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THE EPIDEMIOLOGY OF VARICELLA ZOSTER VIRUS DISEASE IN SWEDEN - BEFORE AND AFTER VACCINATION

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THE EPIDEMIOLOGY OF VARICELLA ZOSTER VIRUS DISEASE IN SWEDEN - BEFORE AND AFTER VACCINATION
THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

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All scientific work is incomplete - whether it be observational or experimental.

All scientific work is liable to be upset or modified by advancing knowledge.

That does not confer upon us a freedom to ignore the knowledge we already have or postpone the action that it appears to demand at a given time.

Sir Austin Bradford-Hill

POPULAR SCIENCE SUMMARY OF THE THESIS

Chickenpox disease gives fever and an itching rash, mainly on the head and upper body. The virus that causes the infection will then hide in the body. Later in life, it can reactivate and cause shingles, which presents as a localised rash on one side of the body. Both chickenpox and shingles can sometimes lead to complications, mainly related to the skin or nervous system. Very few people die of either disease.

The virus that causes chickenpox and shingles is very contagious. Thus, most individuals will be exposed to the virus early in life and fall ill with chickenpox in childhood. As all individuals will be infected at some stage, there are on average as many cases of chickenpox every year as there are children born. The risk of shingles increases with age and is also higher in persons with a weakened immune system. The lifetime risk of shingles is 25-30%. There are safe and effective vaccines against chickenpox used in many countries and there are two fairly new vaccines against shingles. Children vaccinated against chickenpox are less likely to fall ill with chickenpox and probably also to develop shingles later in life. The epidemiology of chickenpox, in particular the age of infection, differs somewhat among regions and countries, due to differences in climate and social mixing.

The exogenous boosting hypothesis suggests that the immunity of persons who have had chickenpox will be boosted when they encounter a contagious person and their risk of shingles is subsequently decreased. This hypothesis is under debate, in particular whether it would mean that general chickenpox vaccination would lead to an increase in shingles.

The aim of this thesis was to describe the burden of disease due to chickenpox in Sweden and to assess how the epidemiology of chickenpox and shingles would change if there were general vaccination against either or both diseases. The purpose was to contribute knowledge to the appraisal of general vaccination against the diseases in Sweden carried out by the Public Health Agency.

In the four studies, we used a range of methods to achieve our aims. We collected data from a wide set of registers and databases, examined medical charts of hospitalised chickenpox cases, carried out laboratory analyses and made a mathematical model of disease transmission.

The main findings were:

Swedes contracted chickenpox early in life. At five years of age, two-thirds of Swedish children had antibodies against chickenpox virus, i.e. had been infected. By twelve years of age more than 90% did.

The infection was mild in most cases and only about 3 in 1,000 chickenpox cases needed admission to hospital.

Many hospitalised chickenpox cases had underlying conditions. However, more than half of the patients with complications were previously healthy.

In the transmission model, general chickenpox vaccination lead to a dramatic decrease in the number of new chickenpox cases and fewer cases of shingles in the long term. The number of shingles cases in the short term depended on attributes of exogenous boosting, such as the strength and duration of protection after exposure to a contagious person.

Shingles vaccination had a more moderate impact on the number of new shingles cases than chickenpox vaccination.

The strategy that prevented the most cases of chickenpox and shingles was a two-dose chickenpox vaccination programme with a short dose interval in early childhood complemented with shingles vaccination in 65 year-olds. However, a cost-effectiveness analysis is needed to evaluate which vaccination strategy has the most favourable health effects for its healthcare and societal costs.

POPULÄRVETENSKAPLIG SAMMANFATTNING

Vattkoppor ger feber och ett kliande utslag främst på huvud och överkropp. Viruset som orsakar infektionen gömmer sig därefter i kroppen. Senare i livet kan det reaktivera och orsaka bältros, ett utslag inom ett begränsat område på ena kroppshalvan. Både vattkoppor och bältros kan ibland ge komplikationer, främst från hud och nervsystem. Väldigt få personer dör av dessa sjukdomar.

Viruset som orsakar vattkoppor och bältros är mycket smittsamt. Därför blir de flesta exponerade för viruset tidigt i livet och insjuknar med vattkoppor i barndomen. Eftersom alla någon gång i livet blir smittade insjuknar det i snitt lika många personer i vattkoppor varje år som det föds barn. Risken för bältros ökar med åldern och är också förhöjd hos personer med nedsatt immunförsvar. Livstidsrisken för bältros är 25-30%. Det finns säkra och effektiva vacciner mot vattkoppor som används i många länder och det finns också två relativt nya vacciner mot bältros. Barn som vaccineras mot vattkoppor har lägre risk att få sjukdomen och sannolikt även att senare i livet utveckla bältros. Epidemiologin av vattkoppor, framför allt ålder vid insjuknande, skiljer sig åt mellan regioner och länder pga skillnader i klimat och i hur man umgås.

Hypotesen om exogen boosting säger att immuniteten hos personer som haft vattkoppor förstärks när de möter en smittsam person och därmed minskar deras risk för bältros. Hypotesen debatteras, framför allt huruvida detta skulle medföra att allmän vattkoppsvaccination leder till en ökning av bältros i befolkningen.

Målet med denna avhandling var att beskriva sjukdomsbördan av vattkoppor i Sverige samt att skatta påverkan på epidemiologin av vattkoppor och bältros om vi vaccinerade mot en eller båda sjukdomarna. Detta gjordes för att ge kunskap till den pågående utredningen vid Folkhälsomyndigheten kring allmän vaccination mot sjukdomarna i Sverige.

I de fyra studierna använde vi oss av en rad olika metoder för att nå målen. Vi samlade data från register och databaser, granskade medicinska journaler för sjukhusvårdade vattkopps-patienter, genomförde laboratorieanalyser och gjorde en matematisk modell för smittspridning.

De viktigaste resultaten var:

Svenskar insjuknade med vattkoppor tidigt i livet. Vid fem års ålder hade två-tredjedelar antikroppar mot vattkoppsvirus, dvs hade haft sjukdomen. I tolvårsåldern hade mer än 90% haft den.

Infektionen var mild för de flesta och bara ca 3 per 1000 vattkoppsfall behövde sjukhusvård.

Många sjukhusvårdade vattkoppsfall hade underliggande sjukdomar. Däremot var mer än hälften av de patienter som fick komplikationer friska sedan tidigare.

I smittspridningsmodellen ledde allmän vattkoppsvaccination till en dramatisk minskning i antalet nya vattkoppsfall samt färre bältrosfall på lång sikt. Antalet bältrosfall på kort sikt var avhängig aspekter hos exogen boosting, som styrka och varaktighet på skyddet efter ett möte med en smittsam person.

Bältrosvaccination medförde en mer begränsad påverkan på antalet bältrosfall än vattkoppsvaccination.

Den strategi som förhindrade flest fall totalt av vattkoppor och bältros var två-dos vattkoppsvaccination med kort dosintervall tidigt i barndomen i kombination med bältrosvaccination för 65-åringar. Dock krävs en hälsoekonomisk analys för att bedöma vilken vaccinationsstrategi som ger bäst utfall vad gäller hälsoeffekter för den kostnad för sjukvård och samhälle som den medför.

ABSTRACT

Primary infection with the varicella zoster virus (VZV) presents as chickenpox, a highly contagious infection. Thereafter the virus establishes latency in nerve ganglia of the host. The virus may reactivate later in life and cause shingles, neurological and/or visceral complications.

The overall aim of this thesis was to provide a baseline for the burden of chickenpox disease in Sweden and to assess the impact of vaccination on the epidemiology of VZV disease in order to contribute knowledge to an appraisal of general vaccination against the diseases in Sweden carried out by the Public Health Agency.

In **Study I,** we obtained data from healthcare registers and databases and found a chickenpox-related hospitalisation rate of 3.56/100,000 person-years, a consultation rate of 20.1/100,000 person-years in specialist care and 109/100,000 person-years in primary care in Sweden in 2007-2013.

In **Study II,** we included patients hospitalised with chickenpox in Stockholm and Gothenburg in 2012-2014. Their median age was 3.6 years. 43.1% of children and 67.4% of adults had an underlying condition. Overall 87.2% and 63.0% developed complications, respectively. There was no increased risk of complications among those with underlying conditions. In addition, in a nation-wide serology study using residual samples from 2011-2013, we found a VZV seroprevalence of 66.7% in 5-year-olds and 91.5% in 12-year-olds.

In **Study III,** we compared demographic and socio-economic factors for children hospitalised with chickenpox, influenza and respiratory syncytial virus with patients with rotavirus, in a paediatric hospital in Stockholm in 2009-2014. We found that admitted chickenpox cases were older and lived in a household with more children than the cases with rotavirus.

In **Study IV,** we explored the impact of chickenpox vaccination on shingles incidence in a mathematical model under a range of assumptions regarding VZV immunity after an encounter with a contagious case, so-called exogenous boosting (EB). We found that EB could be strong, intermediate or weak and still not cause a surge in shingles incidence after chickenpox vaccination. In addition, the same transmission model was used to investigate the impact of various strategies for vaccination against chickenpox and/or shingles in Sweden.

In conclusion, a majority of Swedes had chickenpox in early childhood. The need for hospitalisation was low. More than half of complications were seen in previously healthy patients. Chickenpox vaccination led to a dramatic decrease in chickenpox incidence in our model, whereas the impact on shingles incidence was dependent on the assumed strength and duration of exogenous boosting. Of the assessed vaccination strategies, two-dose chickenpox vaccination in early childhood combined with shingles vaccination (RZV) at 65 years prevented the most VZV cases in the model. However, a cost-effectiveness analysis is needed to evaluate which vaccination strategy has the most reasonable costs for healthcare and society in relation to its health effects.

LIST OF SCIENTIFIC PAPERS

I. **Widgren K**, Giesecke J, Lindquist L, Tegnell A. **The burden of chickenpox disease in Sweden.** BMC Infectious Diseases, 2016, 16, 666.

II. **Widgren K**, Persson Berg L, Mörner A, Lindquist L, Tegnell A, Giesecke J, Studahl M. **Severe chickenpox disease and seroprevalence in Sweden implications for general vaccination.** International Journal of Infectious Diseases, 2021. doi: https://doi.org/10.1016/j.ijid.2021.08.012

III. **Widgren K**, Eriksson M, Bennet R, Giesecke J**. Children hospitalised with four common viral diseases showed epidemiological differences but few socioeconomic variations.** Acta Paediatrica, 2021, 00, 1-9.

IV. **Widgren K**, Leung K, Tomba GS, Giesecke J. **Modelling varicella vaccination – what does a lack of surge in shingles incidence tell us about exogenous boosting?** (Manuscript).

SCIENTIFIC PAPER NOT INCLUDED IN THE THESIS

I. Wolff E, **Widgren K**, Scalia Tomba G, Roth A, Lepp T, Andersson S. **Cost-effectiveness of varicella and herpes zoster vaccination in Sweden: an economic evaluation using a dynamic transmission model.** PLOS ONE 16(5): e0251644.

CONTENTS

LIST OF ABBREVIATIONS

95%CI	95% confidence interval
BV	Breakthrough varicella
CNS	Central nervous system
CSF	Cerebrospinal fluid
DNA	Deoxyribonucleic acid
ECDC	European Centre for Disease Prevention and Control
ESEN2	European sero-epidemiology network
FoI	Force of infection
FoR	Force of reactivation
gpE	Glycoprotein E
HPV	Human papilloma virus
ICD-10	International Statistical Classification of Diseases and Related Health Problems, 10th Revision
NIP	National immunization programme
PCR	Polymerase chain reaction-test
PFU	Plaque forming units
PHAS	Public Health Agency of Sweden (Folkhälsomyndigheten)
R0	Basic reproductive rate
RSV	Respiratory syncytial virus
RZV	Recombinant zoster vaccine, an adjuvanted subunit vaccine
VAB	Temporary parental benefit when caring for a sick child (Vård av barn)
VZV	Varicella zoster virus
WHO	World Health Organization
ZVL	Live, attenuated zoster vaccine

1 INTRODUCTION

On-and-off over the past decades, the topic of general chickenpox and shingles vaccination has been on the agenda in Sweden and other European countries. In 2014-2015, the World Health Organization (WHO) and the European Centre for Disease Prevention and Control (ECDC) published their standpoints on the issue.

In their Position paper on varicella and herpes zoster vaccines, WHO pointed out that the burden of chickenpox is smaller than that of other vaccine-preventable diseases prior to vaccination, yet the value of vaccination is well established. Due to geographic variation in the epidemiology of the disease, they stressed the need for each country to assess the disease burden caused by chickenpox in the country and additionally ensure that vaccination coverage can be maintained above 80% as a lower coverage could shift the age of disease onset upwards. Further, they concluded that there was insufficient data on the new shingles vaccine to make recommendations [1].

In the ECDC Guidance on varicella vaccination, several knowledge gaps were pointed out, highlighting the uncertainty regarding the impact of chickenpox vaccination on the shingles incidence in both vaccinated and unvaccinated individuals [2].

This PhD project was planned to provide baseline data on the epidemiology of chickenpox in Sweden and an assessment of the possible impact of vaccination against chickenpox and/or shingles on the epidemiology of both diseases. At the time, there were up-to-date assessments of the epidemiology of shingles in Sweden. The work on the studies commenced in 2014.

2 LITERATURE REVIEW

2.1 THE VARICELLA ZOSTER VIRUS AND TRANSMISSION

2.1.1 The virus

Around the turn of the last century, J. von Bokay recognized that susceptible children developed chickenpox after exposure to shingles suggesting the same virus caused the two diseases [3]. In 1958, Nobel laureate Thomas H. Weller with colleagues could confirm this suspicion [4, 5]

The varicella zoster virus (VZV) is a double-stranded DNA virus, which belongs to the herpesviridae family. This virus family shares the ability to establish latency in their host. VZV, along with herpes simplex virus 1 and 2, belongs to the subfamily alpha herpesviruses, and has a cytopathic or cell-destroying effect. The VZV genome has at least 71 open reading frames (ORFs). The virus can only infect humans and is neurotropic, i.e. it primarily infects human neurons [3, 6]. However, other cell types can be infected, mainly T lymphocytes [7]. The virus has a worldwide spread. Only one serotype has been identified and five genotypes/clades with different geographic distributions: two European, one Japanese and two with Asian and African distribution [8]. Two additional genotypes have recently been added, suggesting ongoing recombination [9]. Several glycoproteins on the virion and the cell surface of infected cells have been described, the most immunogenic being glycoprotein E (gpE), the main target for VZV-specific immune responses [3, 6, 9, 10].

2.1.2 Transmission

The virus is highly contagious, primarily by aerosol spread of virions from the chickenpox rash, and to a lesser extent from the shingles rash. There might also be transmission via the respiratory route from persons with chickenpox [3].

Chickenpox is contagious from 1-2 days before rash onset until all vesicles have crusted, in total about 7 days. Shingles is also contagious as long as vesicles are active, normally 7-10 days. Contagiousness from both diseases can be prolonged in the immunocompromised. Successful exposure to a contagious chickenpox or shingles case will lead to chickenpox in a susceptible person [3, 11-13].

2.2 PRIMARY INFECTION: CHICKENPOX (VARICELLA)

2.2.1 Clinical picture

The incubation period is 14 days (range 10-21 days). During this time, the virus enters the body via epithelial cells in the mucosa of the oral cavity and upper respiratory tract and replicates in regional lymph nodes. A low-grade viremia occurs and virus spreads to the skin and other organs where further replication takes place and then a second high-grade viremia occurs [14, 15].

The primary infection with varicella zoster virus presents as chickenpox. The infected person develops fever and malaise followed or accompanied by a generalized, pruritic exanthema, often most intense on the face and upper body. It can also affect the mucosa of the mouth and upper respiratory tract. The exanthema develops from macules, to vesicles, to pustules and then to crusts within a few days. Most often, the rash and fever subsides after 5-7 days. Chickenpox is generally a mild to moderate disease in children, but can cause severe complications [3, 15].

2.2.2 Complications

The complication rate is unknown, but only a fraction of cases are hospitalised, previously estimated to be 130-271/100,000 chickenpox cases [16, 17] or 9-75/100,000 person-years in the population below 5 years [18].

A review article of chickenpox in Europe found secondary bacterial skin and soft tissue infections to be the most frequent complications; they constituted 21 - 47% of complications among hospitalised children with chickenpox [19]. The presentations ranged from local superinfections of vesicles to cellulitis, and in rare cases even necrotizing fasciitis, and/or sepsis. The bacterial infections are most often caused by Group A Streptococci or Staphylococcus aureus [19-21].

Neurological complications are also relatively frequent among hospitalised chickenpox cases, 8-38% [19]. Most characteristic is acute cerebellitis with dysarthria, wide-based gait and trunk ataxia [3, 22]. The risk was previously reported to be 1/4,000 chickenpox cases in children below 15 years of age [23], whereas more up-to-date data suggests a lower risk of 1/20,000 chickenpox cases below 5 years [24]. Although frightening in presentation, this condition has a good prognosis. Meningitis is also generally benign, whereas encephalitis and myelitis are more severe neurological complications of chickenpox [3, 22].

Other complications are bacterial pneumonia and osteomyelitis, as well as inflammation caused by the virus, such as pneumonitis or hepatitis. In addition, thrombocytopenia and haemorrhagic complications occur [3, 19]. There is also a four-times increased risk of stroke within 6 months of chickenpox disease in children [25].

Another recent European review article estimated the overall case fatality rate to be 1/100,000 cases [18].

Congenital varicella syndrome is characterised by low birth weight and foetal deformities of skin, extremities and brain. Infection during the first trimester of pregnancy gives a small risk (≈1%) of congenital varicella syndrome; at 13–20 weeks gestation the risk for congenital varicella syndrome is approximately 2%. Only a few cases consistent with congenital varicella syndrome have been reported after 20 weeks gestation [26, 27]. Maternal chickenpox in the perinatal period leads to a high risk of transmission to the baby, either transplacentary or via contact after birth. The disease is most severe if the child is born before protective maternal varicella antibodies are produced [3, 28].

2.2.3 Risk factors

The risk of severe chickenpox disease, complications and death is higher among adults and infants than for children. Thus, age of infection and factors influencing it are important risk factors for severe disease [3, 29].

Immunosuppression is another risk factor for severe disease [3]. Haematological malignancies, acute lymphatic leukaemia in particular, which peaks around the same age as chickenpox, have been connected to severe disease and mortality of up to 10%. Although updated data on the morbidity and mortality in this group are scarce, the prognosis seems to have improved by antiviral therapy and vaccination of susceptible family members and healthcare staff [3, 30].

The severity of the disease also appears to be associated with the infectious dose, i.e. infection within the household leads to more severe disease [31].

2.2.4 Epidemiology

2.2.4.1 Chickenpox epidemiology in the world

Due to the high infectivity, especially in temperate climates, infection occurs in childhood and everyone is affected, i.e. the incidence is about a birth cohort per year [19, 32]. However, there are differences in age of infection, even across Europe. In a large pan-European seroepidemiological study, 38% of 5-year-olds in Italy were seropositive compared with 97% of Dutch 5-year-olds (Figure 1). This large discrepancy is often explained by differences in day-care habits and social contact patterns at a young age [32].

2.2.4.2 Chickenpox epidemiology in Sweden

A serology study using blood samples from 1997 showed a 98% seroprevalence among Swedish 12-year-olds [33], which was corroborated by two other studies; one survey from 2007 with similarly high seroprevalence in 14-16 year-olds born in Sweden and abroad respectively [34] and a immunogenicity study of chickenpox vaccination in 12-year-olds from Stockholm in 1998-2000 [35].

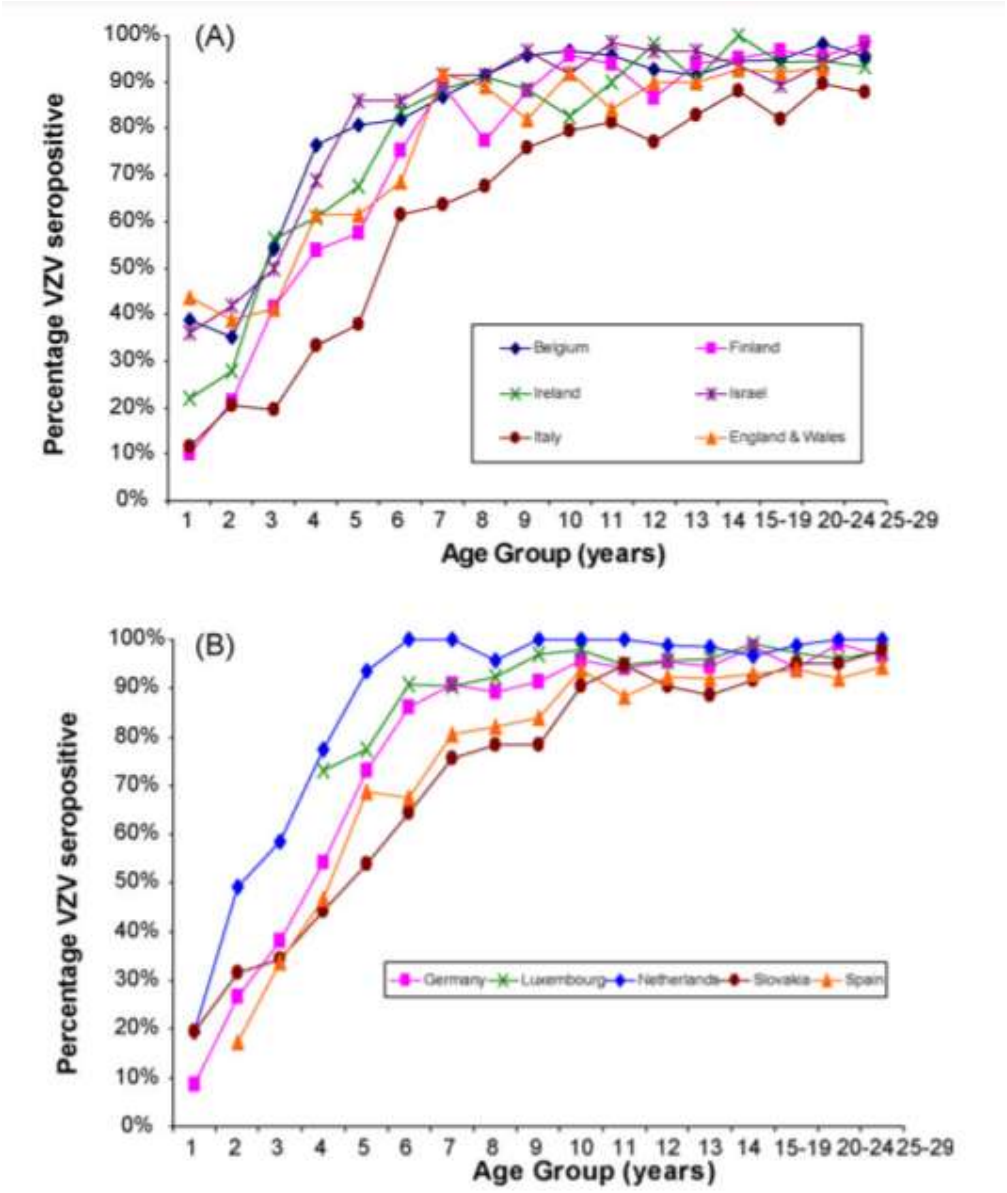


Figure 1. Age-specific VZV seroprevalence in 11 European Countries.
Samples were collected from residual sera (A) or by population sampling (B), 1995-2003.
Source: Nardone et al. "The comparative sero-epidemiology of varicella zoster virus in 11 countries in the European region". Vaccine, 2007. Reprinted with permission from Elsevier.

Linde and Lindberg found that 322 children and 154 adolescents and adults were hospitalised in 1993 in Sweden due to chickenpox, i.e. an overall incidence of 5.4/100,000 person-years [36]. A team from the Astrid Lindgren Children's Hospital in Stockholm has published several studies on the incidence of common vaccine-preventable diseases. This paediatric hospital has a catchment area that covers 10% of all Swedish children. In 1998–2005, the chickenpox hospitalisation rate in children (below 18 years of age) was estimated at 1.6/1,000 varicella cases [37]. The hospitalisation rate for chickenpox in children aged 5 years and below was 30/100,000 person-years in 2003–2008 and 21/100,000 person-years in 2008–2013 [38, 39].

2.3 VIRUS LATENCY AND IMMUNITY

Essentially, immunity against chickenpox is lifelong. Very few people develop a second bout of chickenpox, although the true frequency has not been established [40]. A second episode has been connected to an early or mild first episode [41]. With increasing use of molecular genetics, the occurrence of reinfections has been documented, by e.g. European serotypes in herpes zoster cases in migrants who had their primary infection in another continent [9].

After primary infection, the VZV establishes latency in neurons in ganglia along the entire neuroaxis, primarily in the dorsal root ganglia and cranial nerve ganglia, innervating the upper body, where the chickenpox rash was most intense. VZV can also be found in neurons without skin projection, e.g. enteric and autonomic ganglia. It is presumed that the virus ends up in the ganglia during primary infection, either through retrograde transportation of the virus from the chickenpox-affected skin or through viremia or both [6, 15].

During latency, the viral DNA is present in the cells, but there is limited gene expression or replication. However, the exact mechanism of latency is not described [6, 15, 42]. The study of VZV latency has mainly been limited to the examination of ganglia from deceased humans or to animal models of the closely related simian varicella virus in primates [6, 42].

Primary infection elicits both VZV-specific antibody and T-cell responses. However, T-cell immunity is more important for all aspects of the host versus virus interaction. T-cell immunity is needed for recovery from primary infection and appears to control viral replication during latency. Reactivation of the latent virus may occur when cell-mediated immunity (CMI) decreases, mainly due to age-related immunosenescence and/or immunosuppressive conditions or treatment [3]. Deficiencies in T-cell immunity is a major risk factor for severe VZV disease and recurrence of shingles, whereas individuals with agammaglobulinemia are protected against reinfection since their VZV-specific CMI can mount a response [6, 40].

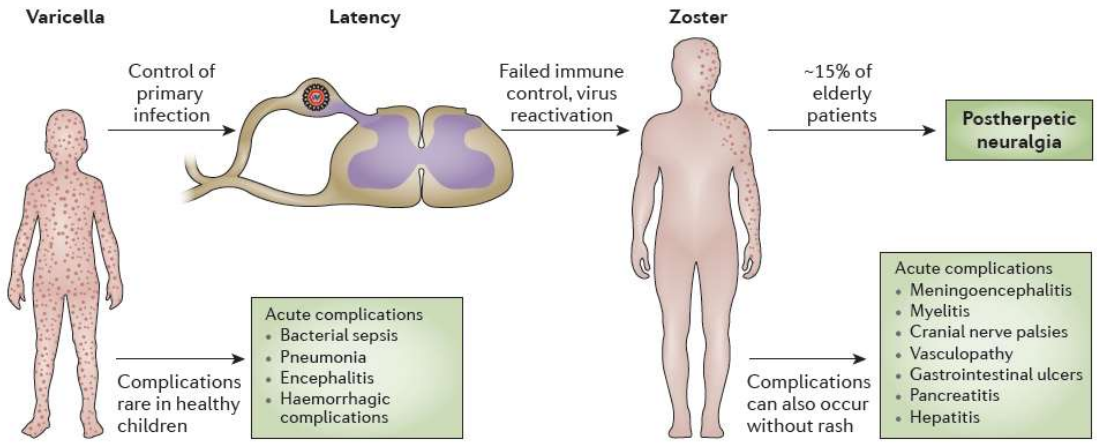


Figure 2. The different phases of varicella zoster virus infection.
Source: Gershon et al. "Varicella zoster virus infection". Nat Rev Dis Primers, 2015. Reprinted with permission from Springer Nature.

2.4 REACTIVATION: SHINGLES (HERPES ZOSTER)

2.4.1 Clinical picture

Classically, VZV reactivation presents as shingles, most often a unilateral vesicular rash localised in an area of skin supplied by the sensory nerves of an affected dorsal root or cranial nerve ganglia (a dermatome), i.e. generally it does not cross the midline of the body. The most common localisation is on the trunk or head, again the area where the chickenpox rash usually was most pronounced [6, 13, 15, 43]. The histopathology of the rash is identical to that of chickenpox, with vesicles developing to pustules and then to crusts. However, there are other differences: the localised distribution, and the longer duration of active rash (7-10 days) [13, 44]. The rash is often preceded or accompanied by acute pain. When the pain precedes the rash, it can be mistaken for other conditions, such as myocardial infarction, cholecystitis, or appendicitis, but the diagnosis becomes evident when the rash appears [44, 45].

Reactivation in cranial nerve ganglia is common. Shingles around the eye, i.e. cranial nerves three, four or six, is a dreaded location, as this can cause sight-threatening conditions [6]. Affection of the seventh cranial nerve ganglion, presenting with facial palsy, and vesicles on or in the ear (zoster oticus) or on the tongue, is called Ramsay-Hunt syndrome. Sometimes the nearby eighth cranial nerve ganglion is affected with subsequent vertigo and hearing loss [22, 46].

2.4.2 Complications

The most frequent complication of shingles is post-herpetic neuralgia (PHN), defined as pain within the affected area persisting for more than 3 months. The pain can last for years. The frequency varies among studies and definitions, usually around 10%. PHN is described as a burning, sometimes shooting pain with disturbed sensory of touch within the affected area. It is often refractory to standard pain medication; instead, anticonvulsants or antidepressants are more effective [6, 13, 15, 44, 46, 47].

Further, neurological complications of shingles include meningitis, encephalitis, myelitis and cranial nerve palsies, or a combination of these. Generally, meningitis has a benign course, whereas encephalitis and myelitis more often lead to disabilities or death [22, 46]. VZV vasculopathy can also lead to either ischemic or haemorrhagic stroke. Two large Nordic studies have shown a marked increased rate (21-34%) of stroke in the first year after a shingles episode, this association being particularly strong in younger adults [48, 49]. The risk is substantially higher subsequent to a zoster ophtalmicus [50, 51].

Other complications include secondary bacterial infections of the affected skin, noted in 2% of shingles cases seen in primary care [45].

Shingles normally leads to viremia. In the immunocompromised host, this can result in generalised zoster, with a multi-organ involvement and/or a generalised rash, which can be a life-threatening condition [13, 44].

2.4.3 Risk factors

As mentioned, the age-related decrease in cell-mediated immunity, known as immunosenescence, leads to an increasing risk of shingles with age, making old age the main risk factor for shingles. Still, in a large population-based study from the USA, the absolute number of cases was similar among those younger than 60 years compared with those older than 60 [52]. The risk of PHN, other complications, and the case fatality ratio increase with age. To what extent the risks increase differs among studies, due to different study designs [45, 53].

Other causes of decreased CMI will also lead to an increased risk of shingles. This can be the case for patients who have had haematological stem cell or solid organ transplants or who have haematological malignancies, HIV (even with successful combined antiretroviral therapy) or other immunosuppressive conditions or therapies [54-56]. Shingles is a marker for insidious cancer, with a low but increased risk of cancer diagnosis within one year of shingles [57]. It is also an AIDS-defining illness [58]. In addition, stress, depression and other illnesses can temporarily decrease CMI and lead to shingles [59]. Even mechanical trauma can trigger shingles in the affected area [60].

All across the life span, shingles affects women considerably more frequently than men [48, 61]. A family history of shingles is associated with a higher risk of shingles [59, 60]. In contrast, being born in a tropical country, as a proxy for late onset of chickenpox, is associated with a lower risk of shingles. In addition, being dark-skinned is associated with a reduced risk of shingles, after adjusting for country of birth [60]. Intrauterine infection and chickenpox in the first year of life are associated with shingles in childhood [62].

Under the heading “Exogenous boosting” below, data on the reduced risk of shingles due to exposure to VZV are described.

2.4.4 Epidemiology

2.4.4.1 Shingles epidemiology in the world

A review of European shingles incidence showed yearly estimates of 200-460/100,000 person-years. The risk is rather low up until the age of 50 years (approximately 100 cases per 100,000 person-years), after which it rises steeply to reach >800/100,000 person-years by the age of 80 years [63]. Similar incidence estimates were found in a world-wide review which included data from North America, Asia and the Pacific [64].

2.4.4.2 Shingles epidemiology in Sweden

In recent years, two studies have assessed the disease burden of shingles in Sweden. Sundström *et al.* used consultations in general practice and Studahl *et al.* used antiviral prescriptions as proxies for shingles. Both reached very similar estimates of incidence; overall about 300/100,000 person-years with markedly increasing rates with age and

significantly higher incidence in women compared with men of all ages above 50 years (Figure 3) [48, 61].

In addition, Studahl *et al.* examined hospitalisations in Sweden in 2006-2010 and found a rate of 13.2/100,000 person-years with shingles as primary or secondary diagnosis. Neurological complications were present in 9.2-12.2% of admitted patients and shingles with eye involvement in 6.1-8.6%. The average mortality rate due to shingles was 0.26/100,000 person-years in men and 0.67/100,000 person-years in women aged 50 years and above [61].

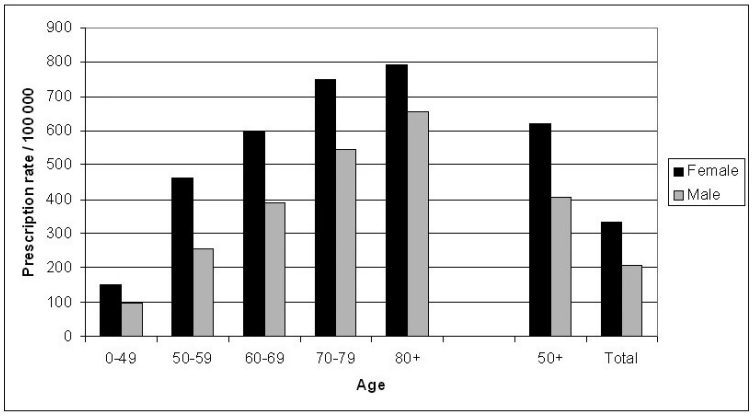


Figure 3. Prescription rate as a proxy for shingles incidence, by age group and gender, in Sweden, 2006-2010.
Source: Studahl et al. "Disease burden of herpes zoster in Sweden--predominance in the elderly and in women - a register based study". BMC Infect Dis. 2013. Reprinted under the terms of the Creative Commons license.

According to notification data for viral meningoencephalitis, VZV is one of the most common pathogens causing this disease in Sweden, along with herpes simplex viruses, tick-borne encephalitis virus and enterovirus (www.folhalsomyndigheten.se).

2.5 REACTIVATION WITHOUT RASH

Apart from shingles with or without complications, virus reactivation can present as a radicular PHN-like pain without a shingles rash, called zoster sin herpete. Complications such as meningitis, encephalitis, myelitis, cranial nerve palsies and vasculopathy with transient ischemic attacks alone or in combination can occur without a shingles rash. Pleocytosis and detection of VZV antibodies or VZV-DNA in cerebrospinal fluid (CSF) confirms the diagnosis [22, 46, 65]. Visceral reactivations without a rash are mainly described in the immunocompromised [65]. In recent years VZV reactivations have been linked to giant cell arteritis [66], achalasia and other enteric disease [67, 68].

2.6 MICROBIOLOGICAL DIAGNOSTICS

Both chickenpox and shingles have distinct characteristics and the diagnoses are generally made on clinical appearance.

VZV-DNA detection with Polymerase Chain Reaction (PCR) using biological samples can confirm the diagnosis. Primarily, vesicle fluid from chickenpox or shingles rashes and CSF from patients with neurological symptoms are used. PCR can also detect VZV-DNA using a range of other biological samples e.g. saliva, serum, urine, vitreal fluid, and trachea-bronchial swabs. PCR has replaced antigen detection, virus isolation and immunofluorescence in routine diagnostics of VZV infection [3, 22, 69, 70].

Serology, i.e. detection of varicella zoster IgG or IgM antibodies using both serum and/or CSF samples, still has a place in diagnostics. Serology of IgG antibodies is used for screening, e.g. to test for immunity in pregnant women and to evaluate latency of VZV in patients prior to initiation of immunosuppressive therapy. A significant rise in IgG titre after a suspected episode of shingles, can confirm the diagnosis. The presence of IgM antibodies can help discriminate primary infection from reactivations, since IgM is elevated mainly in primary infection [3, 15]. The ratio of IgG antibody titres in CSF compared with serum can be used to diagnose VZV-related CNS involvement late in the course of disease, when PCR is no longer positive [22, 69, 70].

Virus isolation can still be of use when drug resistance is suspected. In addition, DNA-sequencing can discriminate vaccine strain from wild-type strains in suspected vaccine failures [15, 71].

2.7 TREATMENT

The nucleoside analogue acyclovir and its prodrugs valaciclovir and famciclovir, inhibit replication of varicella zoster virus. If treatment is started in time, there is a shorter duration of illness, less viral shedding and reduced risk of complications [72, 73]. Resistance of VZV against these drugs is very rare [71].

In Sweden, antiviral treatment is recommended for immunocompetent chickenpox patients of 18 years and above, if started within 24 hours of onset. Younger patients should be treated if severely ill or at risk of severe disease. Shingles therapy is recommended for all patients of 50 years and above, if started within 72 hours of onset. Patients with severe disease or who have either eye or neurological VZV complications, as well as immunocompromised individuals, should always receive antiviral therapy, no matter time since onset [70].

In addition to antivirals, steroid treatment is used in cases with neurological complications (not isolated meningitis) and/or vasculopathy to reduce complications caused by inflammation per se [69].

Postexposure prophylaxis with varicella zoster hyper immunoglobulin (ZVIG) could be given after intense VZV-exposure of susceptible individuals at high risk of severe disease [11, 71, 74].

2.8 VZV DISEASE SURVEILLANCE

Neither chickenpox nor shingles is a notifiable disease in Sweden. Incidence estimates are based on studies. Some countries across Europe have surveillance systems in place for chickenpox and/or shingles. In the most recent report on European varicella and herpes zoster surveillance from 2010, systems included e.g. mandatory case-based reporting, aggregated data reporting from laboratories, and sentinel systems [75].

The entity of viral meningoencephalitis falls under mandatory reporting in accordance with the Communicable Disease Act in Sweden. Neurological complications caused by the varicella zoster virus are included in this group. Cases should be confirmed with either PCR or serology of cerebrospinal fluid (CSF) or have classical symptoms and a documented serological reaction in serum [76].

2.9 CHICKENPOX VACCINES

2.9.1 Available vaccines

All chickenpox vaccines currently available are live attenuated vaccines, containing the Oka strain, which is of the Asian genotype, clade 2. It was isolated from chickenpox vesicles (from a 3-year-old Japanese boy whose family name was Oka) and attenuated by Takahashi and colleagues in the 1970s [3, 77]. The live vaccines mimic natural infection immunologically, by eliciting both VZV-specific antibody and T-cell responses [78].

Three chickenpox vaccines are licensed in Sweden; two of them are currently available on the market and primarily used in private vaccination clinics. Both are monovalent and contain >1,350 plaque forming units (PFU) of the vaccine virus [79, 80]. There is also a quadrivalent vaccine, a combination vaccine against measles, mumps, rubella and chickenpox (MMRV), which has been approved (10,000 PFU), but is currently not available. The vaccines can be given from 9-12 months of age (ww.fass.se) [79, 80].

All live attenuated VZV vaccines have good safety profiles and are well-tolerated. Side-effects such as fever and varicella rash are reported [81, 82]. This rash has on rare occasions been transmitted to susceptible individuals [83]. There is an increased risk of febrile seizures after the first dose of the MMRV vaccine in children below 2 years of age compared with when MMR and varicella vaccines are given separately [84], but not when given to children of 4-6 years [82, 85]. The vaccines are contraindicated in pregnant women and vaccination of immunocompromised individuals is restricted and should not be given e.g. during chemotherapy or to persons with HIV and a low CD4-count [86].

2.9.2 Efficacy and effectiveness

Pre-licensure immunogenicity and efficacy studies of chickenpox vaccines did not use homogenous amounts of antigen, making generalisations to current vaccines difficult. However, vaccine efficacy studies all show good protection [82, 87].

Systematic reviews [11, 82, 88-90] of post-licensure vaccine effectiveness studies show levels of protection in line with the estimates from the meta-analysis by Marin *et al.* In this study the pooled vaccine effectiveness after one dose was 81% (95%CI 78-84%) against all levels of disease and 98% (95%CI 97-99%) against moderate to severe disease, while the protection against all chickenpox disease after two doses was 92% (95%CI 88-95%) [87]. In a multi-centre study carried out across Europe, vaccine efficacy against all chickenpox disease after one dose of MMRV vaccine was 65.4% (95%CI 57.2-72.1%) and 94.9% (95%CI 92.4-96.6%) after two doses. Protection against severe chickenpox was higher [35].

A high proportion of vaccine failures after one dose seems to be primary failures, i.e. an initial failure to respond to the vaccine, though secondary failures were described, i.e. waning with time since vaccination [82, 87, 91, 92]. Follow-up of 10-14 years show that two doses of the vaccine provide a good duration of protection [93, 94]. The most recent of these studies is now more than 7 years old [94].

Breakthrough varicella (BV) is defined as chickenpox more than 42 days after vaccination. Breakthrough disease is generally milder than natural disease with less frequent high-grade fever and >50 lesions as well as less likely for papules to progress to vesicles [95]. BV cases are about half as contagious as natural chickenpox cases [96]. Severe cases of BV and even deaths do occur: they are uncommon and mostly seen in immunocompromised children or after one dose of the vaccine [97].

Beyond BV, the chickenpox vaccination leads to another presentation: vaccine-strain shingles. The vaccine virus, just like the wild-type virus, establishes latency in neural ganglia and can reactivate [9]. However, the rate of reactivation in vaccinated individuals is considerably lower than that in non-vaccinated, and they present with a milder form of herpes zoster disease [98, 99].

2.9.3 Vaccination programmes around the world and their impact

Chickenpox vaccination within the general childhood vaccination programme is in place in countries around the world. In 1996, the USA was the first country to introduce a one-dose chickenpox vaccination programme [100]. In the following years, Canada, Australia and several countries in Central and South America did the same. Japan, the Oka strain's country of origin, introduced a vaccination programme in 2014. In 2004, Germany was the first European country to introduce a general chickenpox vaccination programme [101].

With a one-dose schedule, there were unacceptably many breakthrough infections and school outbreaks continued to occur, as the moderate effectiveness of one dose did not provide herd

immunity to stop community transmission [11, 89, 102]. This led to the addition of a second dose in e.g. USA and Germany [11, 103, 104].

Currently, thirteen European countries have routine chickenpox vaccination. Finland introduced the vaccine in their general programme in 2017 and Iceland in 2020. Neither Norway nor Denmark has general vaccination [105].

Countries with general chickenpox vaccination of young children have seen a dramatic impact on both chickenpox incidence and mortality [90]. In two active surveillance sites in the USA, there was a 90% reduction in chickenpox incidence during the first ten years of a one-dose programme [106]. After the addition of the second dose in 2008 [11] the incidence declined with an additional 67% and 76% respectively during the first five years. Overall, that means a 98% decline in incidence between 1995 and 2010 and more than 85% reduction in hospitalisations [102]. Similarly, both Germany and Italy have experienced marked decreases in chickenpox hospitalisations since the introduction of their programmes [107]. There is also evidence of herd immunity protecting children younger than the vaccination age [108].

Countries with two-dose chickenpox vaccination have implemented somewhat different programmes. Some countries have opted for a short dose interval, e.g. Germany gives the 1st dose around 11-14 months of age and the 2nd dose at 15-23 months, while others have a longer dose interval, e.g. USA gives the 1st dose at 12-15 months and the 2nd dose at 4-6 years [11, 109]. Belgium vaccinates adolescents without a history of chickenpox, verified by negative serology [105].

2.10 SHINGLES VACCINES

2.10.1 Available vaccines and their efficacy

A monovalent live attenuated shingles vaccine (ZVL) with a high dose (>17,000 PFU) of the same Oka vaccine strain as in chickenpox vaccines has been marketed in Sweden since 2013. In the renowned Shingles Prevention Study, the ZVL vaccinees had a significant increase in VZV-specific antibody and CD4 T-cell levels, which decreased over the three-year follow-up [110]. The vaccine efficacy against the burden of shingles illness (a severity-by-duration index) was 61% (95%CI 51.1-69.1%) over 3 years in people aged 60 years and above, with lower efficacy in the older age group. The efficacy against incident shingles was 51.3% (95%CI 44.2–57.6%) and against PHN 66.5% (95%CI 47.5–79.2%) [111]. A complementary study found slightly higher efficacy in 50-59-year-olds [112]. However, in follow-up studies, protection seemed to wane quickly after vaccination and by year 7-11, the vaccine efficacy against shingles was 21.1% (95%CI 10.9–30.4%) [113, 114]. The vaccine has similar contraindications as the chickenpox vaccines, i.e. mainly immunosuppression [86, 115]. This is unfortunate since this group is at increased risk of shingles. The decreasing efficacy with increasing age is another limitation, since age is the most important risk factor for shingles. In

all, the contraindications, the moderate efficacy and the short duration of protection have limited the use and usefulness of this vaccine.

Since 2020, an adjuvanted recombinant vaccine (RZV) containing the highly immunogenic gpE has been on the market in Sweden. The vaccine is given in two doses, two months apart. The vaccine elicits a robust VZV-specific antibody and CD4 T-cell response [116] and has a high vaccine efficacy 97.2% (95%CI 93.7-99.0) in people aged 50 years and above at 3-years follow-up. There was no significant decrease in efficacy with age at vaccination [117, 118]. Recent duration data are promising, showing persistent immune response [119] and an 84% efficacy seven years after vaccination [120].The vaccine is not contraindicated in the immunocompromised, and elicits a robust humoral and cell-mediated immune-response in several of these groups [121], efficacy studies are underway. Overall, this vaccine has some major strengths compared with the ZVL. However, the reactogenicity is more pronounced than for ZVL [122] and currently the cost for private individuals to purchase this vaccine is considerably higher than for the ZVL. Furthermore, supplies have been limited. In Sweden, RZV is approved for all persons from 50 years of age and in risk groups for shingles from 18 years [118].

2.10.2 Vaccination programmes around the world and their impact

The USA has recommended ZVL from the age of 60 years since 2008 [12], but changed their recommendation to RZV in 2017 [123]. Recommendations are similar in Canada [124].

In 2019, the German STIKO issued a recommendation for a two-dose RZV programme for all people aged 60 years and above [125]. The United Kingdom has a shingles vaccination programme for those aged 70 years, with a catch-up programme for 71-79 year-olds. The ZVL vaccine is used. A vaccine uptake of over 60%, gave a 23% reduction in shingles hospitalisation rates and 34% reduction in primary care consultation rates in the eligible cohorts during the first five years of the programme [126].

2.11 EXOGENOUS AND ENDOGENOUS BOOSTING

2.11.1 The exogenous boosting hypothesis

Dr Hope-Simpson first described the theory of varicella latency and boosting in 1965 [127]. His theory has since been changed somewhat but still holds to a large extent [9]. He proposed that immunity decreases with age and that symptomatic VZV reactivations, i.e. shingles, occur when immunity drops below a certain threshold. However, the VZV-specific immunity is boosted on exposure to VZV-infectious individuals, so-called exogenous boosting (Figure 4) [127].

The concept of exogenous boosting has been thoroughly studied. The theory has been corroborated by risk factor studies showing a decreased risk of shingles for adults with children in the household [128, 129], other contacts with children [130], and occupational contact

with ill children [129]. The famed LIVID study from 1998, found a significantly lower risk of shingles in paediatricians compared with dermatologists and psychiatrists [131], but the low response rate makes the validity of these results weak. Other studies have failed to find a correlation with known VZV exposure and risk of shingles [59, 132]. Similarly, a study of nuns and monks in isolated monasteries in France, found them to have similar shingles incidence as the general population [133].

Exogenous boosting has also been studied immunologically. An increase is VZV-specific cell-mediated immunity after exposure to children with infectious chickenpox has been documented, although the studies were limited in size, and some showed only a short-lived increase in CMI in some of the study subjects [134-137].

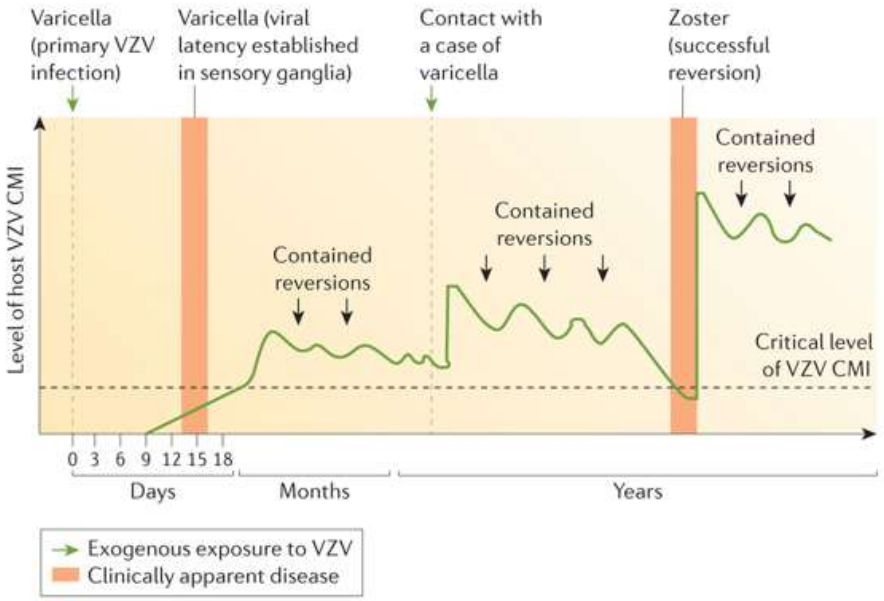


Figure 4. Natural history and pathogenesis of shingles.
Showing exogenous and endogenous ("contained reversions") boosting episodes.
Source: Gershon et al. "Varicella zoster virus infection". Nat Rev Dis Primers, 2015. (Adapted from Hope-Simpson, R. E. The nature of herpes zoster: a long-term study and a new hypothesis. Proc. R. Soc. Med. 58, 9–20 (1965), with permission from The Royal Society of Medicine.) Reprinted with permission from Springer Nature.

2.11.2 Asymptomatic reactivations and endogenous boosting

Hope-Simpson also proposed that asymptomatic reactivation leads to boosting of VZV-specific immunity, so-called endogenous boosting (Figure 4) [127]. Naturally, this concept is more difficult to study. In support of endogenous boosting, subclinical reactivations in immunocompetent individuals were detected using PCR for VZV-DNA in serum or saliva during stress, i.e. during space flight and intensive care treatment [138, 139]. Additionally,

positive PCR for VZV-DNA in peripheral blood mononuclear cells (PBMC) or a significant increase in VZV-IgG antibody titres was captured both with and without symptoms in a range of immunosuppressed individuals [140, 141].

2.12 VZV DISEASE MODELLING

Mathematical models can be used to predict the transmission of infectious diseases, and the impact of vaccination or other interventions. The basic model type is the so-called SEIR model, where the population is assigned to compartments: susceptible (S), exposed (E), infectious (I) and recovered (R). The movement of individuals between compartments is described by differential equations, with rates describing the proportions of the population moving per time unit. These models are deterministic, i.e. given initial values and parameters, the output is determined. Such models can be said to describe average effects on the population. Other model types are e.g. stochastic models, where the values are allowed to vary by chance and the model will give a range within which the outcome may lie. While compartmental models describe the behaviour of large groups of individuals, individual-based models track each person's individual risk of infection. Most studies on the impact of vaccination on the population level have used models of the first type [142].

Both the direct and indirect effects of vaccination can be accounted for in mathematical models. The vaccinated individuals have a direct protection against infection, which will lead to a reduced number of cases and hence, reduced disease transmission in society. As a consequence, unvaccinated individuals will experience fewer opportunities to come in contact with infectious individuals, i.e. they have an indirect protection against infection. This indirect effect is part of the concept of herd immunity [142]. One usually undesired effect of reducing infectious encounters without completely eliminating them is the probable increase of the average age of infection for those who do become infected. This might constitute a problem for infectious diseases that are more severe with increasing age, such as chickenpox [143].

The modelling of chickenpox disease is straightforward and resembles modelling of other infectious diseases. The impact of vaccination is largely dependent on vaccination coverage and effectiveness. However, the close link to the epidemiology of shingles poses a unique challenge to VZV modelling. In particular, the possible impact of reduced virus circulation caused by chickenpox vaccination and the assumed subsequent reduced opportunities for exogenous boosting in individuals with previous chickenpox disease are afflicted with uncertain assumptions. Three different models for the boosting of VZV immunity after exposure to an infectious person have been proposed [144]. Partial immunity models assume a reduced risk of reactivation for a given time period after a boosting episode [145]. The temporary immunity model assumes no risk of reactivation for a time period after exposure and was the most widely used model, especially during the first decade of varicella modelling [128, 146-150]. Later, there was a shift towards the progressive immunity model, which assumes

lifelong reduced reactivation risk with an increasing level of protection with each boosting episode [151-156]. This immunity model was based on Hope-Simpson's exogenous boosting theory [127]. VZV models using either of these immunity models have predicted a surge in shingles incidence after the implementation of chickenpox vaccination. In some models, particularly in the progressive immunity models, this surge would last for decades and at its peak have up to twice the current shingles incidence [155]. In the long run, as the initial population which has primarily had natural infection is gradually replaced by a vaccinated population, the lower risk of reactivation of vaccine-strain virus, i.e. the reduced risk of shingles in chickenpox-vaccinated individuals, would lead to lower shingles incidence. The incidence could also be reduced by shingles vaccination.

General chickenpox vaccination is cost-effective from a societal perspective when only the impact on the disease burden of chickenpox is assessed. When the potential impact on shingles incidence is included, the cost-effectiveness is uncertain [157].

2.13 KNOWLEDGE GAPS REGARDING VZV EPIDEMIOLOGY AND VACCINATION

At the time when this PhD-project began, both the WHO Position Paper on varicella and herpes zoster vaccines [1] and the ECDC Guidance on varicella vaccination in the European Union [2] identified knowledge gaps and potential concerns regarding general VZV-vaccination programmes. Since then, although some knowledge gaps remain, to some extent others have been filled with new evidence.

As previously mentioned, one remaining knowledge gap is the duration of protection from the chickenpox vaccine more than 14 years after vaccination and the potential need for booster doses. At the time, there was also limited knowledge on shingles disease in chickenpox-vaccinated individuals [2].

There was a concern about an upward shift in the mean age of infection, due to a higher level of immunity in the population, as described above. Since chickenpox is more severe with age, even a decline in incidence due to vaccination could lead to an increase in overall disease burden, as each case is more severely ill. A comparable situation was an increase in congenital rubella cases subsequent to low-coverage in a rubella vaccination programme [158]. The concern for an upward shift in age of infection was the main reason why WHO emphasized that countries that implement chickenpox vaccination need to make sure they can maintain a coverage above 80%, since that level should be sufficient to essentially eliminate the epidemic risk from the country [1].

Furthermore, the concern of a surge in shingles incidence with the introduction of general chickenpox vaccination due to a decline in exogenous boosting opportunities has delayed the decision on an introduction in many countries, primarily in Europe [159, 160]. At the start of this PhD-project, the first review article challenging the exogenous boosting hypothesis had just

been published [161]. The systematic multidisciplinary review by Ogunjimi *et al.* from 2013 found sufficient evidence in support of the exogenous boosting mechanism to conclude that it exists, although not in all persons or situations [161].

WHO also concluded that the burden of shingles was unknown in most countries and that the data on ZVL, at the time the only licensed shingles vaccine, was insufficient to make any recommendation [1].

2.14 DEMOGRAPHIC AND SOCIOECONOMIC DETERMINANTS

Dahlgren and Whitehead famously described the social determinants of health as layers around individuals; first the individual lifestyle factors, followed by community influences, living and working conditions, and the outer layer of more general social conditions [162]. Across the world, social and economic circumstances determine how children grow, whether they are healthy or not and their life expectancy. The lower the socioeconomic position, the poorer the health. Even within high-income countries, health has a social gradient [163]. In Sweden, socioeconomic differences in health are clear, people with low educational level have shorter life expectancy and are e.g. more frequently overweight [164]. Infectious diseases in Europe are also influenced by socio-economic factors, with a disproportionately high burden on those with lower income and educational level or belonging to marginalised groups [165]. Notifiable infectious diseases in Swedish adults were also associated with socio-economic status. However, although some diseases were associated with low status, others were associated with factors related to high socio-economic status [166].

2.15 HOW A NEW VACCINE IS INTRODUCED INTO THE CHILDHOOD VACCINATION PROGRAMME IN SWEDEN

The Communicable Diseases Act (SFS 2004:168) regulates the Swedish National Immunization Programmes (NIPs). A disease should be covered by an NIP if vaccination against the disease is expected to:

- effectively prevent the transmission of communicable diseases in the population.
- be socioeconomically cost-effective.
- be sustainable from an ethical and humanitarian perspective.

In the corresponding ordinance (SFS 2004:255), the following 13 factors are listed for the PHAS to take into account when proposing changes to the NIP to the Government:

1. The burden of the disease on society, the healthcare sector, and for individuals.

2. The expected impact of vaccinations on the disease burden and epidemiology.

3. The number of doses that are required to achieve the desired effect.

4. The target groups for vaccination.

5. The safety of the vaccine.

6. The impact on the activities of regions, municipalities, and private healthcare providers as a consequence of carrying out vaccinations.

7. Suitability as regards combining the vaccine with other NIP vaccines.

8. Public acceptance of the vaccine and its impact on attitudes towards vaccines in general.

9. Other available preventive measures or treatments that could be alternatives to an NIP.

10. A socioeconomic cost-effectiveness assessment of the vaccination, and of the costs for and available resources of the state, municipalities, and regions.

11. The possibility of monitoring the impact of the vaccination with regard to the ten above-mentioned factors and the estimated costs for the state for this monitoring.

12. The need and cost for information initiatives for the population and healthcare providers.

13. Medical ethics and humanitarian considerations.

Vaccinations included in NIPs should be offered by regions or municipalities free of charge in accordance with the corresponding legal act (SFS 2012:453).

In 2013-2014, this PhD –project was planned with the intention to provide up-to-date epidemiological data for an anticipated appraisal of general VZV-disease vaccination, primarily for factors 1, 2, 3, 4, and 10 above.

The “National reference group for NIPs” is convened under the auspices of the PHAS. They identify and prioritise any needed changes to the Swedish NIP. On the advice of the reference group and after an internal decision taken by PHAS, an appraisal of chickenpox and/or shingles vaccination was launched in 2018.

3 RESEARCH AIMS

The overall aims of this thesis were:

- to describe the current burden of illness due to chickenpox in Sweden.
- to assess the potential impact of vaccination on the epidemiology of varicella zoster virus disease in Sweden.

3.1 SPECIFIC AIMS

- To describe the burden of disease from chickenpox in Sweden, with special focus on age-specific incidence and severity of disease **(Studies I & II).**
- To describe the extent of and investigate risk factors for severe chickenpox disease in Sweden **(Studies II & III).**
- To explore the differences in demographic and socioeconomic factors among children hospitalised due to chickenpox compared with other viral diseases **(Study III).**
- To assess the impact of various vaccination strategies on the epidemiology of VZV disease in Sweden, including scenarios with chickenpox and shingles vaccines alone or in combination **(Study IV & additional results).**

4 MATERIALS AND METHODS

4.1 OVERVIEW

The first aim of this thesis, to describe the current burden of illness due to chickenpox in Sweden, was phrased that way because two comprehensive assessments of the epidemiology of shingles in Sweden had just been published [48, 61], whereas no recent national assessments of the epidemiology and disease burden of chickenpox had been made. Studies I, II and III were carried out to reach this aim.

The second aim, to assess the potential impact of vaccination on the epidemiology of varicella zoster virus disease in Sweden, deliberately included both chickenpox and shingles. The epidemiology of each of these two diseases are closely connected and vaccination against one of these diseases can have an impact on the epidemiology of the other. Study IV was carried out to reach this aim. The results of additional modelling work is also presented below, in order to fully achieve the aim.

4.2 ICD-10 CODES

The International Classification of Diseases, Tenth Revision, ICD-10, is an international system created by WHO for the classification of conditions and diseases in clinical practice. The codes are used for the monitoring of incidence and prevalence for both healthcare and research purposes [167].

In the Swedish version of the classification system [168], the code B01 for chickenpox has five subcategories, specifying the presence of complications.

B01 Varicella (chickenpox)
B01.0 Varicella meningitis
B01.1 Varicella encephalitis
B01.2 Varicella pneumonia
B01.8 Varicella with other complications
B01.9 Varicella without complication

Similarly, the code B02 for shingles has seven subcategories.

B02 Herpes zoster (shingles)
B02.0 Zoster encephalitis
B02.1 Zoster meningitis
B02.2 Zoster with other nervous system involvement
B02.3 Zoster ocular disease
B02.7 Disseminated zoster
B02.8 Zoster with other complications
B02.9 Zoster without complications

In this thesis, the ICD-10 codes for chickenpox were used to extract relevant records from large national and regional databases. They were also used to identify relevant medical records of patients admitted as a consequence of or with chickenpox.

4.3 MATERIAL: DATA SOURCES

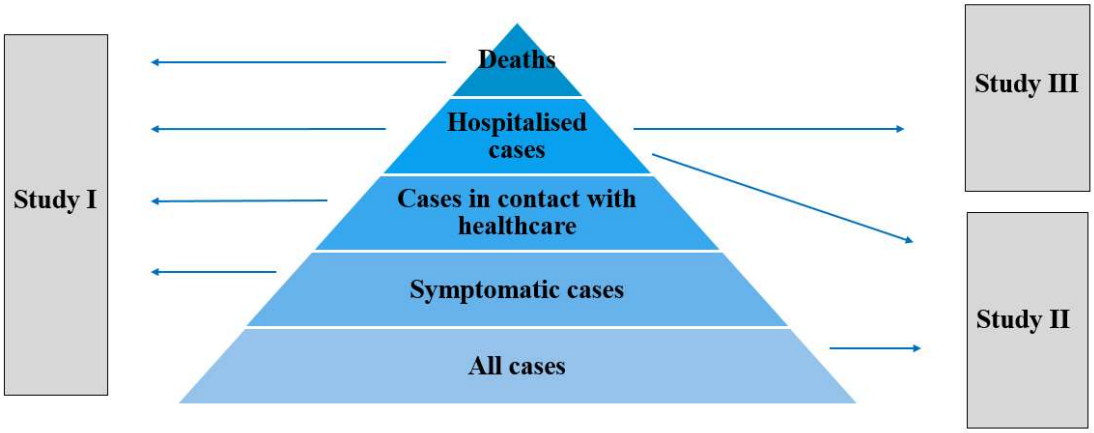


Figure 5. Study overview in relation to the burden of chickenpox disease pyramid

4.3.1 The Cause of Death register

The Cause of Death register is administered by the National Board of Health and Welfare. It holds records with the cause of death for all Swedish citizens who have died in Sweden or abroad. Records from 2007-2012 where ICD-10 codes B01-B01.9 were given as the primary, underlying or contributing cause of death were extracted. This data source provided information on deaths in Figure 5.

4.3.2 The National Patient Register

The National Patient Register is also administered by the National Board of Health and Welfare. It holds records on all inpatient care in Sweden since 1987. Since reporting is mandatory by law, the completeness is very high, 99%, and has also shown a high validity [169]. Records with ICD-10 codes B01-B01.9 either as primary or secondary diagnosis for the years 2007-2012 were extracted. This data source provided information on hospitalised cases in Figure 5.

4.3.3 Sminet2 – database of notifications

Notifications on cases reported in accordance with the Communicable Diseases Act are collected in the Sminet2 database, which is managed by the Public Health Agency of Sweden (PHAS). Notifications are created by both the microbiology laboratory and the medical doctor responsible for the care of the case [170]. Notifications for viral meningoencephalitis caused by varicella zoster virus for the years 2007-2013 were extracted. This data source provided information on hospitalised cases and cases in contact with healthcare in Figure 5.

4.3.4 Medical charts

For **Study II**, medical charts for patients admitted due to chickenpox were identified with ICD-codes B01-B01.9 with primary or secondary diagnosis at the time of discharge. All departments that could care for patients in isolation rooms in the two largest cities of Sweden, Stockholm and Gothenburg, in 2012-2014 were included. The departments in question were: the Departments for Infectious Diseases at Karolinska University Hospital, Danderyd Hospital, Capio S:t Göran's Hospital, and Södersjukhuset and the Paediatric Departments at Astrid Lindgren Children's Hospital and Sachs' Children's Hospital in Stockholm, and the Department for Infectious Diseases and the Paediatric Department at Queen Silvia Children's Hospital, both at Sahlgrenska University Hospital in Gothenburg.

The study team examined all medical charts and collected a wide range of information: dates of birth, admission, discharge, onset of symptoms and complications, as well as data on underlying conditions, medication, exposure, current symptoms, complications, work-up, treatment and outcome.

Study III: Medical charts for patients admitted due to chickenpox, influenza, respiratory syncytial virus (RSV) and rotavirus at the Paediatric Department of Astrid Lindgren Children's Hospital in northern Stockholm in 2009-2014 were identified through ICD-codes B01-B01.9 for chickenpox cases and positive PCR-results for the other three diagnoses, by routine sampling of all patients admitted with respiratory or gastrointestinal symptoms.

The study team corroborated the diagnoses with the information in the medical charts and collected data on age, date of admission, presence of any pre-existing complex chronic conditions [171], and admission to an intensive care unit. They removed all cases resident outside the catchment area.

This data source provided information on hospitalised cases in Figure 5.

4.3.5 The Stockholm Healthcare Databases

The Stockholm Healthcare Databases (VAL) are administered by Stockholm County Council (the current Stockholm Regional Council). They hold the same data as the National Patient Register as well as data on consultations in primary and specialist care, though restricted to Stockholm County. Records on all healthcare contacts with ICD-10 codes B01-B01.9 as

primary or secondary diagnosis for 2007-2013 were extracted. This data source provided information on hospitalised cases and cases in contact with healthcare in Figure 5.

4.3.6 1177 Web searches

The PHAS has an ongoing project with access to anonymous, free text searches on the public healthcare system website (www.1177.se). Continuous monitoring of search terms has been used for e.g. influenza surveillance [172] . Searches for *"vattkoppor"* (the Swedish word for chickenpox) and related words for 2011-2013 were extracted. This data source provided information on symptomatic cases in Figure 5.

4.3.7 Temporary parental benefit when caring for a sick child (VAB)

The Swedish Social Insurance Agency receives claims for temporary benefit from parents who stay at home to care for their sick children. The parents report the complaints of the child by ticking boxes with set alternatives of symptoms and diseases. Aggregated data on the number of children ill with chickenpox per age and year and the aggregated number of calendar days of sick leave in 2011-2013 were available. This data source provided information on symptomatic cases in Figure 5.

4.3.8 Serology samples

The PHAS has collected residual blood and serum samples from clinical chemistry laboratories for influenza surveillance purposes [173]. We used samples collected in 2011-2013 from eleven sites in nine regions across the country. Samples were primarily from primary care patients and only from those aged 0, 1, 2, 3, 4, 5, 12, and 13 years. This data source provided information on all cases in Figure 5.

4.3.9 Statistics Sweden Population Registers

Statistics Sweden's website provides tables on yearly average population size by age, which were used as a denominator in incidence estimates.

Datasets with 1) all admitted chickenpox cases in Stockholm and Gothenburg in 2012-2014 and 2) all admitted cases with four viral diseases at the Stockholm paediatric hospital in 2009-2014 were sent to Statistics Sweden. They matched the records with the Total population register [174] and the Longitudinal integrated database for health insurance and labour market studies (LISA) [175] using the patients' personal identity number (PIN). Demographic variables, namely, gender, municipality, country of birth were added to datasets 1 and 2, and year of birth of the mother, country of birth, single/co-habiting status, disposable income, level of education, and number of children in the household for both parents were added to dataset 2. The personal identifiers were removed and the code key was kept at Statistics Sweden.

4.4 STUDY DESIGN AND METHODS

All statistical analyses were carried out in Stata Statistical Software, Release 13. (StataCorp LP, TX, USA).

4.4.1 Study I

Study I is a descriptive study, where data on chickenpox-related events in accessible national and regional registers and databases (4.3.1-3, 5-7, and 9 above) were compiled. Chickenpox-related records were identified as described above. Records were aggregated either on age of the case for each year or on month of the event.

Incidence estimates were stratified by 1-year age groups for 0-9 year olds and the following wider age groups in the ages above: 10-14 years, 15-24 years, 25-44 years, 45-64 years and 65 years and above. Only the first healthcare contact of each type was used. Both primary and secondary diagnoses were included. Incidence was calculated as number of cases per 100,000 inhabitants in the same age group per year.

4.4.2 Study II

4.4.2.1 Medical chart review

This study is a descriptive study of hospitalised child and adult patients with chickenpox.

The analyses were stratified by age: children (<18 years) and adults (≥18 years). We described continuous variables in median and ranges, and compared them with Wilcoxon/Mann-Whitney's test, since data were skewed. The categorical variables were described in percentages and compared using χ^2-test.

4.4.2.2 Serology study

The serology study is a cross-sectional study analysing age-specific seroprevalence across Sweden.

The blood and serum samples collected by the PHAS were analysed for varicella zoster-specific IgG-antibodies using ELISA Enzygnost® Anti-VZV/IgG. The manufacturer has defined the lower and upper cut-off values to 50 and 100 mIU/ml, respectively. Results in between the cut-off values were classified as equivocal and recorded as positive, as suggested by deOry *et al.* [176]. Age-specific seroprevalences in 1-year age groups were calculated with 95% confidence intervals, assuming a binomial distribution. There were between 99 and 137 samples for each age group. A similar sample size was used by the European sero-epidemiology network (ESEN2) and considered adequate to assess age-specific seroprevalences [32].

4.4.3 Study III

This study was designed in order to put characteristics of chickenpox patients into context by comparing them with those of children admitted with other common viral diseases.

It is in essence a case-control study were cases admitted with chickenpox, as well as with RSV and influenza, respectively, were compared with controls who were admitted with rotavirus. The odds of exposure, in this case demographic and socio-economic factors, were compared between cases and controls using both univariable and stepwise backward multivariable logistic regression.

We carried out a complete case analysis, i.e. we excluded cases with missing values for key variables. In addition to the main analysis, four sensitivity analyses were run. One included only children below 5 years of age, while another included only those admitted to a paediatric intensive care unit. In the third sensitivity analysis we excluded influenza cases admitted in 2009 (the year of the 2009 influenza pandemic) and rotavirus cases admitted in 2014 (when rotavirus vaccination was introduced in Stockholm). In the final post-hoc sensitivity analysis, we excluded the level of education variable in order to increase the number of complete cases.

4.4.4 Study IV

This study was a methodological exploration of immunity scenarios. It was developed during the work on the mathematical model for the Additional modelling described below.

The transmission model was a deterministic, compartmental, age-structured, dynamic model. The flow chart, with compartments and rates, is presented in Figure 6a.

The model described the natural history of varicella zoster virus disease. All individuals were born protected with maternal antibodies (M), and moved to susceptible (S) with the waning of this protection. At an age-dependant rate, the force of infection (FoI), they were exposed (E) to VZV and became infectious (I) after the incubation period. When recovered, they became susceptible to shingles (SZ). At an age-dependant rate, the latent virus would reactivate and cause shingles (ZI), from which the individual would recover and finally move to the recovered from shingles compartment (ZR). In the susceptible to shingles compartment, an individual was also susceptible to boosting.

Individuals could be vaccinated against chickenpox disease. The first dose of the vaccine gave either instant failure, protection with a constant waning rate (V1) or partial protection where exposure would lead to breakthrough cases (Sb). The second dose of the vaccine gave unprotected or partially protected individuals protection with a constant waning rate (V1) but for most individuals it gave protection without (or next to none) waning (V2). Individuals in all of these compartments were susceptible to boosting, i.e. for individuals who had had chickenpox, exposure to VZV was assumed to lead to temporary and/or partial immunity (ZP).

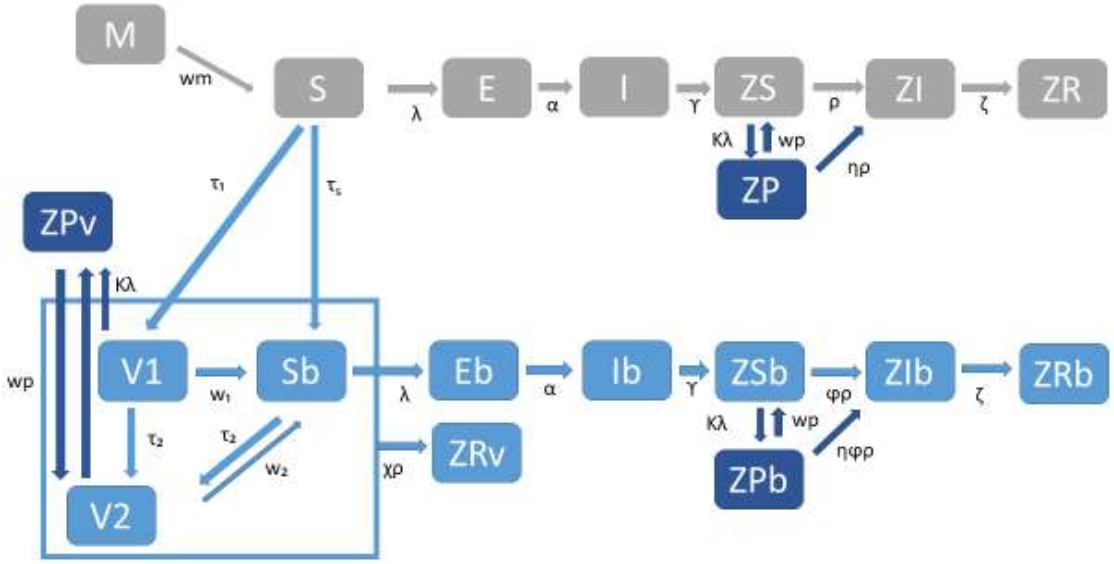


Figure 6a. Flow chart of the transmission model, with natural infection and chickenpox vaccination.

Grey compartments and arrows are related to natural infection, navy blue to exogenous boosting, and light blue to chickenpox vaccination. Compartments: M = maternally-transferred immunity; S = susceptible; E = exposed; I = infectious; ZS = shingles susceptible; ZI = shingles infectious; ZR = shingles recovered; ZP = shingles protected by boosting, V1 = chickenpox vaccinated, 1st dose; V2 =chickenpox vaccinated, 2 doses; (other compartments: -b= breakthrough, -v= vaccinated). For details on transition rates, see Appendix of Study IV.

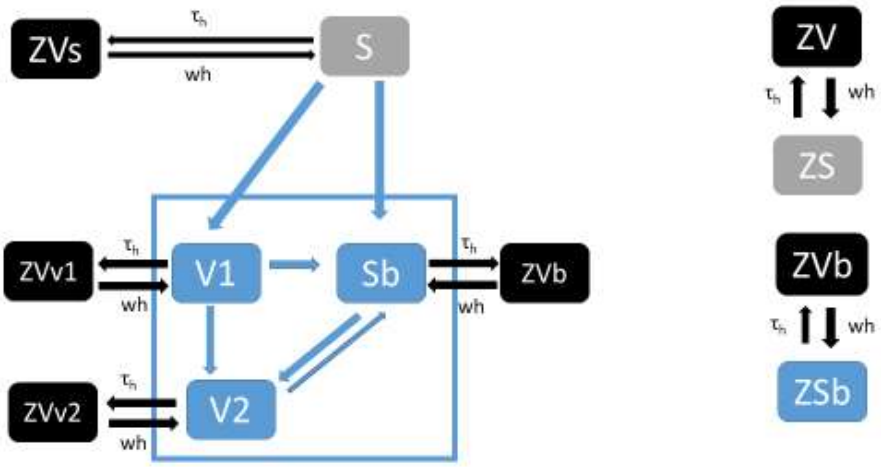


Figure 6b. Additional compartments to the flow chart, representing shingles vaccination.

Black compartments and arrows are related to shingles vaccination. Compartments: ZV = shingles vaccinated after natural infection; ZVb = shingles vaccinated after breakthrough infection; ZVs = shingles vaccinated after being susceptible; ZVv1 = shingles vaccinated after one successful dose of chickenpox vaccination; ZVv2 = shingles vaccinated after two successful doses of chickenpox vaccination. Details on transition rates are available on request.

The number of births per year and the mortality profile were based on data from Statistics Sweden (www.scb.se) as of 2012. The population was assumed to be stable, so the age profile differed from the actual Swedish age profile. The seroprevalence data from **Study II** were used to estimate age-specific chickenpox incidence, but results from infants below 6 months were excluded in order to reduce the impact of maternal antibodies. These data were supplemented with Finnish seroprevalence data for older age groups [32]. For shingles incidence, we used age-specific healthcare contacts in Västra Götaland Region from Sundström *et al*. [48]. The "synthetic" total Sweden contact matrix given by Fumanelli *et al*. [177] was used to describe the intensity of contacts within and among age groups. The model was run until a steady endemic state was obtained. Further model parameters are presented in Table 1.

Table 1. Assumptions for parameters in the transmission model.
Values for sensitivity analyses in brackets.

	Value	Source
Epidemiology and transmission assumptions		
Average chickenpox incubation period ($1/\alpha$)	14 days	[3]
Average chickenpox contagious period ($1/\gamma$)	7 days	[3]
Shingles contagiousness	5% of chickenpox FoI	(*)
Shingles contagious period ($1/\zeta$)	10 days	[3]
Average duration maternal immunity (1/WM)	3 months	[178]
It has been assumed that chickenpox and shingles can occur at most once during lifetime and that neither affects mortality.		
Vaccine assumptions		
First dose of chickenpox vaccine		
Take (T1)	81% (90%)	[87]
Fail (F1)	4%	[91, 179]
Waning (W1)	2%/year	[3]
Second dose of chickenpox vaccine		
Take (T2)	92%	[87]
Fail (F2)	0%	[91]
Waning rate (W2)	0%/year (0.5%/year)	
Contagiousness of breakthrough cases	50% of chickenpox FoI	[96]
Reactivation rate of vaccine virus vs natural virus (χ)	10%	[98]
Breakthrough chickenpox cases who go on to develop shingles later in life are assumed to do so from wild-type strain.		
Shingles vaccine		
Vaccine efficacy	At 55 years: 96.9% At 65 years: 97.4% At 75 years: 91.3%	[118]
Mean duration	20 years	[120]
Programme assumptions		
Chickenpox vaccination coverage	Children: 95% (85%) 11-12-year-olds: Dose 1: 80%, dose 2: 70%	
Shingles vaccination coverage	50% (70%)	

We explored the impact of five different immunity scenarios by varying the assumed strength and duration of protection after exposure to an infectious individual to their extremes (Table 2). In this model, the protection was not cumulative. The age-dependent force of reactivation (FoR) was fitted to the estimated pre-vaccination shingles incidence, using a simple parametric function [180]. The parameters of the function were dependent on each boosting scenario, since the background FoR rate had to be adapted to the age profiles of the population proportions in different states of shingles susceptibility, in order to fit to the pre-vaccination shingles incidence. Chickenpox vaccination according to strategy 2, i.e. two doses at 12 and 18 months, was applied to compare immunity scenarios. The model was run for 100 years after introduction of vaccination.

Table 2. Scenarios for the impact on immunity from exogenous boosting

Name	Description	Average duration of protection against shingles	Protection against shingles, expressed as reduction of FoR
I	short and full	4 years	100%
K	intermediate and full	30 years	100%
J	long and strong	Infinity	90%
D	long and intermediate	Infinity	50%
B	intermediate and intermediate	20 years	30%

4.4.5 Additional modelling

The same model was used to explore the impact of the various vaccination strategies: chickenpox vaccination only, shingles vaccination only and chickenpox and shingles vaccination in combination, on the epidemiology of VZV disease (Table 3). We also tested the sensitivity of the results by varying the assumptions in sensitivity analyses. Assumed parameters for the model are again presented in Table 1. Vaccination coverage for children was based on MMR vaccination coverage in Sweden, for adolescents on human papilloma virus (HPV) vaccination coverage and for adults and elderly on influenza vaccination coverage [181, 182].

Shingles vaccination was not modelled in Study IV. Thus, we added compartments to describe the flow of individuals from shingles vaccination, described in Figure 6b. Shingles vaccination with two doses of the adjuvanted subunit vaccine (RZV) was offered to all of the relevant age (S, V1, V2, Sb, SZ, SZb) and moved individuals depending on coverage and effectiveness of the vaccine to a temporarily protected compartment (ZV). At a constant waning rate individuals moved from the protected compartment back to the compartments they were in at time of vaccination. Immunity scenario I was used in all vaccination strategy scenarios and sensitivity analyses. The model was run for 100 years after introduction of vaccination.

Table 3. Chickenpox and/or shingles vaccination strategies

Name	Number of doses	Age at vaccination
Chickenpox vaccination only		
1	1	12 months
2	2	12 + 18 months
3	2	12 months + 5 years
4	2	12 month + 7 years
5	2	18 months + 7 years
6	2	11 years + 12 years
Shingles vaccination only		
7	2	55 years
8	2	65 years
9	2	75 years
Chickenpox and shingles vaccination in combination		
10	A combination of strategies 2 and 7	
11	A combination of strategies 2 and 8	
12	A combination of strategies 2 and 9	

4.5 ETHICAL CONSIDERATIONS

All ethical approvals for this thesis were obtained from the Regional Ethical Review Board in Stockholm, Sweden.

Ethical approval Dnr 2014/584-31/1 allowed us to obtain large volumes of register data from a range of healthcare registers for Study I. Very little information on each individual was obtained, which prevented any identification of the individual person. Register-based research is a uniquely equal and non-maleficent way to systematically collect information and follow up a large group of people.

Ethical approvals Dnr 2015/588-31/4 and 2015/1119-32 allowed us to review medical charts from hospitalised patients in Studies II and III. This approval meant we did not need informed consent from the individual patients. This could be considered a violation to the autonomy of the patients. To attain informed consent from each of them or their guardians would have jeopardized the feasibility of the studies and potentially resulted in loss of data, non-valid results and uncertain conclusions. To decrease the risk of violating the autonomy of the included patients, we attained approval from the Heads of Departments and we limited the number of researchers who reviewed the medical charts to two for each study. In addition, our study subjects were monitored retrospectively purely in order to establish the situation and the studies did not involve any experiment nor did it in any way intervene with the medical treatment and care of the study subjects. Thus, it should not affect the study subjects in any way.

Furthermore, the ethical approvals allowed us to link the information we attained from the medical chart review with data from the population registers at Statistics Sweden. This procedure was carried out under strict protocol in order to prevent any possibility to identify the patients after register data had been added to the records.

Finally, amendment Dnr 2016/1050-32 to Ethical approval Dnr 2014/584-31/1 gave us approval to post-hoc analyse previously collected blood and serum samples for VZV-antibodies. These were residual samples from laboratories and the procedure did not affect the medical treatment or care of the patient.

To sum up, the overriding aim of this thesis was beneficence, i.e. a striving to do good. The output of this research will guide a Swedish decision on how to best protect the population from harm, where other countries have reached heterogeneous decisions. It would be unethical not to reach a decision and also unethical for the decision not to be based on evidence.

5 RESULTS

5.1 THE EPIDEMIOLOGY OF CHICKENPOX BEFORE VACCINATION

5.1.1 Study I

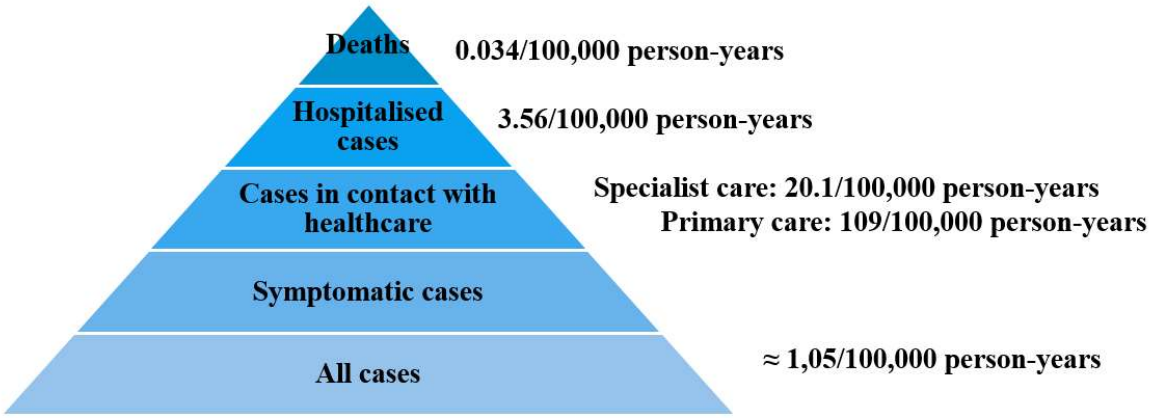


Figure 7. Burden of chickenpox disease pyramid with the Swedish incidence for each severity level

5.1.1.1 Deaths

Chickenpox was not reported as the primary cause of death in any of the records. However, for an average of 3.2 deaths per year, it was reported as an underlying or contributing cause. Thus, the mortality rate was 0.034/100,000 person-years (Figure 7). The median age of the deceased was 58 years (range 1 to 91 years), where seven individuals were below 15 years of age.

5.1.1.2 Hospitalisations

There were on average 333 (range 280 to 386) patients hospitalised with chickenpox as primary or secondary diagnosis per year, which gave an admission rate of 3.56/100,000 person-years (Figure 7). The average length of hospitalisation was 5.2 days, with an average annual 1,740 hospital in-patient days in the country. The peak incidence was in 1 year-olds and the median age at admission 4 years.

5.1.1.3 Viral meningoencephalitis notifications

A majority of notifications lacked data from the physician in charge of the patient and consequently details about clinical presentation and the presence of rash. Thus, it was not possible to ascertain whether the condition was due to primary infection or reactivation. The average number of yearly notifications for VZV neurological disease was 98.1, with an average incidence of 0.97/100,000 person-years. The median age was 46 years.

5.1.1.4 ICD-10 complication codes

There was an increasing trend over the age groups in the proportion of hospitalised chickenpox cases with an ICD-10 code for complicated chickenpox (OR 1.03, p<0.001), from 26.6% in 0-year-olds to 54.1% in the age group 65 years and above.

5.1.1.5 Contacts in primary and secondary healthcare

The consultation rate in specialist care was 20.1/100,000 person-years with the peak incidence in 0-year-olds and a median age of 3 years. The consultation rate in primary care was 109/100,000 person-years, with a peak age in 2-year-olds and a median age of 3 years (Figure 7).

5.1.1.6 1177 Web searches

The monitoring of 1177 web searches captured the seasonal variations of chickenpox disease in the community with high numbers in winter and spring months, and the lowest numbers in August and September, mirroring the seasonal variations in hospitalisations and consultations in primary care (Figure 8).

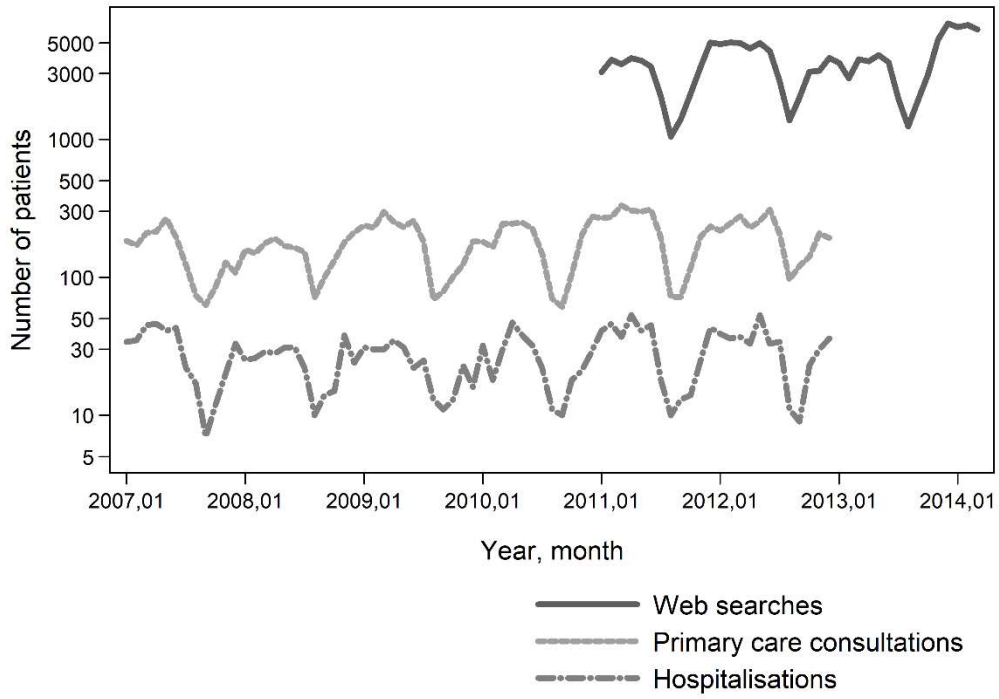


Figure 8. Number of chickenpox-related 1177 web searches, consultations in primary care (only Stockholm County) and hospitalisations, by month, in Sweden.
Note that the y-axis has a logarithmic scale.

5.1.1.7 Temporary parental benefit when caring for a sick child (VAB)

The cumulative incidence of chickenpox-related VAB reached 23.0% of all children during their childhood (<15 years of age), assuming a stable population size. The peak incidence was seen in 2-year-olds (Figure 9). The average duration of VAB was 3.5 days.

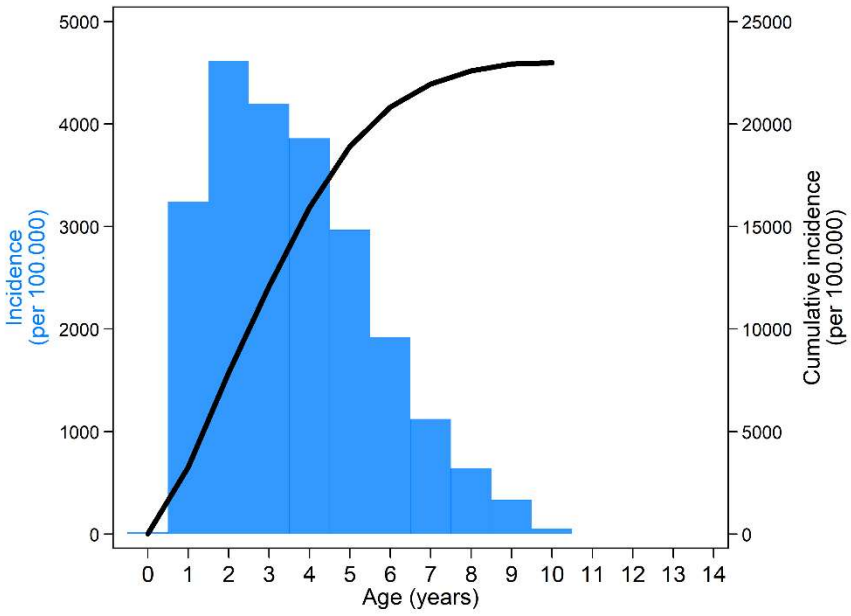


Figure 9. Modelled incidence and cumulative incidence of children whose parents reported chickenpox-related temporary parental benefit (VAB) in Sweden.

5.1.2 Study II

5.1.2.1 Chart review

We studied all cases hospitalised with chickenpox in the regions of Stockholm and Gothenburg in 2012-2014. In total, 362 records of 314 unique patients were identified. After duplicate records were merged to one and records on cases from abroad and from other regions, patients exposed but not ill, patients explicitly stated to suffer from shingles, patients with assumed reactivations and individuals not found in the population registers of Statistics Sweden were excluded, 264 (84%) cases remained. Their characteristics and complications are presented separately for children (<18 years) and adults (≥18 years).

The median age of admitted cases was 3.6 years (range 0-49.5 years). Among admitted children (n=218), 1.8% were born outside Sweden, and 43.1% had a reported underlying illness. For adults (n=46), 63.0% were foreign-born, primarily in the Middle East, Africa and Asia, and 67.4% had a reported underlying condition (including pregnancy). Overall, only 6.8% of patients were on medical treatment affecting the immune system (Table 4).

Information on whether there was a known recent VZV exposure was documented in 153 case records, 57.5% had an exposure within the same household and an additional 26.1% outside the household. Contacts were almost exclusively chickenpox and only in rare instances shingles cases.

The overall most common complication was dehydration, defined as a documented need for parenteral rehydration. Among children, 82.6% of cases had a complication other than dehydration, most frequently secondary bacterial skin infections or neurological complications, primarily cerebellitis and febrile seizures. Among adults, 52.2% had a complication other than dehydration: most frequently gastrointestinal, respiratory or skin complications. (Table 4).

The median length of hospital stay was 3 days (range 0-45 days), 15% of patients were hospitalised for more than one week. Eight patients were admitted to an intensive care unit, primarily due to organ failure related to sepsis or for seizure observation. Five cases who were hospitalised during primary infection later developed sequela, where the link to the chickenpox episode was sometimes unconfirmed. There were no deaths among hospitalised cases.

Among the hospitalised cases, there was no increased risk to develop complications for those with underlying conditions compared with those without. In fact, 121 of the 219 (55.3%) cases with complications were previously healthy.

We compared the information in the medical charts with the ICD-10 coding and found an ICD-10 code for chickenpox to have a positive predictive value of 90.1%. An ICD-10 code for chickenpox with complication had a specificity of 93.3% and a sensitivity of 41.1%. When dehydration alone was not considered a complication, the sensitivity was 43.6% and the specificity remained unchanged. For patients with an ICD-10 code for complicated

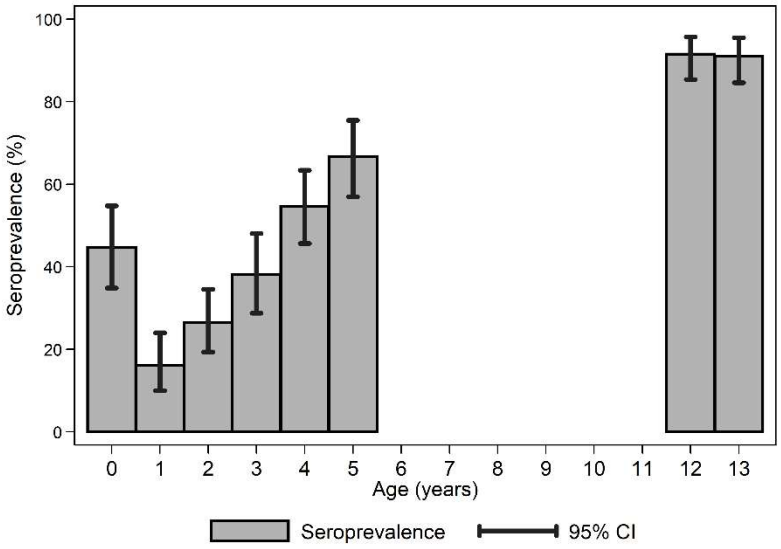
chickenpox, the coding corresponded well to the type of complication reported in the medical chart.

Table 4. Underlying characteristics and outcome of hospitalised chickenpox cases.
**) Groups were not mutually exclusive. **) High-dose corticosteroids, current/previous chemotherapy, immunosuppressants.*

	Children n (%)	Adults n (%)
N	218	46
Characteristic		
Age group		
0 years	45 (20.6)	
1-4 years	122 (56.0)	
5-12 years	44 (20.2)	
13-17 years	7 (3.2)	
≥ 18 years		46 (100)
Female	91 (41.7)	24 (52.2)
Birth country		
Sweden	214 (98.2)	17 (37.0)
Any underlying condition*	94 (43.1)	31 (67.4)
Respiratory disease	38 (17.4)	7 (15.2)
Cardiac disease	7 (3.2)	2 (4.4)
Neurological disease	17 (7.8)	4 (8.7)
Malignancy	6 (2.8)	1 (2.2)
Immunocompromising condition	3 (1.4)	2 (4.4)
Reumatic/autoimmune disease	9 (4.1)	6 (13.0)
Diabetes mellitus/metabolic dis.	6 (2.8)	2 (4.4)
Other	37 (17.0)	13 (28.3)
Pregnancy (% of females)		6 (25.0)
Immunosuppressive treatment**	14 (6.4)	4 (8.7)
Outcome		
Any complication*	190 (87.2)	29 (63.0)
Septicemia	5 (2.3)	1 (2.2)
Skin complication	65 (29.8)	5 (10.9)
Neurological complication	45 (20.6)	4 (8.7)
Respiratory complication	30 (13.8)	5 (10.9)
Gastrointestinal complication	28 (12.8)	6 (13.0)
Coagulopathy	11 (5.1)	0 (0)
Dehydration	69 (31.7)	9 (19.6)
Other	66 (30.3)	12 (26.1)
Admission to intensive care unit	7 (3.2)	1 (2.2)

5.1.2.2 Age-specific seroprevalence

A total of 957 blood and serum samples were analysed for VZV IgG-antibodies. The age-specific seroprevalences are presented in Figure 10. By the age of 5 years, the seroprevalence was 66.7% and by 12 years 91.5%. During the first few months of life, the seroprevalence was almost 100%, decreasing to low levels at 6-9 months, representing the waning of circulating maternal antibodies.



Age in years	Seroprevalence %	(95%CI)
0	44.7	(34.9-54.8)
1	16.1	(10.0-24.0)
2	26.4	(19.3-34.5)
3	38.1	(28.8-48.1)
4	54.6	(45.7-63.4)
5	66.7	(56.9-75.4)
12	91.5	(85.4-95.7)
13	91.1	(84.6-95.5)

Figure 10. Age-specific VZV seroprevalence in Sweden, 2011-2013.

5.1.2.3 Age of hospitalised cases and age-specific seroprevalence

The median age of admission was 3.6 years and the median age for acquisition of antibodies according to the age-specific seroprevalence was about 4 years of age. There was a higher proportion of infants, adolescents and adults among hospitalised cases compared to the incidence in these ages according to the age-specific seroprevalence.

5.1.3 Study III

In this study, we identified 3,590 patient records. When we removed duplicate records, records of cases resident outside the catchment area, records without PIN or data in the registers of Statistics Sweden, 3,445 records remained for the descriptive analysis. Due to missing data, our complete case analysis included 3,125 cases in the regression analyses.

Chickenpox cases (n=112), influenza cases (n=387) and RSV cases (n=1813) were compared with rotavirus cases (n=1133). Descriptive analyses showed median ages for chickenpox 2.7 years, influenza 2.4 years, RSV 0.4 years and rotavirus 1.2 years. Children with chickenpox (4.5%, OR 3.13 (95%CI 1.13–8.57), influenza (11.1%, OR 7.64 (95%CI 4.26–13.69) and RSV (8.1%, OR 5.14 (95%CI 3.08–8.57) were more likely to be admitted to a paediatric intensive care unit compared with rotavirus cases (1.6%).

There were statistically significant differences among the case groups that remained across sensitivity analyses, e.g. the age differences. Influenza and RSV cases were more likely to have underlying conditions than rotavirus cases were, as were the chickenpox cases, although the numbers were too small to be statistically significant. Chickenpox, influenza and RSV cases lived with more children in the household. RSV case mothers were more frequently born in Sweden (Table 5). In addition, there were socio-economic factors that were significant in some sensitivity analyses but not in others: mothers of influenza cases were less frequently born in Sweden and more frequently single and mothers and fathers of RSV cases had a higher disposable income.

Table 5. Significant results from the main multivariable analyses of demographic and socio-economic differences between hospitalised children with influenza, RSV and chickenpox compared with hospitalised children with rotavirus.
All variables with values in each column were included in the respective final models.

	Rotavirus	Influenza	RSV	Chickenpox
		aOR (95% CI)	aOR (95% CI)	aOR (95% CI)
Age	ref	1.36 (1.28–1.44)	0.61 (0.56–0.66)	1.32 (1.22–1.43)
Underlying chronic condition	ref	3.65 (2.43–5.48)	2.24 (1.53–3.26)	
Mother born in Sweden	ref		1.53 (1.26–1.87)	
Father's income				
1st Q	ref		1	
2nd Q			1.33 (1.04–1.69)	
3rd Q			1.29 (1.00–1.66)	
4th Q			1.43 (1.11–1.85)	
Cohabiting mother	ref	0.62 (0.42–0.92)		
Children in household of mother	ref	1.28 (1.14–1.45)	1.43 (1.30–1.56)	1.36 (1.15–1.62)

5.2 THE EPIDEMIOLOGY OF CHICKENPOX AND SHINGLES AFTER VACCINATION

In the deterministic, compartmental, age-structured, dynamic model, we explored the impact of five different immunity scenarios and a set of different vaccination strategies.

5.2.1 Study IV

For the different immunity scenarios to produce the pre-vaccination shingles incidence, the scenario-specific background age-dependent reactivation rates and age profiles of shingles susceptibility status showed large differences among scenarios.

The impact of chickenpox vaccination on chickenpox incidence did not differ among immunity scenarios. Within a decade almost all natural chickenpox had gone (Figure 11).

Regarding the impact of chickenpox vaccination on shingles incidence in the immunity scenario with full and short-lived protection (I), shingles incidence decreased, whereas there was a marked surge in the scenario with full protection of intermediate duration (K). Shingles incidence persisted almost at the current level in the scenario with lifelong and strong protection (J). Both the scenario with lifelong and intermediate protection (D) and the scenario with intermediate protection in terms of both strength and duration (B) resulted in a decline in shingles incidence. The vaccine-strain shingles incidence mirrored the background FoR for each scenario (Figure 11).

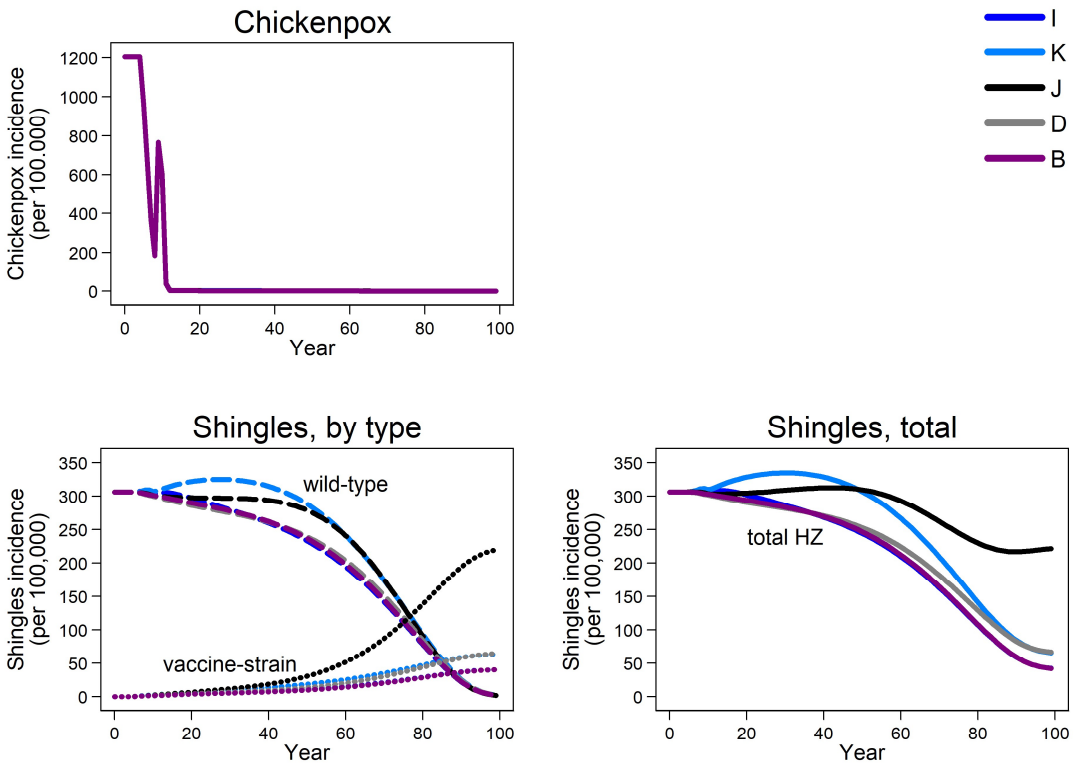


Figure 11. Impact on chickenpox and shingles incidence of general chickenpox vaccination with five immunity scenarios

5.2.2 Additional modelling

As these results were based on a simulated population, the numbers should not be taken as direct predictions for the actual Swedish population, but should be used to make comparisons among scenarios.

5.2.2.1 Chickenpox vaccination only

Figure 12 shows the predicted impact of the alternative vaccination strategies. With the strategy of one dose chickenpox vaccination in childhood (strategy 1), the chickenpox incidence was reduced, but virus circulation continued and created fluctuations in chickenpox incidence over the first decades to later stabilize at a level of around 6% of natural cases and of 17% breakthrough varicella cases of the original level.

All two-dose strategies with vaccination of young children (strategies 2-5) showed fluctuations in the chickenpox incidence during the first decade of the programmes. From about 12 years into the programme, the chickenpox incidence, both natural and breakthrough, diminished drastically. The group of susceptible individuals successively became older and larger, with an increase of 54% over the modelled period.

Vaccination in adolescence (strategy 6) reduced the chickenpox incidence to a level of 90% and breakthrough incidence to a level of 1.2% of the original level of chickenpox incidence.

With vaccination in young children the shingles incidence decreased in the long run and vaccine-strain shingles appeared, whereas the decrease was more modest with vaccination in adolescence.

Figure 13 shows the sensitivity of these results with regards to epidemiological factors such as coverage, take of vaccine dose 1, waning rate after dose 2 and reactivation rate after vaccination applied to vaccination strategy 2 (vaccination at 12 and 18 months). Doubling the reactivation rate had the biggest impact on the total number of VZV-cases (chickenpox and shingles), with an increase of 5%, as it nearly doubled the number of vaccine-strain shingles over the 100 years.

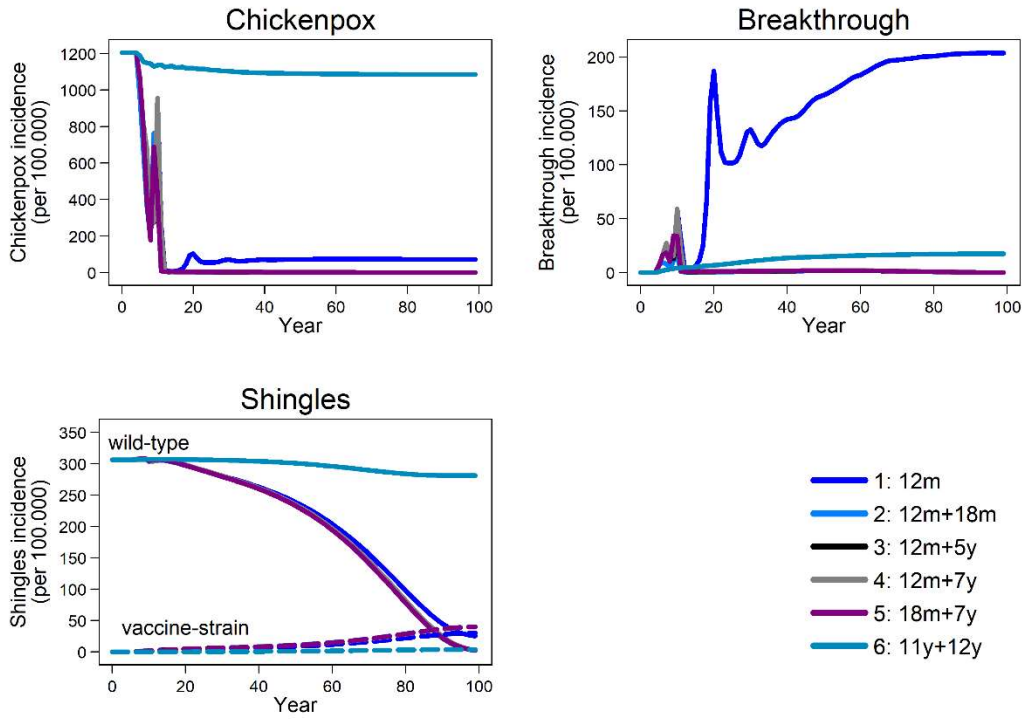


Figure 12. Impact of chickenpox vaccination strategies on chickenpox, breakthrough varicella and shingles incidence

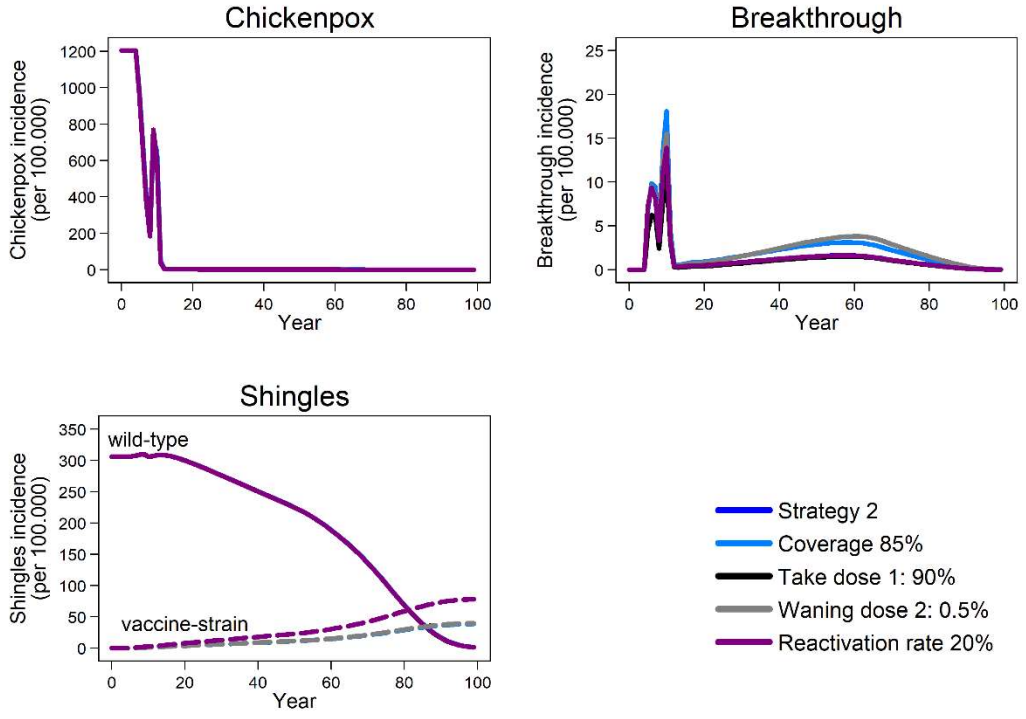


Figure 13. Sensitivity analyses to the impact of chickenpox vaccination on chickenpox, breakthrough varicella and shingles incidence

5.2.2.2 Shingles vaccination only

Figure 14 shows the predicted impact of vaccination with the adjuvanted, recombinant shingles vaccine, without chickenpox vaccination. The incidence of chickenpox remained nearly on the current level, except for the fraction of cases prevented in old age by the shingles vaccination and cases prevented by reduced transmission from contagious shingles cases (not shown). Shingles vaccination decreased the wild-type shingles incidence over time until it reached a plateau; this plateau was higher but reached quicker the higher the age of the vaccination was. Vaccination at 65 years of age prevented more VZV-cases than vaccination at 55 years and 75 years of age. With an assumed coverage of 70%, vaccination of 65-year-olds had a plateau at 18.1% below the original wild-type shingles incidence in the entire population and a 35.4% reduced incidence in the age group of 65 years and above. Vaccination of 55 year-olds with a coverage of 70% prevented nearly as many cases in the population.

5.2.2.3 Chickenpox and shingles vaccination in combination

The shingles vaccination strategies were combined with chickenpox vaccination strategy 2 (vaccination at 12 and 18 months). The incidence of natural and breakthrough chickenpox was very similar to after chickenpox vaccination only, shown in Figure 12. The incidence of wild-type and vaccine-strain shingles with each combined vaccination strategy are presented in Figure 15; shingles cases were prevented both by the chickenpox vaccine, in the long run, and to a lesser extent the shingles vaccine.

The combined strategy of chickenpox vaccination 2 and shingles vaccination at 65 years with 70% coverage prevented the most VZV-cases. The combined strategy reduced the overall number of VZV-cases over the 100 years to 18% of that without vaccination. This reduction was mainly explained by the reduction in chickenpox incidence.

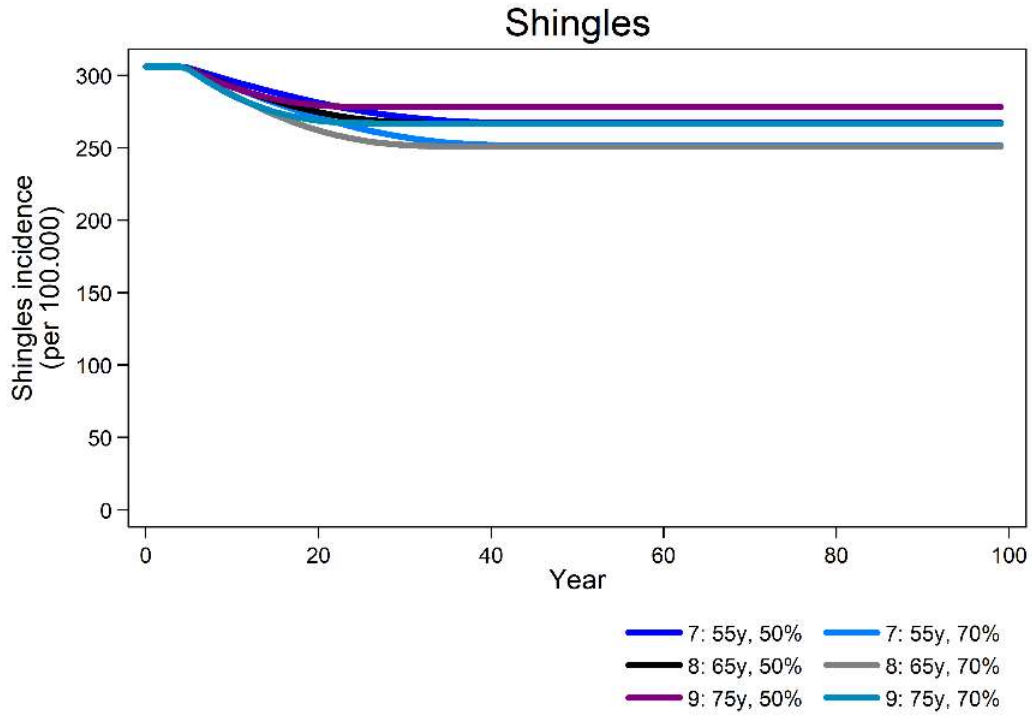


Figure 14. Impact of shingles vaccination strategies on shingles incidence

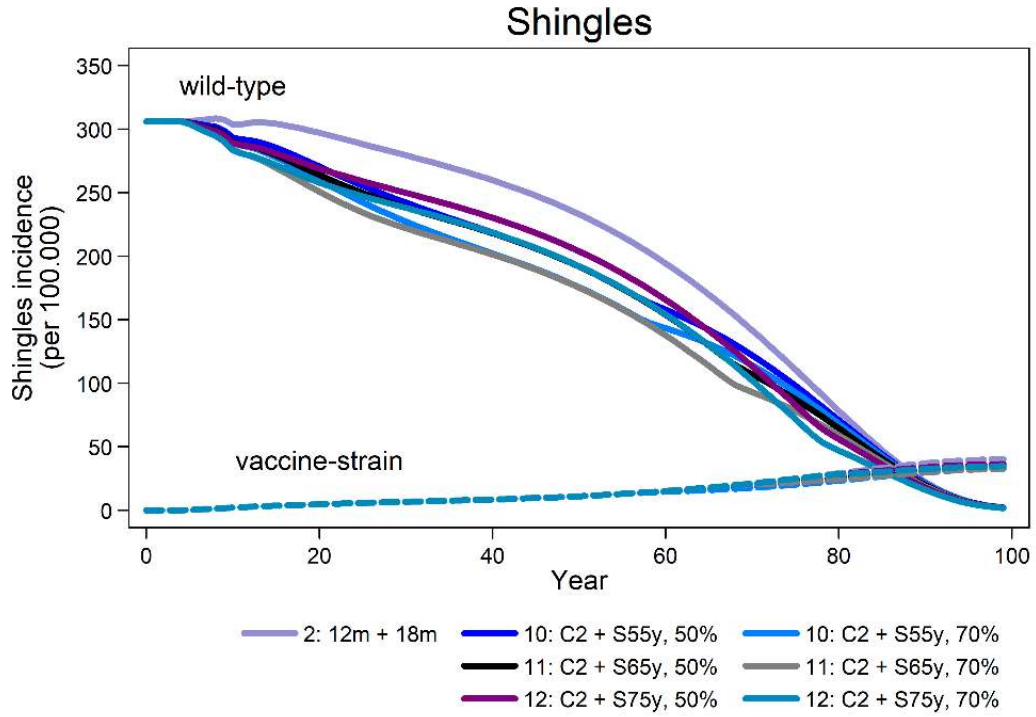


Figure 15. Impact of chickenpox vaccination strategy 2 in combination with shingles vaccination strategies on shingles incidence.

6 DISCUSSION

6.1 THE EPIDEMIOLOGY OF CHICKENPOX BEFORE VACCINATION

Studies I and II, and in part **Study III**, were designed to obtain a baseline for the burden of chickenpox disease in Sweden. This information provided a basis for the ongoing appraisal of general chickenpox vaccination by the PHAS. In addition, a baseline for disease burden is essential if a vaccination programme is to be introduced, in order to monitor and evaluate its impact.

6.1.1 Main findings

- During the first five years of life, two-thirds of Swedish children had contracted chickenpox. By twelve years of age, over 90% of Swedes had been infected.
- Approximately three per 1,000 chickenpox cases were hospitalised. The overall hospitalisation rate was 3.56/100,000 person-years and the hospitalisation rate in children below 15 years of age was 15.3/100,000 person-years, which corresponds to reports from other European countries. Consultations in primary and specialist care were lower in Sweden than elsewhere.
- Fourty-seven percent of the hospitalised chickenpox cases had underlying conditions, including immunocompromising conditions. However, 55% of complications among admitted chickenpox cases were seen in previously healthy individuals. Most frequent were dehydration, bacterial skin infections and neurological complications.
- Hospitalised chickenpox cases were more likely to have siblings compared with rotavirus cases, suggesting household transmission.

6.1.2 Age of infection

The results from the serology analyses in **Study II** showed that Swedish children were exposed to chickenpox at a fast rate during the first few years of life and that by the age of 5 years, 66.7% of children had VZV-antibodies. By the age of 12 years, 91.5% were seropositive, a slightly lower figure than the 98% seen in previous Swedish studies [33, 183], which could be explained by migration from low-endemic areas, changed contact patterns but also by chance.

Bollaerts *et al.* divided European countries without chickenpox vaccination into three groups: those with early, medium or late exposure [184]. Our results suggest Sweden belongs to the medium group with (just) below 70% seroprevalence at 5 years, but (assumed) over 90% by the age of 10 years. Compared to the countries in the ESEN2 project the Swedish age-specific seroprevalences lie in the middle (Figure 16). The differences in age of exposure across Europe have been explained by differences in day-care habits and social mixing among the youngest age groups [32]. In Sweden, day-care attendance is very high, more than 85% at the age of 2 years (www.skolverket.se) and thus, we anticipated a young age of infection. However, our medium group position could be explained by the long state-subsidised

parental leave of 16 months. Although most Swedish children will be exposed to other children at a day-care facility, that might happen later than in many other countries.

The median age of infection was relatively consistent at 3-4 years across most data sources in **Study I and II**, though the precise age distribution varied among severity levels. The median age of notifications and deaths was considerably higher, 46 and 58 years respectively, which suggests these, were largely caused by VZV reactivations and not primary infection.

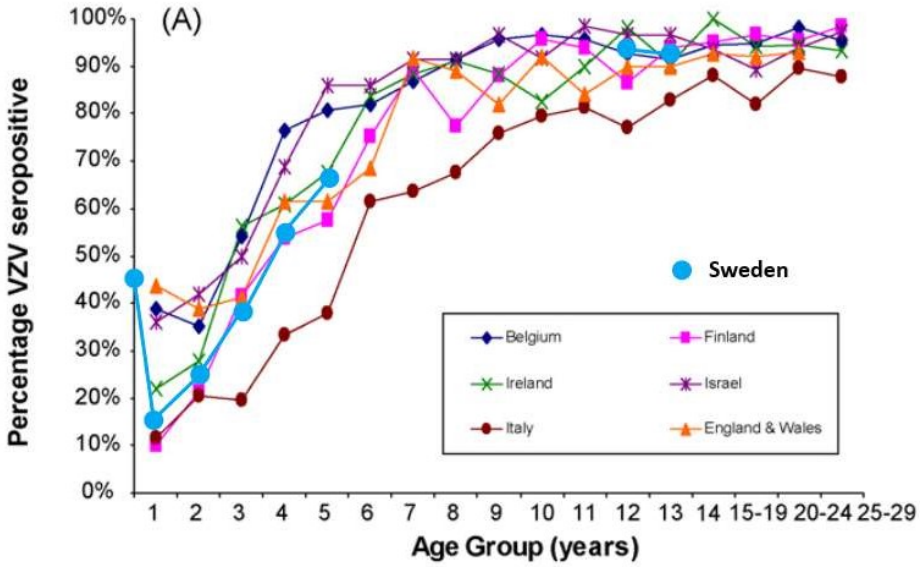


Figure 16. Age-specific VZV seroprevalence in 11 European countries with the addition of Swedish data (in blue).
Source: Adaptation of Nardone et al. "The comparative sero-epidemiology of varicella zoster virus in 11 countries in the European region". Vaccine, 2007 [32]. Adapted with permission from Elsevier.

6.1.3 Incidence

From the seroprevalence levels in **Study II**, it can be inferred that the overall disease incidence is at least 1,045 cases per 100,000 person-years in Sweden.

The hospitalisation rate in children below 15 years of age of 15.3/100,000 person-years described in **Study I** was in similar range to other European countries, 14.1-28/100,000 person-years (children variously defined as <14-17 years) [19]. We found the highest hospitalisation rates in children below 5 years of age. According to a pan-European review comparing modelled hospitalisation rates, Sweden had among the lower rates for children [18]. Our estimates were similar or slightly higher than in the review. Compared to the three other viral diseases, rotavirus, RSV and influenza, included in **Study III**, chickenpox has the lowest hospitalisation rate in young children [185-187] and subsequently contributed to the lowest number of cases in our study.

Incidence of consultations in specialist and primary care were 20.1 and 109 per 100,000 person-years, respectively. This is considerably lower than in other European countries [188-190] and seen in Sweden for consultations overall. Low doctor consultations rates could be explained by a health-care organisation where these consultations are replaced by visits to nurses and other health professionals. Low rates are also more frequent in countries with salaried doctors, such as Sweden, as opposed to the higher rates in countries where doctors are paid fee-for-service [191].

6.1.4 Risk groups and vulnerable individuals

Individuals with underlying conditions are overrepresented in the upper parts of the disease burden pyramid [3]. A serious course of varicella disease in the immunocompromised group is well-described [192] and was more frequent before the introduction of antiviral treatment [193, 194]. In **Study II,** we found a high proportion of patients with an underlying conditions among hospitalised chickenpox cases, both among children (43.1%) and adults (67.4%), implying an overrepresentation of this group. However, within the group of admitted chickenpox patients, there was not an increased risk of complications among those with underlying risk factors. This could be due to pre-emptive antiviral treatment successfully preventing complications [17]. That 19 of the 20 (95%) patients with potentially immunocompromising diagnoses or treatments in the study received antiviral treatment supports this theory. However, bias could also explain the lack of a risk association: by a lower threshold for patients with underlying conditions to seek healthcare, or a lower threshold among healthcare staff to admit them. Most likely, the reason was a combination of the above. Moreover, admission in itself is a sign of severity, even if not accompanied by a documented complication.

Foreign-born individuals were heavily overrepresented among admitted adult chickenpox cases in **Study II.** In the relevant catchment areas, they represented 23% of the adult population, whereas they made up 63% of the admitted adult patients. In particular, individuals from Africa and South-East Asia were overrepresented, which is compatible with the low-endemicity in those parts of the world [195, 196].

In **Study III**, we examined demographic and socio-economic differences among groups of children admitted on account of four common viral diseases. We found that chickenpox cases had siblings to a higher extent than rotavirus cases did, which is compatible with severity in household transmission due to a high infectious dose [31]. Surprisingly, none of the included chickenpox cases above 5 years of age (n= 22) were born abroad. Few socio-economic differences could be robustly confirmed. However, there was a pattern in the results: an association of chickenpox and influenza cases with factors related to low socio-economy, an association of RSV cases with factors related to high socio-economy, and rotavirus cases in between.

We also compared the proportion of cases in each age group among incident cases according to the serology results and among hospitalised cases in **Study II** and found an

overrepresentation of infants, adolescents and adults among hospitalised cases. All three are well-known risk groups for severe disease [3].

6.1.5 Severe disease and complications

Very few people die of chickenpox [18, 19]. In **Study I**, we found that on average 3.2 deaths per year in Sweden were related to chickenpox, i.e. an annual death rate of 0.034/100,000 population. The reported hospitalisation rate corresponds to approximately 3 per 1,000 chickenpox cases. According to **Study II**, the complication rate was even lower.

In **Study II**, we described the panorama of complications among admitted cases. Similar to what has been described internationally [17, 19, 20], children most frequently suffered from secondary bacterial skin infections and neurological complications. Whereas, adults primarily suffered from gastrointestinal and respiratory complications and bacterial skin infections. Many patients had a moderate disease, and the median length of hospital stay was only 3 days. However, there were some very severe cases with considerably longer hospitalisations; three percent of admitted cases needed intensive care treatment and 1.9% suffered permanent sequelae, although the link to the chickenpox episode could not always be established.

6.1.6 General vaccination and target groups for vaccination

Unarguably, chickenpox carries a very large disease burden in Sweden and elsewhere. As has been shown above, this is primarily due to the high incidence, while the vast majority of cases are mild to moderate. In many countries, the objective of general vaccination programmes is to prevent premature mortality or morbidity. Another objective could be to reduce healthcare costs or economic loss to society, in this case because of absenteeism when parents stay at home from work to care for their sick children [197]. The formulation of the objective is crucial when it comes to the sanctioning of a general chickenpox vaccination programme. In Sweden, the objectives for general vaccination programmes are to effectively prevent transmission, to be socioeconomically cost-effective and to be sustainable from an ethical and humanitarian perspective, in accordance with the Communicable Diseases Act (SFS 2014:168).

Since chickenpox disease affects everyone in Sweden, all would benefit from general vaccination by not suffering from a mild disease. In fact, all would benefit also by not risking a severe disease, since a majority of complications was seen in healthy individuals, even though the risk of severe disease was extremely low. Another mentioned rationale for general chickenpox vaccination has been to achieve herd immunity in order to protect vulnerable individuals from morbidity and even mortality, in particular for those for whom the vaccine is contraindicated [198].

There are other strategies than general vaccination to consider. Vaccination of family members and close contacts of risk patients, has been encouraged to limit severe disease in this group in Sweden and e.g. the United Kingdom [74]. Risk group vaccination is another approach. The vaccination of adolescents without a history of chickenpox would be a risk

group approach, which could prevent severe cases in adolescents and adults [199]. According to the results in **Study II** history-negative migrants could be another target group for vaccination. In a situation with general vaccination, these two groups could be targeted for catch-up programmes.

6.1.7 Future surveillance of chickenpox and shingles disease

Since neither chickenpox nor shingles is a notifiable disease in Sweden, a plan to monitor the impact of vaccination is needed if vaccination is to be implemented. Surveillance systems for VZV disease is present in some European countries [75]. However, as chickenpox is often a mild disease, a large proportion of cases will not come in contact with the healthcare system and thus go without reporting [18]. Furthermore, the implementation of a new surveillance system, with e.g. case-based reporting, takes a lot of resources from the healthcare system, especially for such a common disease [200]. Instead, one of the underlying objectives of **Study I** was to assess the feasibility of using either of the existing data sources for continuous monitoring of the disease burden.

To speculate, one strategy for the first decade of general chickenpox vaccination could be to set up surveillance with a case definition of hospitalised chickenpox cases, thus only monitoring severe cases. The National Patient Register, which was identified as a reliable nation-wide data source, would form the basis for such passive surveillance. The main limitation being the timeliness, since the reporting to the register is monthly [201]. When chickenpox has become more sporadic, a switch to case-based reporting could be made, as it would be more useful when the objective of the surveillance system turns to outbreak management. A valuable complement would be DNA-sequencing to establish whether breakthrough varicella and shingles in vaccinated individuals are due to wild-type or vaccine-strain virus [15].

With regards to shingles surveillance, monitoring of shingles out-patient care consultations would be more sensitive than monitoring hospitalisations, when assessing the impact of vaccination. In recent years, the data on out-patient care consultations in the National Patient Register have improved in completeness [202] and could be used. Shingles surveillance is of essence not only to monitor the impact of shingles vaccination, but also the impact of chickenpox vaccination, as is apparent from the modelling work in this thesis.

6.1.8 Limitations

6.1.8.1 Data quality in healthcare registers

Study I relied on the data quality of healthcare registers. **Study II** gave us the opportunity to assess the accuracy of ICD-10 coding in medical charts, which is the data source for the National Patient register. We found a few cases which had been incorrectly given a chickenpox diagnosis. Of the 293 individual cases from the catchment area, 5.8% were not chickenpox but other VZV-related admissions: VZV-exposed but not ill, shingles cases or suspected reactivations. In fact, only two diagnoses (0.7%) were totally wrong. In all, the

positive predictive value for an ICD-10 code for chickenpox was 90.1%. We had no means of assessing to what extent chickenpox cases were not given a correct ICD-10 code (B01-B01.9), i.e. the sensitivity of B01.x. In an evaluation of the National Patient Register, a particularly high PPV and lower sensitivity was found [169].

Furthermore, in the medical chart reviews in **Study II** we found considerable underreporting of complications in terms of ICD-10 code for complicated disease. These codes are sometimes used to assess severity of disease, as we did in **Study I**. Such interpretations need to keep the potential underreporting in mind.

The above findings highlight a limitation of register-based studies, namely data quality, in particular the aspect of accuracy. An additional limitation is connected to VZV-related surveillance, namely how chickenpox and shingles are intertwined. Clinically, it is not always relevant to establish whether a case with e.g. a neurological VZV complication suffers from primary infection or reactivated disease. The ICD-10 code given in the medical chart could be either B01 or B02. For example, a majority of deaths reported as chickenpox-related are probably connected to reactivations, considering the high median age of 58 years.

6.1.8.2 Control groups

The selection of a relevant control group in observational studies is fundamental for reaching valid results [203]. Finding a suitable control group for a disease that affects absolutely everyone, like chickenpox, is a complex matter and decided by what aspects of the disease are being studied.

Study II was primarily designed as a descriptive study of severe disease, hence its hospital-based approach. We did discuss adding a control group in order to better explore risk factors for severe disease. A control group should be representative of the source population of the cases [203]. Since chickenpox affects everyone, a sample of the entire population seems like a straightforward choice of control group. However, there are obstacles with such an approach. The first is data, as it is difficult to attain information on underlying conditions in the population comparable to that found in the medical charts. When it comes to infectious diseases, there is also the prerequisite of exposure to the pathogen, as there could be differences between cases and controls in this aspect that could bias results. Here, the exposure to the pathogen is not what we want to study. In fact, a control group, which is truly representative of the source population for the cases, would be a sample of the population who were currently or recently ill with chickenpox but not needing hospital care. This would potentially provide the best assessment of risk factors for severe disease and not factors influencing exposure to the pathogen. We did not consider this feasible.

For **Study III** we decided to use a common approach for case-control studies; we compared hospitalised chickenpox cases with children hospitalised with other common viral infections. We found that the least explored risk factors for chickenpox were demographic and socio-economic determinants and therefore we focused on these. Comparing cases with “cases” limits bias when it comes to e.g. healthcare-seeking behaviour and data collection method.

However, there is the issue of both cases and controls being non-healthy and potentially differ from the general population. Thus, they could share risk factors that we failed to detect with this study design [203]. In order to fully explore demographic and socio-economic determinants for infectious hospitalisations in children we should have compared them to the population, by obtaining register data on the entire paediatric population in the catchment area.

6.2 THE EPIDEMIOLOGY OF CHICKENPOX AND SHINGLES AFTER VACCINATION

The modelling in **Study IV** and presented as **additional results** was carried out to achieve the second overall aim of this thesis, i.e. to assess the impact of vaccination on the epidemiology of VZV disease in Sweden. Again, these results informed the ongoing appraisal of general chickenpox and/or shingles vaccination in Sweden.

6.2.1 Main findings

- The impact of chickenpox vaccination on shingles incidence from the exploration of various mechanisms of exogenous boosting were highly varied, due to interplay among factors: the level and duration of protection from a boosting event, the background reactivation rate, and the age profile for shingles susceptibility states at the start of vaccination, which all depended on the immunity scenario.
- The absence of a surge in shingles incidence in the first 20-30 years with general chickenpox vaccination was seen in scenarios with strong, intermediate or weak boosting.
- We found a two-dose chickenpox vaccination programme in early childhood to have the biggest impact on the reduction of chickenpox incidence, about twelve years into the programme there was a reduction to 0.4% of the current level. A short inveral between the doses gave the fewest breakthrough cases.
- Results were not very sensitive to assumption regarding vaccine coverage, effectiveness or waning or reactivation rates.
- Chickenpox vaccination was also very efficient in preventing shingles in the long term perspective. Shingles vaccination had a more moderate impact on the shingles incidence.
- Chickenpox vaccination at 12 and 18 months in combination with shingles vaccination given at 65 years of age prevented the most VZV cases over 100 years in the model. However, cost-effectiveness analyses are needed to evaluate the best vaccination strategy in terms of health effects for its healthcare and societal costs.

6.2.2 Chickenpox vaccination strategies

All chickenpox vaccination strategies resulted in sharp declines in both natural and breakthrough chickenpox, followed by one or a couple of smaller epidemics in the first decade or decades of the programme. This well-known cyclic phenomenon depends on the accumulation of susceptible individuals, mainly through new births. When a threshold of enough susceptible individuals is reached, the number of new infectious individuals per time unit will increase. This increase will continue until the number of new susceptible individuals (births) is smaller than the number of new infectious individuals per time unit and there will be a decrease in incidence [142, 146].

6.2.2.1 One or two doses?

Our modelling confirms what several countries have experienced in reality: a one-dose programme would not efficiently limit virus circulation and the number of breakthrough cases would be unsatisfactory [11, 89]. Thus, many countries with routine chickenpox vaccination have two-dose programmes. However, some countries in Asia and South America have kept a one-dose programme [101], presumably as it is highly effective in preventing severe disease [90]. In the USA, adding the second dose was not assessed to be cost-saving, even though a two-dose programme as such was [204]. However, the costs of outbreak control were large enough to mandate the addition of a second dose [205].

With the one-dose programme, we saw an anticipated age shift upwards in median age of infection. In some countries, such as the USA, a similar age shift was observed in real life, but as the age-specific incidence rates in older ages were lower than in the pre-vaccination era, there was no net increase in morbidity [92].

6.2.2.2 Dose interval in a two-dose programme.

A two-dose chickenpox vaccination programme produces a higher vaccine effectiveness than one dose [87] and would have a more favourable outcome.

A short interval between doses gave a lower number of breakthrough varicella cases in the model. It should be noted that our assumptions reflect a high proportion of vaccine failures being primary failures [82, 87, 91]. On the other hand, a longer dose interval could be motivated by an anticipated increase in long-term duration of protection [206]. For chickenpox vaccination, it has not been established whether dose interval has an impact on duration of protection. A three-month and a three-year dose interval had equal capacity to elicit T-cell protection with longevity [207].

Antibody levels after one or two doses seem to decline with time since vaccination [208]. However, waning of protection after two doses seems limited [87, 88] but needs to be monitored. It is still not known whether there is a need for an additional booster dose in adulthood, i.e. this knowledge gap remains.

6.2.2.3 Age of vaccination

As an alternative strategy, we investigated the impact of vaccination in adolescence, a strategy used in some European countries, e.g. Belgium [105]. The rationale is to prevent severe cases in adolescence and adulthood by vaccination to a lower cost (fewer vaccinees) [206] and presumably to allow virus circulation in the paediatric population in order to maintain exogenous boosting. Thus, the results are heavily influenced by the assumptions regarding boosting of immunity. We found a reduction in cases with about 10%, seen in older age groups, but as severity is not included in the model, no further conclusions could be drawn.

There are some evidence that vaccination early in life is associated with a higher risk of breakthrough disease [82, 91], but we did not take this into account when comparing the impact of various two-dose strategies since estimates of this increased risk vary.

6.2.2.4 Susceptible individuals

Chickenpox vaccination at 12 and 18 months changed the group of susceptible individuals. The size of the group who were susceptible before infection or vaccination slowly decreased over the 100 year modelled period, whereas a group of individuals susceptible to breakthrough infection appeared and increased markedly. Thus, the total susceptible group became successively larger and older. Although virus circulation decreased, sporadic cases continued to occur and posed a risk to susceptible individuals. Susceptible individuals would also be at risk when travelling to endemic countries, which currently comprise the majority of the world.

6.2.2.5 Optimal vaccination strategy

From these findings, it appears that a chickenpox vaccination strategy with two doses at a young age and with a short dose interval would most effectively limit the number of new VZV cases. In the Swedish vaccination programme, a first dose of the monovalent chickenpox vaccine at 12 months of age and a second dose with the tetravalent MMRV vaccine given at 18 months of age, instead of the MMR currently given at this age [209], would be appropriate. That way any increased risk of febrile seizures in connection to giving the first dose with a tetravalent vaccine [82] would be avoided.

6.2.3 Direct impact of chickenpox vaccination on shingles incidence

The direct impact of chickenpox vaccination on shingles incidence was one of the knowledge gaps identified by ECDC [2]. Assumptions regarding reactivation of vaccine-strain virus in our model and many other models were based on shingles incidence in an active surveillance site in the USA. There, chickenpox-vaccinated children had 4-12 times lower risk of developing shingles compared with their peers who had had natural infection [98]. The considerably lower incidence of shingles in vaccinated individuals, i.e. the lower reactivation rate of latent vaccine-strain compared with wild-type virus, has been corroborated by the step-wise decline in shingles incidence in each age group of children in the USA as

vaccinated cohorts of children replace unvaccinated cohorts [210]. This positive impact seen in nationwide administrative databases change the current knowledge about chickenpox vaccines and confirm that they are also highly effective against shingles. However, the long-term impact, i.e. the reactivation rate when these vaccinated children grow old, is still unknown. Will the balance between host and latent attenuated virus remain?

6.2.4 Indirect impact of chickenpox vaccination on shingles incidence – exogenous boosting

The indirect impact of chickenpox vaccination on shingles incidence, i.e. the role of exogenous boosting, is still an unresolved question and a matter of debate [211].

The surge in shingles incidence predicted by mathematical modellers as the result of general chickenpox vaccination has been a major factor in many European countries' hesitancy to implement chickenpox vaccination [159, 160, 206]. The worldwide trends in increasing shingles incidence [64] have helped maintain this concern. In support of the exogenous boosting hypothesis, Poletti suggested it could explain country differences in shingles incidence. Countries with high VZV circulation at a young age, i.e. with a high FoI, had a lower incidence of shingles at old age due to a high force of boosting [180].

The systematic literature review by Ogunjimi *et al.*, mentioned in the Literature review section of this thesis, examined the role of exogenous boosting. They reviewed epidemiological risk factor studies, VZV-immunity post-exposure studies, surveillance in countries with general vaccination and mathematical modelling studies and concluded that exogenous boosting exists, although not in all persons or situations [161]. Others have followed in their wake. Harder, Talbird and Harpaz with their respective teams have come to similar conclusions: although exogenous boosting might exist, the size of the impact from chickenpox vaccination might be rather small on the population level [212-214]. These statements were primarily based on studies of shingles incidence trends. In the USA, the country with the longest history of universal chickenpox vaccination, shingles incidence has been closely monitored. Several studies have examined the data without finding a deviation from the background shingles trends in connection with the implementation of chickenpox vaccination [52, 215, 216]. The increase started before general chickenpox vaccination began, it could be seen in countries with and without vaccination and the size and age patterns differed among settings. Thus, these trends, apart from removed exogenous boosting, have been attributed to improved diagnostics and reporting, demographic factors and an increased proportion of population at risk e.g. the immunocompromised and elderly [64, 211, 217, 218]. In addition, the role of asymptomatic reactivations, i.e. endogenous boosting, has been studied and is thought to be important in maintaining VZV immunity [219].

In **Study IV**, we showed how exogenous boosting could exist and explain the findings from epidemiological risk factor studies and immunology studies and at the same time not lead to a surge in shingles incidence when removed, which would be compatible with the surveillance data described above. Boosting could be strong, intermediate or weak and still not give a

surge in shingles incidence post-vaccination. All the five immunity scenarios with different strength and duration of protection from boosting had to be able to produce the current age-specific shingles incidence under ongoing boosting. This meant the age-specific background reactivation rate, i.e. in a situation without boosting, looked very different among scenarios and so did the age distribution of the shingles susceptibility status in the population before vaccination. As these factors played together, the impact on removed exogenous booting in the different immunity scenarios were sometimes counterintuitive.

6.2.5 Shingles vaccination strategies

Shingles vaccination prevents reactivation and has consequently no indirect effect, i.e. no impact on shingles in unvaccinated individuals. It did however have limited impact on virus transmission and thus new chickenpox cases in our model.

Vaccination with RZV prevented a large proportion of shingles cases in the vaccinated part of the population. A plateau or steady state in shingles incidence was reached when everyone above the vaccination age had been offered the vaccination, which meant it was reached quicker with vaccination later in life. The proportion of the population who became protected at the age of vaccination was decided by the coverage (50% or 70%) and the vaccine efficacy (here 91.3-97.4%). In this model, the protection in the vaccinated cohort waned exponentially, with an average time of 20 years until loss of protection. This means there was a gradual reduction in the proportion who was protected according to the exponential waning. Some lost protection before 20 years and some later than 20 years. Naturally, the number of people who survived decreased with age. Thus, loss of protection early affected more people than loss of protection later. This explains why it was more favourable to vaccinate at 65y years compared to 75 years. Vaccination at 65 years prevented the most shingles cases, but the difference to the impact of vaccination at 55 years was marginal. Here, apart from the mortality factor there was a balance between a larger population in the younger age group and a higher shingles incidence in the older age group. With all three vaccination strategies, the balance between these factors made the final reduction of shingles cases fewer than the anticipated >90% (vaccine efficacy) of vaccinated individuals (coverage).

To establish whether vaccination at 55 years or 65 years would be most favourable, there is a need for a cost-effectiveness analysis, which would weigh the health effects from each strategy against its costs for healthcare and in society. With a societal perspective, cases of working age costs more than cases in retired age groups. We have previously carried out a health-economic evaluation of chickenpox vaccination and/or shingles vaccination with the live shingles vaccine (ZVL). In conclusion, vaccination against chickenpox was cost-effective, but not vaccination against shingles with the live vaccine [220].

In the long run the impact on shingles incidence of shingles vaccination would still be limited compared to that of chickenpox vaccination, though the latter is afflicted with uncertain assumptions.

6.2.6 Limitations

Modelling is very useful when the dynamics of a disease are known. On the other hand, when many assumptions need to be made, as in the case of VZV, one needs to be humble in the interpretation of the modelling results and take into account how sensitive they are to these assumptions. During the work on the mathematical modelling part of this thesis it became evident that while the assumptions regarding aspects of the vaccine did not alter results much, the results were very sensitive to which assumptions were made regarding exogenous boosting. Thus, the explorations of immunity scenarios in **Study IV**.

On another note, we chose not to present the modelling results regarding the live shingles vaccine (ZVL) since they are problematic. A major risk factor for shingles and other VZV reactivations is immunosuppression and the ZVL is contraindicated or should be used restrictively in certain groups of people with immunosuppressive treatment or disease [86, 115]. Hence, a disproportionately large group of cases in each age group would not be prevented with this vaccine, something that is not taken into account in most models.

Furthermore, incidence estimates for reactivations in the model were based on shingles incidence in primary care [48]. VZV reactivations without a rash, e.g. neurological complications were not included in these incidence estimates. Such reactivations can be severe [22]. Since there is also growing evidence of other conditions that can be linked to reactivations of VZV, such as temporal arteritis, and enteric disease [66, 67] it is fair to say that our shingles incidence estimates are an underestimation of the true incidence of VZV reactivations, just like in other VZV modelling work. Consequently, the modelled impact of chickenpox and shingles vaccination will be an underestimation of the true impact.

Shingles incidence estimates might be underestimated for more reasons. For instance, as mentioned regarding chickenpox, there might also be mild cases of shingles who never have a healthcare contact and are subsequently not found in healthcare register data [218]. We attempted to assess the degree of underestimation in register data of primary care consultations or antiviral prescriptions [48, 61]. Participants in a pre-existing web-panel at the PHAS (Hälsorapport), described in detail by Byström *et al* [221], were sent a survey on shingles. We found that the reported shingles incidence by age group was somewhat closer to rates of primary care consultations than rates of antiviral prescriptions among the more than 4,000 respondents. This was anticipated since not all primary care visits will lead to prescriptions. However, there was no convincing age difference in the proportion of cases who had had a primary care visit, which was expected, as the disease is often milder in younger adults [45].

6.3 THE RIGHT VACCINE - ERADICATION

All the current chickenpox vaccines are live vaccines that do not protect against primary infection. Instead, the vaccine virus mimics primary infection, which is mild or without symptoms, after which the vaccine virus establishes latency and in essence prevents wild-type virus from doing so. Reactivations are fewer and milder than from wild-type virus [3, 15, 78]. A vaccine that prevented primary infection would also prevent latency – a mechanism comparable to that of vaccines against two other chronic infections, hepatitis B and HPV – which would be a more attractive alternative [222, 223]. The platform used for the recombinant shingles vaccine could be one mechanism to explore [15] and currently, studies are ongoing in younger age groups to prevent reactivation (www.clinicaltrials.gov). Perhaps chickenpox vaccine development could take advantage of the developments in vaccine research that the covid pandemic has created. For example, mRNA vaccines have proven useful as they can elicit a strong immune response towards a single antigen [224].

A vaccine preventing primary infection could even make eradication of VZV possible, as it only infects humans [225]. Although possible, this might not be feasible. It would take worldwide high-coverage vaccination to achieve this and there will be other pathogens higher on the agenda for such an undertaking.

7 CONCLUSIONS

- Chickenpox is highly endemic in Sweden and nearly all individuals will contract the disease during childhood. By five years of age, two-thirds of children were seropositive. By twelve years of age, 91.5% of Swedes had been infected.

- Only a fraction of chickenpox cases had complications and needed hospital care (0.3%). The hospitalisation rate was 3.56/100,000 person-years.

- Fourty-seven percent of the hospitalised chickenpox cases had underlying conditions. Though, 55% of complications among hospitalised chickenpox cases were seen in previously healthy patients.

- The absence of a surge in shingles incidence after introduction of general chickenpox vaccination was compatible with weak, intermediate or even strong exogenous boosting in our transmission model.

- A two-dose chickenpox vaccination programme with a short dose-interval at a young age in combination with a two-dose shingles vaccination (RZV) programme at 65 years of age prevented the most VZV cases in our model. However, a cost-effectiveness analysis is needed to evaluate which vaccination strategy has the most reasonable costs for healthcare and society in relation to its health effects.

- In the long term perspective, chickenpox vaccination prevented more shingles cases than shingles vaccination did in our model.

8 POINTS OF PERSPECTIVE

During the work on this thesis, an expert group appointed by PHAS began the appraisal of general chickenpox and/or shingles vaccination in Sweden. The results from the thesis has fed into the evaluation. The work on the appraisal, like many other non-covid-related initiatives and actions in public health and healthcare over these past 18 months, has had to stand back due to the covid-19 pandemic. The work on the appraisal will be resumed as soon as possible. The decision regarding general chickenpox and/or shingles vaccination in Sweden is much anticipated.

The concern that general chickenpox vaccination would lead to an increased shingles incidence is still unconfirmed. The absence of a surge in shingles incidence has led to a change in paradigm regarding the concept of exogenous boosting over the past few years. Chickenpox vaccines are safe and effective. General vaccination has had a dramatic impact on the morbidity and mortality of chickenpox. Its promising impact on shingles incidence in vaccinated individuals is an additional aspect in its favour. Particularly since the disease burden of VZV reactivations is probably larger than currently known. With increasing experience from countries with general chickenpox vaccination, the fear of a surge in shingles incidence has become less of an accepted reason for not vaccinating, according to the scientific community. Hopefully, the coming years will provide the final incidence data and immunological studies to resolve this question.

A perfect chickenpox vaccine would prevent primary infection and latency. There is still uncertainty regarding the long-term impact of the current chickenpox vaccine on both protection against chickenpox and the risk of reactivation of vaccine-strain virus. While using this good vaccine we need to strive to develop a “perfect” vaccine. A vaccine which would also prevent primary infection from vaccine-strain virus, would not be associated with the same uncertainties around the interactions between the attenuated vaccine virus and its host in the long term. There is potential to explore new vaccine platforms, the adjuvanted recombinant vaccine currently used against reactivation and e.g. mRNA-vaccines.

In this thesis, the burden of chickenpox disease and the epidemiological advantages and disadvantages of vaccination against chickenpox and shingles were assessed. The results from the modelling of chickenpox vaccination was included in a recent health-economic evaluation. This evaluation will be complemented with the impact of RZV, a new shingles vaccine with high efficacy and promising duration results. The costs for a general vaccination programme and the benefit in preventing the large disease burden of chickenpox and shingles needs to be weighed against the health effects of other healthcare and societal costs.

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