella vaccine: a 10-year review. J Infect Dis. 2008;197 Suppl 2:S165-9.

84. Gabutti G, Bolognesi N, Sandri F, Florescu C, Stefanati A. Varicella zoster virus vaccines: an update. Immunotargets Ther. 2019;8:15-28.

85. Ahern S, Walsh KA, Paone S, Browne J, Carrigan M, Harrington P, et al. Safety of varicella vaccination strategies: An overview of reviews. Rev Med Virol. 2023;33(2):e2416.

86. Chun C, Weinmann S, Riedlinger K, Mullooly JP, Houston H, Schmid DS, et al. Laboratory characteristics of suspected herpes zoster in vaccinated children. Pediatr Infect Dis J. 2011;30(8):719-21.

87. Weinmann S, Chun C, Schmid DS, Roberts M, Vandermeer M, Riedlinger K, et al. Incidence and clinical characteristics of herpes zoster among children in the varicella vaccine era, 2005-2009. J Infect Dis. 2013;208(11):1859-68.

88. Moodley A, Swanson J, Grose C, Bonthius DJ. Severe Herpes Zoster Following Varicella Vaccination in Immunocompetent Young Children. J Child Neurol. 2019;34(4):184-8.

89. European Medicines Agency. Monovalent and multivalent measles, mumps, rubella and / or varicella vaccines 2012 [Available from: https://www.ema.europa.eu/en/medicines/human/referrals/monovalent-multivalent-measles-mumps-rubella-varicella-vaccines.

90. Ma SJ, Li X, Xiong YQ, Yao AL, Chen Q. Combination Measles-Mumps-Rubella-Varicella Vaccine in Healthy Children: A Systematic Review and Meta-analysis of Immunogenicity and Safety. Medicine (Baltimore). 2015;94(44):e1721.

91. Leung JH, Hirai HW, Tsoi KK. Immunogenicity and reactogenicity of tetravalent vaccine for measles, mumps, rubella and varicella (MMRV) in healthy children: a meta-analysis of randomized controlled trials. Expert Rev Vaccines. 2015;14(8):1149-57.

92. MacDonald SE, Dover DC, Simmonds KA, Svenson LW. Risk of febrile seizures after first dose of measles–mumps–rubella–varicella vaccine: a population-based cohort study. Canadian Medical Association Journal. 2014;186(11):824-9.

93. Schink T, Holstiege J, Kowalzik F, Zepp F, Garbe E. Risk of febrile convulsions after MMRV vaccination in comparison to MMR or MMR+V vaccination. Vaccine. 2014;32(6):645-50.

94. Klein NP, Fireman B, Yih WK, Lewis E, Kulldorff M, Ray P, et al. Measles-Mumps-Rubella-Varicella Combination Vaccine and the Risk of Febrile Seizures. Pediatrics. 2010;126(1):e1-e8.

95. Klein NP, Lewis E, Baxter R, Weintraub E, Glanz J, Naleway A, et al. Measles-containing vaccines and febrile seizures in children age 4 to 6 years. Pediatrics. 2012;129(5):809-14.

96. Hope-Simpson RE. The Nature of Herpes Zoster: A Long-Term Study and a New Hypothesis. Proc R Soc Med. 1965;58:9-20.

97. Forbes H, Douglas I, Finn A, Breuer J, Bhaskaran K, Smeeth L, et al. Risk of herpes zoster after exposure to varicella to explore the exogenous boosting hypothesis: self controlled case series study using UK electronic healthcare data. BMJ. 2020;368:l6987.

98. Ogunjimi B, Van Damme P, Beutels P. Herpes Zoster Risk Reduction through Exposure to Chickenpox Patients: A Systematic Multidisciplinary Review. PLoS One. 2013;8(6):e66485.

99. Harder T, Siedler A. Systematic review and meta-analysis of chickenpox vaccination and risk of herpes zoster: a quantitative view on the "exogenous boosting hypothesis". Clin Infect Dis. 2018.

100. Harpaz R, Leung JW. The Epidemiology of Herpes Zoster in the United States During the Era of Varicella and Herpes Zoster Vaccines: Changing Patterns Among Children. Clin Infect Dis. 2018.

101. Talbird SE, La EM, Mauskopf J, Altland A, Daniels V, Wolfson LJ. Understanding the role of exogenous boosting in modeling varicella vaccination. Expert Rev Vaccines. 2018;17(11):1021-35.

102. Thomas SL, Wheeler JG, Hall AJ. Contacts with varicella or with children and protection against herpes zoster in adults: a case-control study. Lancet. 2002;360(9334):678-82.

103. Population Statistics [Internet]. 2023. Available from: https://www.scb.se/en/finding-statistics/statistics-by-subject-area/population/population-composition/population-statistics/#_Tablesandgraphs

104. Regioner SKo. Rikshandboken 2023 [Available from: https://www.rikshandboken-bhv.se/

105. Skolverket. Inskrivna barn i förskolan. https://www.skolverket.se/skolutveckling/statistik/sok-statistik-om-forskola-skola-och-vuxenutbildning?sok=SokC&verkform=F%C3%B6rskola&omrade=Barn%20och%20grupper&lasar=2022&run=12023.

106. Centers for Disease Control and Protection. Vaccine Recommendations and Guidelines of the ACIP: Centers for Disease Control and Protection; [Available from: https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/administration.html#ref-08.

107. Klein NP, Fireman B, Yih WK, Lewis E, Kulldorff M, Ray P, et al. Measles-mumps-rubella-varicella combination vaccine and the risk of febrile seizures. Pediatrics. 2010;126(1):e1-8.

108. Dube E, Gagnon D, MacDonald N, Bocquier A, Peretti-Watel P, Verger P. Underlying factors impacting vaccine hesitancy in high income countries: a review of qualitative studies. Expert Rev Vaccines. 2018;17(11):989-1004.

109. Yaqub O, Castle-Clarke S, Sevdalis N, Chataway J. Attitudes to vaccination: a critical review. Soc Sci Med. 2014;112:1-11.

110. Benin AL, Wisler-Scher DJ, Colson E, Shapiro ED, Holmboe ES. Qualitative analysis of mothers' decision-making about vaccines for infants: the importance of trust. Pediatrics. 2006;117(5):1532-41.

111. Freed GL, Clark SJ, Butchart AT, Singer DC, Davis MM. Sources and perceived credibility of vaccine-safety information for parents. Pediatrics. 2011;127 Suppl 1:S107-12.

112. Hagemann C, Streng A, Kraemer A, Liese JG. Heterogeneity in coverage for measles and varicella vaccination in toddlers - analysis of factors influencing parental acceptance. BMC Public Health. 2017;17(1):724.

113. Reuss AM, Feig M, Kappelmayer L, Siedler A, Eckmanns T, Poggensee G. Varicella vaccination coverage of children under two years of age in Germany. BMC Public Health. 2010;10:502.

114. Streng A, Seeger K, Grote V, Liese JG. Varicella vaccination coverage in Bavaria (Germany) after general vaccine recommendation in 2004. Vaccine. 2010;28(35):5738-45.

115. Charania NA, Watson DG, Turner NM. Perceptions of caregivers and providers regarding the potential introduction of the varicella vaccine to the childhood immunisation schedule in New Zealand: A qualitative exploratory study. J Paediatr Child Health. 2018;54(1):28-35.

116. Tam WW, Chan J, Lo KK, Lee A, Chan PK, Chan D, et al. Parental Attitudes and Factors Associated With Varicella Vaccination in Preschool and Schoolchildren in Hong Kong: A Cross-Sectional Study. Medicine (Baltimore). 2015;94(36):e1519.

117. van Lier A, Tostmann A, Harmsen IA, de Melker HE, Hautvast JL, Ruijs WL. Negative attitude and low intention to vaccinate universally against varicella among public health professionals and parents in the Netherlands: two internet surveys. BMC Infect Dis. 2016;16:127.

118. THL. Vaccinationsprogram för barn och vuxna [July 18]. Available from: https://thl.fi/sv/web/infektionssjukdomar-och-vaccinationer/information-om-vaccinationer/det-nationella-vaccinationsprogrammet/vaccinationsprogram-for-barn-och-vuxna#vaccination_av_barn.

119. THL. Vaccinationstäckning bland barn födda 2020 och 2015. 2023.

120. Wallace AS, Mantel C, Mayers G, Mansoor O, Gindler JS, Hyde TB. Experiences with provider and parental attitudes and practices regarding the administration of multiple injections during infant vaccination visits: lessons for vaccine introduction. Vaccine. 2014;32(41):5301-10.

121. Schuler M, Schaedelin S, Aebi C, Berger C, Crisinel PA, Diana A, et al. Attitudes of Swiss Health Care Providers Toward Childhood Immunizations. Pediatr Infect Dis J. 2017;36(6):e167-e74.

122. Gilca V, Boulianne N, Dube E, Sauvageau C, Ouakki M. Attitudes of nurses toward current and proposed vaccines for public programs: a questionnaire survey. Int J Nurs Stud. 2009;46(9):1219-35.

123. Dube E, Gilca V, Sauvageau C, Bettinger JA, Boucher FD, McNeil S, et al. Clinicians' opinions on new vaccination programs implementation. Vaccine. 2012;30(31):4632-7.

124. Svenska Infektionsläkarföreningen (Swedish Infectious Disease Association). Vårdprogram för virala CNS infektioner (Treatment guidelines for viral CNS infections).

125. Public Health England. The green book. Chapter 34 Varicella Public Health England.

126. Ek T BM. Varicella hos barncancerpatienter [Varicella in peadiatric cancer patients] 2014 [Available from: http://www.blf.net/onko/page16/page16.html.

127. Brunell PA, Ross A, Miller LH, Kuo B. Prevention of varicella by zoster immune globulin. N Engl J Med. 1969;280(22):1191-4.

128. Läkemedelsverket och Referensgruppen för antiviral terapi (Swedish Medical Products Agency and the Reference group for antiviral therapy). Farmakoterapi vid herpes simplex-, varicella- och herpes zoosterinfektioner. . Information från Läkemedelsverket (Information from the Swedish Medical Products Agency). 2005;4:34-47.

129. Arbeter AM, Starr SE, Plotkin SA. Varicella vaccine studies in healthy children and adults. Pediatrics. 1986;78(4 Pt 2):748-56.

130. Varilrix EMEA/H/A-30/1499. European Medicines Agency; 2020.

131. Ludvigsson JF, Andersson E, Ekbom A, Feychting M, Kim JL, Reuterwall C, et al. External review and validation of the Swedish national inpatient register. BMC Public Health. 2011;11:450.

Appendix A: Contributing experts

Internal experts from the PHAS

2022-2024

Sören Andersson, prof, Head of 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, tidigare representant EMA Vaccine Working Party, Unit for vaccine programmes

Frida Kasteng, analyst, health economist, Unit for analysis

Disa Hansson, analyst, mathematical modeller, Unit for analysis

Sofie Larsson, analyst, health economist, Unit for analysis

Carl Lundberg, analyst, health economist, Unit for Coordinated Public Health

Lisa Brouwers, Head of Unit, 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, previously representant 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

Katarina Widgren, analyst, infectiologist, Unit for vaccine programmes

Rose-Marie Carlsson, analyst, infectiologist, Unit for vaccine programmes

Ingrid Uhnoo, analyst, infectiologist, previously analyst the Swedish Medicine Agency, previously representant 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

Nordic Collaborating group for systematic literature review

Kari Johansen. Public Health Agency of Sweden

Lene Juvet. Norwegian Public Health Institute

Silje Lae Solberg. Norwegian Public Health Institute

Eli Heen. Norwegian Public Health Institute

Ingun Heiene Tveteraas. Norwegian Public Health Institute

Hanne Nokleby. Norwegian Public Health Institute

Joakim Overbo. Norwegian Public Health Institute

Annika Ersson. Public Health Agency of Sweden

Kamilla Sigridur Josefsdottir. Centre for Health Security and Communicable Disease Control

Ida Aase Glode Helmuth. Danish Health Authority

Heini Salo. Finnish Institute for Health and Welfare

External experts from the Swedish Medicine Agency, the National Board of Health and Welfare and the Dental and Pharmaceutical Benefits Agency and specialist associations within the Swedish Society of Medicine and the Swedish Medical Association

Sveriges Infektionsläkarförening (Fredrik Kahn, infectiologist, Anja Rosdahl, infectiologist, Martin Angelin, infectiologist)

Smittskyddsläkarföreningen (Katarina Widgren, ass county officer)

Sveriges Förening för Allmänmedicin (Margareta Ehnebom, general practicioner)

Svensk Geriatrisk förening (Dorota Religa, professor in geriatrics)

Svensk Reumatologisk förening (Jon Einarsson, rheumatologist; Meliha Kapetanovic, rheumatologist; Iva Gunnarsson, rheumatologist)

Sveriges läkares intresseförening för primär immunbrist (Fredrik Kahn, infectiologist)

Skolläkarföreningen (Helena Lüning, MD student health)

Skolsköterskeföreningen (Ulrika Brännström, nurse within student health)

Barnhälsovården (Jeanette Björnell, nurse within the child health care)

Barnhälsovårdsöverläkarna (Leif Ekholm, paediatrician)

Barnläkarföreningen (Viktor Peny, paediatrician)

Referensgruppen för antiviral terapi (RAV) (Jan Albert, professor, clinical virology)

Läkemedelsverket (Charlotta Bergquist, head of unit, Unit for efficacy and safety; Bernice Aronsson, analyst, paediatrician)

The National Board of Health and Welfare, Department of registry and statistics, Statistikservice (Henrik Nordin, head of unit; Mattias Åman Svensson, statistician)

Tandvårds- och Läkemedelsförmånsverket (TLV) (Sonny Larsson, pharmacist)

Experts within child oncology, immunodeficiency, infectious diseases, clinical virology and vaccinology with special expertice

2022-2024

Marta Granström, professor emeritus, Karolinska Institutet, specialist in clinical virology and bacteriology, previous representant EMA Vaccine Working Party, EMA Paediatric Committee (PDCO)

Per Ljungman, professor, Karolinska Institutet, specialist in internal medicine and hematology

Anna Nilsson, child oncology, lektor i pediatrik, avdelningschef för barnonkologiska forskningsenheten, Karolinska Institutet

Marie Studahl, professor in infectious diseases, infectiologist, Göteborg University

2018-2020

Anna Nilsson, child oncology, lektor i pediatrik, avdelningschef för barnonkologiska forskningsenheten, Karolinska Institutet

Marie Studahl, professor in infectious diseases, infectiologist, Göteborg University

Thomas Bergström, professor, specialist in clinical virology and bacteriology, Göteborg University

Margareta Ehnebom, general practitioner

Kathy-Falkenstein-Hagander, paediatrician

Jeanette Björnell, nurse within the child health care

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.

Folkhälsomyndigheten
PUBLIC HEALTH AGENCY OF SWEDEN

Solna Nobels väg 18, 171 82 Solna. **Östersund** Campusvägen 20. Box 505, 831 26 Östersund.

www.folkhalsomyndigheten.se