Infections associated with varicella-zoster virus in Norway: disease burden and healthcare resource utilization

Grazina Mirinaviciute

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Department of Infectious Diseases Epidemiology and Modelling, Division of Infection Control and Environmental Health, Norwegian Institute of Public Health

Institute of Basic Medical Sciences, Faculty of Medicine, University of Oslo

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Contents

I. Summary

This doctoral project estimated medically attended burden of varicella (chickenpox) and herpes zoster (shingles) (HZ) for the first time in Norway. Our aim was to inform the national policy decision on the use of varicella and herpes zoster vaccines, which have good effectiveness and safety profiles. We also aimed to inform current screening policies for varicella in obstetric populations in order to choose appropriate strategy for protecting susceptible women, ideally before conception. Thus, we characterized the health care burden of varicella and herpes zoster in the pre-vaccine era by assessing seroprevalence against varicella zoster virus (VZV) in general population and among pregnant women, also estimating the burden of medically attended varicella and HZ.

To evaluate seroprevalence, we tested over 2,200 samples from a nationally representative subset of population along with 1,184 samples from pregnant women within the Norwegian Mother and Child Cohort Study (MoBa). For burden of disease studies, we linked individual patient data of approximately 160,000 patients from different national registries to examine varicella and HZ vaccinations, also varicella- and HZ-coded primary care consultations, hospitalizations, outpatient hospital visits, deaths and viral infections of central nervous system in the whole population of Norway during 2008–2014. We estimated health care contact rates and described the epidemiology of medically attended varicella and HZ.

Our findings suggest that varicella and herpes zoster cause a considerable health care burden in Norway. We found that only 73% of Norwegian population had immunity against VZV, which is lower than in most of European countries (>90%), suggesting that there are susceptible individuals in population. We also found that several women were infected with VZV during their pregnancies, thereby increasing the risk of unfavourable health outcomes both for themselves and their offspring.

Universal varicella vaccination with a two-dose program in the USA demonstrated a dramatic impact by reduced overall varicella incidence and hospitalization rates in children <5 years of age by over 90% and mortality by over 80%. HZ vaccination also resulted in a 50% reduction of HZ incidence as well as reduction of postherpetic neuralgia – one of the most common and debilitating HZ complications, which affects about 30% of HZ patients.

Our study provided the evidence base needed for public health decision making to address the burden of disease in the most vulnerable population groups – children, pregnant women and elderly. Currently Norway neither implements universal varicella vaccination in childhood nor herpes zoster vaccination in adults. There is an urgent need to develop robust knowledge-based national vaccine recommendations for both diseases. In addition, screening guidelines for VZV susceptibility in pregnancy should be revised so that susceptible women could be offered vaccination before conception. This research data enable comparison of varicella and HZ epidemiology and burden of disease with other settings and raise awareness about these conditions among policy makers and health care professionals. Our research also paves the way for further studies to assess cost-effectiveness of vaccination and identify the most appropriate strategy to control both varicella and HZ in Norway.

II. Acknowledgements

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III. Abbreviations

ACIP – Advisory Committee on Immunization Practices
AIDS – acquired immunodeficiency syndrome
Anti-VZV/IgG – antibody - varicella zoster virus immunoglobulin G
ANOVA – One-way analysis of variance
CDR – the Cause of Death Registry
CFR – case-fatality rate
CNS – the central nervous system
CVS – congenital varicella syndrome
DNA – deoxyribonucleic acid
DTP-IPV-Hib-HepB – vaccine against diphtheria, tetanus, pertussis - inactivated polio vaccine - Haemophilus influenzae type b, hepatitis B
ELISA – enzyme-linked immunoassay
GP – general practitioner
HIV – the human immunodeficiency viruses
HZ – herpes zoster
ICD-10 – the International Classification of Diseases, tenth edition
ICPC-2 – the International Classification for Primary Care, Second edition
ID – identity
IgA – immunoglobulin A
IgG – immunoglobulin G
IgM – immunoglobulin M
IQR – interquartile range
MMR– vaccine against measles, mumps and rubella
MMRV – vaccine against measles, mumps, rubella and varicella
MoBa – the Norwegian Mother and Child Cohort Study
NIPH – the Norwegian Institute of Public Health
NPR – the Norwegian patient registry
OD – optical density
OECD – the Organisation for Economic Co-operation and Development
PCR – polymerase chain reaction
PHN – postherpetic neuralgia
SD – standard deviation
US – the United States of America
USD – the United States dollar
UK – the United Kingdom
VAERS – Vaccine Adverse Event Reporting System, US
VZIG – varicella zoster immunoglobulin
VZV – varicella zoster virus
wild-type VZV – wild-type varicella zoster virus
WHO – the World Health Organisation
95% CI – 95% confidence interval

IV. List of papers

Paper I

Rimseliene G, Vainio K, Gibory M, Valcarcel Salamanca B, Flem E. Varicella-zoster virus susceptibility and primary healthcare consultations in Norway. BMC Infectious Diseases. 2016. DOI: 10.1186/s12879-016-1581-4

Paper II

Mirinaviciute G, Kristensen E, Nakstad B, Flem E. Varicella-related Primary Health-care Visits, Hospitalizations and Mortality in Norway, 2008-2014. Pediatr Infect Dis J. 2017. 36(11):1032-1038. DOI: 10.1097/INF.0000000000001656.

Paper III

Mirinaviciute G, Quist-Paulsen E, Broch Brantsæter A, Flem E. The burden of herpes zoster disease in Norway. Submitted to Vaccine.

Paper IV

Mirinaviciute G, Barlinn R, Gjeruldsen Dudman S, Flem E. Immunity to varicella zoster virus among pregnant women in the Norwegian Mother and Child Cohort Study. PLOS ONE. 2019. https://doi.org/10.1371/journal.pone.0221084

During the preparation for the defence the paper III was published in Vaccine on 2019-12-13, DOI: 10.1016/j.vaccine.2019.11.054

1 Introduction

1.1 VZV virus

1.1.1 Wild-type VZV

Varicella zoster virus (VZV) is a highly contagious neurotropic human alphaherpesvirus carrying a double-stranded deoxyribonucleic acid (DNA) [1, 2]. It was first detected in 1952. VZV causes two distinct diseases: primary infection with VZV induces varicella (chickenpox) and at a later time reactivation of the virus results in herpes-zoster (shingles), which in approximately one third of the cases develop to a persistent pain – postherpetic neuralgia [1]. So far, VZV is known to naturally infect only humans; after infection it becomes latent in sensory (dorsal root and trigeminal ganglia), enteric, and other autonomic neurons [2, 3].

VZV is highly contagious, it spreads with air droplets and direct contact with skin vesicles – where the concentration of the virus is highest [1]. The incubation period lasts from ten to 21 days, and the infectiousness is highest one to two days before the rash appears until vesicles crust (usually 5 days) [4].

1.2 VZV genome

VZV genome has been considered to be highly stable with little antigenic variability or virulence differences expected among wild-type isolates [5, 6]. There is only one serotype of VZV, but there are five clades identified in different geographic areas in the world: clades 1, 3 and 5 are of European origin; clade 2 includes Asian strains, such as the parental Oka strain, from which varicella and zoster vaccines were derived; and clade 4 contains African strains [1]. Moreover, VZV genome was found to remain highly stable during latency [3].

1.3 Symptoms and complications of varicella

Varicella is an acute disease characterized by itching rash and fever affecting mainly children, often diagnosed by characteristic symptoms [4], especially in countries without universal varicella vaccination. It is usually benign and self-limiting, but in 2%–6% of the cases, it causes serious complications (bacterial skin super-infection, pneumonia, encephalitis), resulting in occasional deaths [7]. VZV infection can also result in complications including myelitis, cranial nerve palsies, meningitis, stroke (vasculopathy), retinitis, and gastroenterological infections, such as ulcers, pancreatitis and hepatitis [1]. Furthermore, asymptomatic VZV reactivation is thought to occur more frequently [1, 3], and has been associated with other diseases, such as giant cell arteritis and enteric zoster [8]. Adults, immunocompromised individuals, and infants have more severe forms of varicella and higher risk of death than children [1]. Left untreated, varicella can cause severe conditions in pregnant women and infant, such as VZV pneumonia and congenital varicella syndrome [9, 10], which lead to a higher mortality from varicella in this group [11, 12]. Infected individuals acquire a long-lasting immunity after recovery [1].

1.4 Symptoms and complications of herpes zoster

Herpes zoster is a painful disease characterised by a blistering skin rash caused by reactivation of latent VZV, first described by E. Hope-Simpson in 1965 [13]. It is usually a self-limiting disease, however some individuals may develop severe complications, such as postherpetic neuralgia (PHN) in 10%–50% of patients [14], or zoster ophthalmicus in 5%–

14% of the patients [15, 16]. Neurological complications have been associated with reactivation of VZV and HZ, including encephalitis, meningitis, myelitis [17], and increased risk of stroke [18].

The lifetime risk of HZ is 23%–30% [19]. It increases at ages ≥50 years and peaks at ≥80 years following the decrease of VZV-specific cell-mediated immunity [20-22]. Higher HZ risk is also reported in persons with immunosuppression due to cancer, the human immunodeficiency viruses (HIV) infection, or organ transplantation [23]. HZ affects the quality of life, and results in multiple healthcare visits, hospitalizations, and deaths [24].

1.5 VZV in pregnant women

Occurrence of varicella is rare among pregnant women with estimated 0.5–3 cases per 1,000 pregnancies [11, 25]. However, even a small risk of infection in this sensitive and vulnerable group may have serious consequences for both a mother and a child. Varicella during pregnancy may cause spontaneous abortion, premature birth and still birth [11, 26]. VZV-associated pneumonia is the most frequent complication occurring in 10%–20% of pregnant women infected with varicella [10, 27]. Congenital varicella syndrome, first described by Laforet et al. in 1947 [9, 28], occurs at 0.8 per 100,000 live births with 30% mortality rate, and the risk of neonatal varicella is estimated at 5.8 per 100,000 live births [27, 29].

Susceptibility to varicella is higher in pregnant women originating from tropical and subtropical climates. For example, in Egypt 11.2% of pregnant women were VZV-seronegative (range: 6%–17%), with the highest seronegativity in younger age groups [30]. Also, approximately 10% of South Asian women born in Asia and residing in Europe were found to be seronegative to varicella [31, 32]. In Europe, less than 5% of pregnant women were susceptible to varicella, however in Spain and Italy this proportion was 12% and 10.6%, respectively [33, 34].

Varicella can be prevented by vaccination of susceptible women before conception or VZV screening during pregnancy and postpartum vaccination for those without evidence of immunity. However, universal antenatal screening for VZV is usually not recommended, likewise in Norway – except when there is no evidence of previous varicella disease or varicella vaccination [35-39]. This is due to high seroprevalence and relatively low susceptibility to varicella among pregnant women. For susceptible pregnant women exposed to varicella treatment with varicella zoster immunoglobulin (VZIG) is recommended.

1.6 Laboratory methods for VZV detection

Laboratory testing is used for diagnosis of suspected cases, and severe cases, to determine susceptibility to varicella, or if suspected vaccine-related adverse events were caused by vaccine-strain VZV [40].

The most common commercial laboratory method for varicella diagnosis, also used in Norway, is enzyme-linked immunoassay (ELISA). This method has a high sensitivity and specificity (ranging from 99% to 100%) for detections of VZV antibodies (immunoglobulins G, M and A (IgG, IgM and IgA)) against wild-type VZV. However, ELISA is less sensitive for detection of vaccine VZV IgG [40]. Other tests include: direct fluorescent antibody detection for detection of VZV antigen, whereas the polymerase chain reaction (PCR) is used

for VZV DNA detection [40, 41]. The latter method is used for differentiation between wild and vaccine VZV.

1.7 Epidemiology of VZV

Varicella occurs worldwide with epidemics reccurring every 2–3 years and has a strong seasonal pattern, manifesting mainly in winter and spring time [1]. In temperate climates over 90% of individuals acquire the infection by the age of 15 years [42, 43], whereas in tropical countries, this proportion is lower in children and higher among adults – due to climate factors influencing the virus spread [44].

1.7.1 VZV seroprevalence

The seroprevalence of VZV differs across the world with a lower seroprevalence in adults found in tropical and subtropical climates and higher rates found in temperate climates, e.g. from 58% in Puerto Rico to 86%–99% in Mexico [43, 45, 46]. In Europe, the majority of children acquire VZV infection before adulthood in age groups <5 and 5–9 years with a variability seen in different countries [43]. In 16 European countries, except Greece, over 80% of 10-year olds were VZV-IgG seropositive, and 90% developed immunity by the age of 15 years, except Greece (86.6%) and Italy (85.3%) [43]. These differences in age distribution of VZV infection reflect the social and educational structure differences between the countries [47]. Annually VZV affects a part of the population in Europe, which equals to the entire European birth cohort [7], thus varicella is estimated to cause considerable economical expenses due to health care visits and work absenteeism [48, 49].

1.7.2 Burden of varicella

The burden and epidemiology of varicella differ between countries due to various reporting and surveillance systems and health care seeking patterns [33]. According to WHO, each year varicella causes an estimated 4.2 million severe complications leading to hospitalization, and 4,200 deaths globally [50]. Varicella incidence in Latin American and Caribbean countries varied from 147 cases per 100,000 population in Venezuela, to 393 cases per 100,000 in Argentina [46]. In the US, varicella hospitalization rates in pre-vaccine era were 5 cases per 100,000 population [51]. Highest hospitalization rates were reported in children 1–4 years of age from 38.6 per 100,000 population in Australia to 172 per 100,000 in Canada [51].

In Europe, an estimated 5.5 million (95% CI: 4.7–6.4) cases of varicella are occurring annually in the absence of universal varicella vaccination [52]. Although, there is a variation of the burden of varicella between the countries the overall majority of the cases (3 million; 95% CI: 2.7–3.3) occur in children <5 years of age [52]. Pre-vaccine rates of primary health care consultations for varicella in Europe were reported between 281 and 777 cases per 100,000 person-years [53-58]. Varicella hospitalization rates across all ages varied from 1.3 to 11 cases per 100,000 population [54-57, 59-64]. Higher hospitalization rates—14–130 cases per 100,000—were reported among children, especially in infants below age 1 year [62].

A reported varicella-associated mortality in Brazil ranged from 0.88 cases per 100,000 population aged <1 year to 0.02 cases per 100,000 population aged 15–19 years; case fatality rate in hospitalized patients was 2% [46]. During the pre-vaccine era in the US, varicella mortality rates ranged from 0.2 cases per 1 million population in 1986 to 0.45 per million population (in 1994) [65]. In England, in-hospital mortality rate was 0.036 cases per 100,000 person-years and the majority of deaths occurred in adults aged ≥60 years [63].

1.7.3 Burden of herpes zoster

The estimated burden of HZ in healthcare was similar in industrialized countries. General Practitioner (GP) consultation rates in the US were 3 cases per 1,000 person-years with a peak of 10–11 cases per 1,000 person-years among adults aged ≥80 years [23]. In Western Europe, both GP consultation and hospitalisation rates were reported from one to two cases per 1,000 person-years in children <10 years of age, to seven and eight cases in adults ≥50 years of age. The incidences peaked at 10–11 cases per 1,000 person-years among 80-year-olds with 8.8 per 100,000 in the UK [19, 63, 66]. Hospitalisation rates ranged from two to 25 per 100,000 person-years in North America and Asia, with even higher rates reported in the elderly [15]. Higher incidence rates are reported in women [19, 23, 63]. In Sweden and Denmark, the HZ hospitalization rates were 13 per 100,000 population with a predominance in women [67, 68].

Overall, an estimated HZ-associated mortality in Europe ranged from 0 to 0.07 per 100,000, and the case fatality rate was 2 and 61 per100 000 in those 45–65 and ≥65 years, respectively. A similar increase with age was seen for the hospital fatality rate; 0.6% in those 45–65 years in the UK and 7.1% in those ≥80 in Spain. [69]. In Sweden, the HZ mortality rate in patients ≥50 years of age varied between 0.67 per 100,000 in women and 0.26 per 100,000 in men [68]. Denmark reported an overall standardized mortality rate of 1.8 per 100,000 population [67].

1.8 Prevention and control

A non-specific treatment and treatment with antivirals as well as use of immunoglobulin and prevention with effective vaccines are available against both, varicella and herpes zoster. Vaccination is considered the best preventive measure against both diseases and their complications, and is described in detail in the following subchapters.

For non-specific treatment, varicella patients are usually advised to use lotions to reduce itching and prevent skin infection. If needed, fever reducing medications, such as paracetamol can be used. However, children with varicella should not receive aspirin and/or ibuprofen, for their association with Reye's syndrome and with life-threatening skin infections, respectively [70-72].

Antiviral treatment with nucleoside analogues, such as acyclovir, valacyclovir, famciclovir and biruvidin is normally not indicated for immunocompetent varicella or herpes zoster patients [73], but for individuals with immunosuppression or those at increased risk of complications [74]. Antivirals have shown an effectiveness in reducing pain, decreasing viral shedding and preventing complications; antiviral treatment should be provided as soon as possible following the occurrence [73].

Treatment with VZIG is used after varicella exposure for susceptible pregnant women, and new-borns whose mothers develop varicella close to delivery and within one week after delivery, as well as immunocompromised individuals [74]. VZIG is an expensive treatment reaching USD 1,317 per package in Norway (NIPH, 2019) [75]. During 2008–2012, the Norwegian Institute of Public Health distributed 1,843 doses of VZIG (Varicellon), including those fully reimbursed, mainly for children <15 years of age (unpublished data). VZIG in Norway can be obtained from three producers with an exemption for approval: Varicellon P® (CSL Behring, King of Prussia, Pennsylvania, USA), Varitec CP® (Biotest Pharma GmbH, Dreieich, HE, Germany) and Varizig® (Emergent Biosolutions, Rockville, Maryland, USA).

1.8.1 Varicella vaccines

The first varicella vaccine was produced in Japan in 1970's [76]. Since then, several vaccines containing live-attenuated Oka strain varicella virus (except the vaccine developed in South Korea) were licensed worldwide [77]. In Europe, two single-antigen vaccines are available: Varilrix® (GlaxoSmithKline Biologicals, Rixensart, Belgium) and Varivax® (Merck Sharp & Dohme), and a combination vaccine with measles, mumps, and rubella (MMRV) ProQuad® (Merck Sharp & Dohme Vaccins, Lyon, France) [78]. Priorix-Tetra® (GlaxoSmithKline Biologicals, Rixensart, Belgium) is another MMRV vaccine available on the market, but not licensed in Europe [79]. The two MMRV vaccines use the same varicella strain, albeit the vaccine formulations differ slightly in terms of attenuated virus titers [80].

The World Health Organisation (WHO) has recommended the use of varicella vaccine since 1998 [50, 81]. Since then vaccination with either one or two doses was implemented in about 30 countries worldwide, including several European countries (Finland, Germany, Greece, Italy, Latvia, Liechtenstein, Luxembourg, and Spain) [7, 46, 51, 82].

A number of countries, including Norway, recommend varicella vaccination only for specific risk groups, such as healthy, seronegative close contacts >12 months of age, who are at risk for severe course of varicella; seronegative children with acute lymphocytic leukaemia in stable remission or chronic diseases (juvenile arthritis, kidney disease); seronegative persons who shall undergo organ transplantation; adolescents and adults who have not had chickenpox. Vaccine is contraindicated for persons with immune deficiency, and receiving immunosuppressive treatment (14). Barriers for varicella vaccine introduction include low disease awareness, lack of disease burden and cost-effectiveness estimates, perception of varicella as a benign disease among parents and health care providers, and concerns associated with increase in herpes zoster after universal varicella vaccination [83].

The estimated vaccine effectiveness of both monovalent varicella vaccines Varilrix® and Varivax® is 70% –90% with one dose and up to 98% with two dose schemes [84, 85]. These vaccines are indicated for healthy individuals from the age of 9 months up to 12 years. Two doses are recommended to be administered subcutaneously at interval of minimum 3 months for children 9–12 months; for children from 12 months to 12 years also adolescents and adults the second dose should be given after an interval of at least 6 weeks, but in no circumstances less than 4 weeks. In Norway, the private market price of varicella vaccines ranges between NOK 330 (Varilrix®) and NOK 475.90 (Varivax®) per dose [86].

A combined MMRV vaccine is indicated for simultaneous vaccination against measles, mumps, rubella, and varicella in individuals from 12 months of age. It is recommended to administer two doses of MMRV, or first dose of MMRV followed by a second dose of monovalent varicella vaccine to ensure optimal protection against varicella [78, 79]. The second dose should be administered not earlier than four weeks after the first dose and preferably within three months following the first dose. MMRV can be administered to individuals between 9 to 12 months of age under special circumstances (e.g., to conform with national vaccination schedules, outbreak situations, or travel to a region with a high prevalence of measles) with a second dose given after minimum three months following the first dose to ensure protection against measles and varicella [78]. ProQuad® may be used as the second dose in individuals who have previously received MMR and varicella vaccine

[78]. The vaccine is contraindicated to individuals with hypersensitivity to any of vaccines with MMRV components, individuals with different malignant neoplasms affecting the haematopoietic and lymphatic system, those with receiving immunosuppressive therapy, with severe humoral or cellular (primary or acquired) immunodeficiency, active untreated tuberculosis. MMRV is contraindicated for pregnant women. Furthermore, pregnancy should be avoided for one month following vaccination [78]. To reduce the risk of transmission of vaccine type VZV, vaccine recipients should attempt to avoid close contacts with high-risk individuals susceptible to varicella (immunocompromised individuals, pregnant women susceptible to varicella, and new-born infants of mothers susceptible to varicella [78].

MMRV efficacy and safety was tested with different schedules and formulations, and its immunogenicity was comparable with MMR given alone or co-administered with monovalent varicella vaccine [80, 87]. The combined MMRV vaccine has approximately 14 times higher titer of VZV than the monovalent VZV vaccine [88]. MMRV has an acceptable safety profile. There is an increase in febrile seizures following the first dose of MMRV (one in 3,000–4,000 doses of MMR administered) as compared to administration of monovalent varicella vaccine concomitantly with MMR, but the absolute risk is low [89]. This risk increased more than 2-fold if vaccinated with first dose at 16- to 23-months of age, rather than at 12 to 15 months [80, 90]. The use of combination vaccines has the following advantages: simplified vaccine delivery, increased vaccination compliance, decreased cumulative exposure to vaccine additives, and reduced healthcare costs [80]. However, MMRV showed 2%–6% lower protection against mumps, and 20% lower protection against rubella, but higher protection levels against measles [80]. Nevertheless, stronger protection against all four viruses, especially against varicella, was documented after the second dose, administered 4–6 months later [80]. Similar results were obtained in five additional studies when children 15-months to 6-years of age were administered the MMRV vaccine after an initial dose of MMR or MMR plus VZV vaccine [80]. MMR and MMRV vaccines are well tolerated and rarely associated with serious adverse events. The overall rate of adverse events that occurred within a 5-day period at the site of MMR vaccine injection was higher among subjects administered the vaccine subcutaneously (21.5%) compared to those injected intramuscular (15.8%). Redness and swelling at the injection site occurred at a slightly higher rate among subjects who received the vaccine subcutaneously rather than intramuscular [80]. The first dose of varicella-containing vaccine (either monovalent or MMRV) can be administered concomitantly with other paediatric vaccines DTP-IPV-Hib-HepB and a conjugate pneumococcal vaccine [80, 91, 92].

Breakthrough varicella, caused by a wild-type VZV, may occur within 42 days (two incubation periods of varicella) following vaccination with at least one dose of any varicella vaccine, and without other apparent cause [93]. It usually has a milder and shorter course of disease. However, even occurring less frequent than in unvaccinated populations, severe cases of breakthrough varicella were reported presenting with extensive rash, pneumonia, sepsis, neurological, hematologic, ocular, renal, and hepatic complications, and even death [93].

1.8.2 Herpes zoster vaccines

Currently two vaccines are available against HZ: a live-attenuated vaccine Zostavax® (Merck Sharp & Dohme Corporation, USA) [94] and a subunit recombinant zoster vaccine Shingrix®, containing VZV glycoprotein E (GlaxoSmithkline Biologicals SA, Rixensart, Belgium) [95]. The efficacy of both vaccines differs despite relatively short follow-up period.

Zostavax® has been available in Europe, including Norway since 2006 [94]. It has been evaluated in two large controlled clinical trials involving more than 60,000 people [96-98]. The reported vaccine efficacy for the incidence of HZ was 48.7% in people ≥60 years, and 64.9% for the incidence of PHN; waning vaccine protection with age has been reported [99, 100]. A single dose of this vaccine is recommended to adults from 50 years of age and contraindicated for persons with immunosuppression. Zostavax has an established safety profile and vaccine effectiveness of the first dose and a booster dose has been demonstrated in several real world settings [101]. The HZ vaccination has been introduced in to the national immunization programmes in the UK (September 2013) and Australia (November 2016) [102, 103]. In both countries, the vaccine is administered to adults 70 years, followed by a catch-up program for people 71 to79 years of age. In Norway, HZ vaccination is indicated for adults ≥50 years at the cost of approximately USD 124 to163 [86].

Shingrix® was licensed in Europe in 2018 [95]. It has demonstrated efficacy of 97% against HZ and 89% against PHN across all age groups ≥50 years for at least 4 years after vaccination, and 91% and 89%, respectively, in adults aged ≥70 years [95, 104, 105]. Adverse events after recombinant zoster vaccine seemed to be mostly temporary and were manageable with standard care [95, 104]. Eight months after licensure of the recombinant zoster vaccine in the US, 3.2 mln doses were distributed and 4,381 adverse events were reported, of which 130 (3%) were classified as serious adverse events, such as pyrexia and chills, suggesting similar pre-licensure vaccine safety profile [106]. However, recently increased numbers of cases with Guillain-Barré syndrome were detected by the US Vaccine Adverse Event Reporting System (VAERS) [107]. The vaccination course consists of 2 injections given 2 to 6 months apart and can be used for persons with immunosuppression [108]. Since 2017, the Advisory Committee on Immunization Practices (ACIP) recommends Shingrix for healthy adults ≥50 years[109]. The vaccine can be given also following the immunization with Zostavax® and to pregnant breastfeeding women [109]. Shingrix is not yet available in Norway [86]. The duration of the vaccine induced immunity is not fully established for both vaccines.

1.8.3 Vaccine-type VZV associated disease

Post-marketing experience with live varicella vaccine (Oka/Merck) suggests that transmission of vaccine strain varicella virus may rarely occur in healthy vaccine recipients (who develop or do not develop a varicella-like rash) and contacts susceptible to varicella, as well as high-risk individuals susceptible to varicella [78]. Severe rash, pneumonia, hepatitis, and herpes zoster meningitis have been reported in the US; so far, two fatal cases of immunocompromised children in the US and Germany in two recent decades [110, 111]. A case of HZ caused by vaccine-strain has been recently documented [112].

1.9 Norway – country profile and healthcare system

Norway is a country in Northern Europe with a population of 5.3 million and annual birth cohort of approximately 58,000 infants (2018) [113]. Life expectancy in Norway was 84 years for women and 80 years for men in 2017; cardiovascular diseases and cancer accounted for more than a half of deaths [114].

The Norwegian healthcare system is publicly financed and all residents have universal access to healthcare. Health expenditure represented 9.9% of gross domestic product in 2015 [115]. Norway ranks among the highest in the Organisation for Economic Co-operation and

Development (OECD) in terms of absolute expenditure per capita (NOK 60,000, or USD 6,122 in 2015). Public financing accounts for 85% of this spending [115].

Healthcare in Norway is based on a cost-sharing principle where a patient covers ca 30% for a visit; hospital admissions and inpatient treatment also healthcare for children (<18 years) are free [115]. Normally, during working hours, an individual seeking healthcare, e.g. with varicella or herpes zoster, contacts GP, which, if necessary, refers the patient to a specialist or hospital. Outside working hours such individual is referred to emergency primary consultation or so called walk-in centres where nurses triage patients and answer calls, with several doctors seeing patients all through the day and night [115]. Cases with varicella, mostly children, would predominantly be managed in primary healthcare and few, mostly severe cases, would be hospitalized. Varicella cases are less prone to be hospitalized, as the disease is highly infective and requires isolation facilities. Benign varicella cases would not consult a GP, because in Norway parents are entitled to a paid sick leave of up to 10 days per calendar year in case of a child's illness without presenting a confirmation from a health care provider. Similarly, some patients with mild HZ would not seek medical help because they feel well enough to work or use their right to a short-term sick leave without providing a certificate from a healthcare practitioner.

Norway has a comprehensive national immunization programme with routine vaccine coverage above 90% [116]. Varicella and HZ vaccines are not included in the national immunization program. Vaccination recommendations are available for risk groups only [74]. Varicella and HZ are not notifiable, and little is known about the burden and epidemiology of these diseases. Only viral infections, including VZV, of the central nervous system (CNS) are notified to the National Surveillance System for Communicable Diseases (MSIS). MSIS reported 2,237 VZV infection of CNS during 1997–2012, and VZV was the third most frequent virus, mainly detected in adults [117]. Mortality from childhood diseases in Norway is rare [114], however several paediatric deaths from varicella have been reported in the past decades [117]. Thus, varicella vaccination may reduce the associated disease and economic burden.

2 Study aim and objectives

The aim of this PhD project was to estimate the burden of disease associated with varicella-zoster virus (VZV) infections in Norway. The rationale of the study is to assess the need for introduction of varicella and herpes zoster vaccination into the national immunization programs. We defined several objectives for this study:

a) to assess seroepidemiology of VZV in the Norwegian population and pregnant women;
b) to estimate healthcare-associated burden of varicella and HZ diseases in the form of primary healthcare visits, hospitalizations, and vaccinations;
c) to estimate varicella and HZ-associated mortality.

3 Materials and Methods

In this part we shortly describe materials and methods used for this PhD project. Detailed description of the methods of each study is available in papers I–IV. For the seroprevalence studies (paper I and IV) we used residual sera, and for number of cases of varicella and HZ related primary healthcare visits and hospitalizations we used data from several health registries (paper II and III).

3.1 Seroprevalence in general population

3.1.1 Study population

To estimate VZV serorevalence in general population in Norway we used residual sera samples collected within another study – a method widely used in other countries [42, 118].

We conducted a cross-sectional seroprevalence study, using anonymized residual sera collected from patients of all ages who sought either primary or hospital care in Norway in 2006–2008, 2011, and 2014. Sera specimens were collected from all 19 counties throughout Norway. Overall, 2,103 samples from patients aged 0–92 years were included in the study [118].

3.1.2 Laboratory analyses

IgG antibody levels were measured using a commercial indirect enzyme-linked immunosorbent assay (ELISA); Enzygnost anti-VZV-IgG Virus/IgG, Siemens Healthcare Diagnostics AS, Erlangen, Germany) with the automated EVOLIS™ System from Bio-Rad and the DS2 Processing System from DYNEX. According to the manufacturer, the sensitivity of this method is 99.3% and the specificity is 100%. The assay was run in accordance with the manufacturer's instructions. The positive and negative controls from the kit were used to validate the assay and results. We had no kit independent controls available. The cut-off for qualitative evaluation of positivity was a corrected optical density (OD) >0.2 at 450 nm. Samples with ODs <0.1 were counted as negative, and samples with ODs between 0.1 and 0.2 were considered equivocal. Equivocal samples were not re-tested. The sera were stored at −20 °C at the Norwegian Institute of Public Health where the testing was performed [118].

3.1.3 Statistical analyses

VZV seropositivity was estimated as a proportion with the corresponding 95% CI. We used the chi-square test to examine differences in seropositivity by age, sex and geographical regions. We also performed multivariable logistic regression analysis to assess the association between VZV seroprevalence, which was classified as positive or negative, and a set of explanatory variables (sex, age, geographic region). We assessed the fit of the different models using likelihood ratio tests. Statistical significance was set at a P-value <0.05.

3.2 Seroprevalence in pregnant women

We determined the susceptibility to VZV and the reliability of self-reported history of VZV infection in the Norwegian obstetric population.

3.2.1 Study population

For the cross-sectional VZV seroprevalence study of pregnant women in Norway we used samples from a separate case-control study nested within the Norwegian Mother and Child

Cohort study (MoBa) [119, 120]. The MoBa study is an ongoing population-based pregnancy cohort study conducted by the Norwegian Institute of Public Health, which now includes 114,500 children, 95,200 mothers and 75,200 fathers from all over Norway, recruited between 1999–2008 [121, 122]. The 1,350 women were randomly selected to form a control group of the study where their plasma samples were tested for cytomegalovirus, and parvovirus B19 [119]. Of these, 1,184 women had sufficient sample volume to allow examination of IgG antibodies for VZV, and thus were included in our study.

3.2.2 Laboratory analyses

The samples were analysed using a commercial enzyme immunoassay for specific IgG antibodies to Varicella-Zoster virus (VZV) Enzygnost®, Anti-VZV/IgG (Siemens, Healthcare Diagnostics AS, Erlangen, Germany), following manufacturer's instructions. IgG cut-off levels were set in accordance with manufacturer's recommendation. Equivocal sample were retested in duplicate. If a sample collected at pregnancy week 17–19 was negative, the second maternal sample taken at delivery was examined for the presence of IgG. Detection of IgG in the sample taken at delivery indicated seroconversion, suggesting that VZV infection was acquired during pregnancy. Plasma samples were stored at -20°C until testing was performed at the Norwegian Institute of Public Health.

3.2.3 Statistical analyses

We used descriptive analysis and logistic regression analyses to compare the proportions of seropositive and seronegative, as well as seroconverted women. Exposure variables were mother's age, child's gestational age, year of child's birth and mother's country of birth. Categorical data were analysed using Pearson's chi-square test and Fisher's exact test. One-way analysis of variance (ANOVA) was used for continuous variables.

We used stratified analysis to explore associations between mean values of optical density (of VZV IgG antibodies), number of children in the household and day care attendance. Additionally, we estimated Spearman's rank correlation coefficient (r_S).

3.3 Burden of varicella and herpes zoster diseases

3.3.1 Registry-based data

We conducted a national registry-based study on the use of healthcare resources and mortality in patients with varicella and HZ. The entire population of Norway (5.3 million in 2018) was included [123]. Data from registries are often used for research of burden of disease [63, 64, 67, 68, 124, 125].

We used individual patient data from the following national registries: the Norwegian Immunization Registry (HZ and varicella vaccinations), the Norwegian Health Economics Administration (varicella-coded and HZ-coded primary healthcare consultations), the Norwegian Patient Registry (NPR, varicella and HZ-coded hospital contacts), and the Cause of Death Registry (CDR, varicella and HZ-coded deaths). Data were extracted for the period of 2008–2014 except for data from the CDR, which covered the period of 1996–2012. Data from each source were extracted based on specified criteria, details of which are provided in Table 1. Data on primary healthcare consultations and hospital contacts were linked to identify patients consulting both primary and hospital care. Furthermore, the individual immunization status of each patient was verified by linking the data to the immunization registry.

Table 1. Data sources and type of data extracted for varicella and herpes zoster (HZ).

Data type	Data source	Period of data extraction	Extraction criteria	Extracted variables
Vaccinations against herpes zoster	National Immunization Registry	2003–2012	All registered varicella and herpes zoster vaccinations	Patient ID, age, sex, type of vaccine, a date of vaccination for each received dose
Primary healthcare contacts	Norwegian Health Economics Administration	2008–2014	All registered contacts as coded by varicella code A72, and herpes zoster code S70 by the International Classification for Primary Care, Second edition (ICPC-2)	Patient ID, age, sex, information on care provider (General practitioner, emergency clinic), and type of diagnosis (primary, secondary)
Hospital contacts	Norwegian Patient Registry	2008–2014	All registered contacts as coded by varicella codes B01—B019, and herpes zoster codes B02—B029 by the International Classification of Diseases - tenth edition (ICD-10)	Patient ID, age, sex, date of admission and discharge, type of hospital care (inpatient, outpatient, and ambulatory care)*, outcome of hospital stay, respectively accompanying non-varicella, and non-herpes zoster diagnoses coded by the ICD-10 codes.
Deaths	Cause of Death Registry	1996–2012	All registered deaths with varicella codes B01–B019, and herpes zoster codes B02—B029 by the International Classification of Diseases - tenth edition (ICD-10)	Anonymous data with age, sex, date of death and respectively accompanying non-varicella and non-herpes zoster diagnoses.

Viral infections of CNS	Norwegian Surveillance System for Communicable Diseases	1997–2012	All reported viral infections of CNS, including those caused by varicella zoster virus.	Patient ID, age, sex, sample type (e.g. cerebrospinal fluid), date of sampling, laboratory method (polymerase chain reaction (PCR), culture), etiologic agent, the name of the laboratory where the sample was tested, and type of report (clinician and/or laboratory-based report).

*inpatient – is a patient who stayed at the hospital more than 5 hours; outpatient – a patient who stayed at the hospital less than 5 hours; ambulatory care – a care that requires more resources than in outpatient, but patient does not stay overnight in the hospital.

3.3.2 Statistical analysis

For both diseases, we applied similar methods with some differences, which are further described. We calculated the annual age- and sex-specific incidence rates per 100,000 population for varicella-related (paper II) and HZ-related (paper III) healthcare contacts in primary and hospital care. Incidence rates were calculated using the first record with a varicella and HZ-associated diagnosis for each patient registered during 2008–2014. Incidence rates were estimated separately for primary care (GP or emergency) and hospital care (inpatient, outpatient, ambulatory). For hospital care, registration of varicella or HZ as the primary or secondary diagnosis was recorded. The population data by age, sex, and year were obtained from the Statistics Norway [123]. For hospitalized patients the length of hospital stay in days was calculated.

Multivariate regression analysis was performed to assess an association between the length of hospital stay, stay at intensive care, age, sex and diagnostic group. We tested associations for interactions for the same factors and calculated regression coefficients for significant interactions. In addition, for HZ we compared age-specific differences by sex in different patient groups by performing a Kruskal-Wallis H test.

The hospital discharge diagnoses, for varicella and HZ patients, were categorized, respectively, into different groups based on their accompanying codes from the ICD-10. The diagnostic grouping was performed by two pediatricians for varicella study, and two infectious disease specialists for HZ study. Patients were subsequently assessed if they were presumably immunocompromised and/or had an underlying condition or comorbidity and were grouped accordingly. Severity of underlying conditions and comorbidities for varicella and HZ patients was categorized using the Charlson comorbidity index that categorized patients into the following groups: no comorbidity (score 0), moderate (score 1), severe (score

2), and very severe comorbidity (score ≥3). Nineteen diseases are weighted in this index according to the strength of their association with mortality [67].

To estimate varicella-related and HZ-related mortality, we calculated crude and age- and sex-adjusted mortality rates per 100,000 by using the World Health Organization's population data for Scandinavian countries [126]. We used Poisson regression analysis to assess secular trends in the number of varicella/HZ patients in primary healthcare, hospitals, and varicella/HZ-associated deaths.

4 Ethical aspects

All studies in this project have been approved by the Regional Committee for Medical and Health Research Ethics, Oslo, Norway. For the registry-based studies an exemption from patient's consent to use data from the registries has been permitted.

For the seroprevalence study in pregnant women, the permission to use sera samples for VZV testing and VZV related parts of questionnaires has been obtained from MoBa steering committee, following the ethical approval from the Regional Committee for Medical and Health Research Ethics, Oslo, Norway. In addition, the study underwent an internal review at the Department of Research, Administrative Support and Legal Services at MoBa has previously been approved by the Norwegian Data Inspectorate and recommended by the Regional Ethical Committee. The participants of the MoBa study are informed that they can withdraw at any time.

5 Synopsis of study results

5.1 Seroprevalence in general population

In paper I we describe VZV seroepidemiology in general population. Of the 2,103 samples tested, 73.2% (95% CI: 71.3–75.1) were VZV positive. The samples were collected from patients aged 0 to 92 years, and 51.9% were from males. The seropositivity increased with age. However, in children under one year of age it was 58.9% and decreased to 11.2% at the age of one year, likely reflecting a short-lived immunity conferred by maternal antibodies [127, 128]. By school entry age, which is 6 or 7 years old, 69.8% and 71.4% of children, respectively, were immune to varicella. By age 20 years, 86.4% of the Norwegian population had acquired natural varicella immunity, and by age 35–39 years, 95.7% of subjects had detectable anti-VZV antibodies.

An estimated overall seropositivity in females of reproductive age was 88.6 %. The defined reproductive age for women in Norway is 15 to 49 years [129]. The average proportion of seronegative females in this age group was 5.3%. The proportion of non-immune women was highest (13%) in those 20–24 years, and declined in the older age groups.

Of the seven geographic regions defined by the population density [130], the VZV seroprevalence was lower (59%) in sparsely populated central Norway and highest (86%) in densely populated Southeast Norway.

5.2 Seroprevalence in pregnant women

In paper IV we describe the results of the seroprevalence study in Norwegian obstetric population. Of the 1,184 tested women, 98.58% were VZV-IgG positive, 14 VZV-IgG

negative and three VZ-IgG equivocal in the first sample taken at pregnancy week 17–19. After second testing of blood samples taken at delivery, 0.83% (n = 10) were still seronegative, while 0.34% (n = 4) seroconverted during pregnancy, and three (0.25%) women had an equivocal test results. Overall, 14 (1.2%) women were considered susceptible to varicella. The mean age of the women was 30 years (standard deviation (SD): 4.381, age range: 18–45 years) and 91% of babies were born between gestational weeks 38–42. The majority of women (92%) were born in Norway. Among women born abroad only one seroconverted and another one tested seronegative in both samples.

A history of varicella before pregnancy was reported only by one woman, and none had varicella or herpes zoster diagnosed during pregnancy. Household exposure to different childhood diseases during pregnancy was reported by 12% (n = 143) of the women. Of these, 25 women indicated exposure to varicella in the beginning of their pregnancy (before week 17–19), 23 of which were living together with children aged <6 years at the time. All were VZV-seropositive.

No reports were identified for congenital varicella syndrome (CVS). However, unspecified birth defects were reported by 44 women, all of which were VZV-seropositive and none were vaccinated.

VZV-seroconverted women and VZV-seropositive women did not differ by country of birth, age, child's gestational age, and year of child's birth. In addition, there was no difference between VZV-seropositive and VZV-seronegative women for these characteristics.

5.3 Burden of varicella

During 2008–2014, the average annual incidence of varicella-related primary healthcare contacts was 221 patients (range: 164–274) per 100,000 population, and varicella-related hospitalizations was 7.3 (range: 5.7–8.8) patients per 100,000. This translates to an average annual number of 14,299 primary healthcare contacts made by 10,881 patients and 433 hospital contacts made by 361 patients. The highest incidences in primary healthcare and hospitalizations were in one-year old children: 2,654 patients per 100,000 and 78.1 patients per 100,000, respectively. A lower threshold for hospitalization at a younger age and not necessarily disease severity may explain such increase in healthcare contacts in small children. The incidences of both, primary care and hospitalizations, decreased around the age 10 years and remained stable in older age groups with an exception of a slight increase observed among 25–34 year-old persons.

The annual number of varicella primary healthcare contacts was stable over the 7-year study period, but a significant increase was observed annually in November, February and June. Similar seasonal distribution was in varicella-associated hospital contacts.

In primary care, <5 year-old children accounted for 55.2%, and 20–39 year-old adults represented 9.6%. Whereas among hospitalised patients, 67% were <10 year-old children and 14% were 20–39 year-old adults. Among patients with varicella, 96.8% contacted primary health care only, 1.9% contacted hospital only and 1.3% patients were in contact with both primary care and hospital sectors. The latter category had also a higher number of contacts per patient (on average three contacts per patient versus one contact in other groups). The annual number of varicella healthcare contacts was stable over 7-year study period, but a significant increase was observed annually in November, February and June.

Varicella as primary diagnosis was reported in the majority of the cases in primary care (96%) and hospitals (75%). As a secondary diagnosis varicella was more frequent among inpatient patients.

The median length of hospital stay among inpatient cases was 3 days (interquartile range (IQR): 1–6). The length significantly increased by one day for each 10 years of age (95% CI: 0.8–1.2); patients with varicella-related complications stayed in hospital 2.2 days longer, and immunocompromised patients stayed a week longer.

Among hospitalized patients 9% had moderate-to-severe comorbidities according to the Charlson comorbidity index. The severity of comorbidities and the length of hospital stay increased with older age. Among all patients with complications and comorbidities, between 30% and 80% were children 0–19 years of age, except for patients with HIV and acquired immunodeficiency syndrome (AIDS). The most frequent complications were neurologic complications followed by conditions affecting a lower respiratory tract and skin. HIV and AIDS were reported in 0.4% of varicella patients, malignancies in 2.6%, autoimmune diseases in 4.4%, and 1.3% of the patients had undergone organ transplantations.

During 2008–2014, 25 pregnant women were hospitalized with varicella (13 had varicella as primary and 12 as secondary diagnosis), and 10 cases of congenital varicella syndrome (CVS; 0–3 cases annually) were identified. Among these, CVS was listed as primary diagnosis in 7 patients.

During 1997–2012, the VZV was the third most frequent virus (16.3%) detected among 2,237 patients with reported viral infections of CNS. VZV was preceded by enteroviruses (52.9%) and other Herpes viruses (Epstein Barr-virus and Herpes simplex viruses; 22.9%). Among patients with detected VZV in CNS, median age was 44 years (IQR: 25–72).

During 1996–2012, 46 deaths were registered with varicella-related ICD-10 codes listed either as the underlying (n = 26) or contributing cause of death, corresponding to a crude mortality rate of 0.06 deaths per 100,000. The median age of deceased cases was 75.5 years (IQR: 38–83). Children <18 years of age accounted for 11% (n = 5) of varicella deaths; of these two new-borns had CVS that was listed as underlying cause of death. Among children who died of varicella, an underlying condition was reported only in one patient, suggesting that other deaths may have occurred in previously healthy individuals. Neurologic complications (varicella meningitis and encephalitis) accounted for 43.5% of all registered deaths and were predominant across all age groups. Varicella pneumonia was reported in 17% of deaths, all in adults.

Among hospital varicella cases, eight in-hospital deaths were reported during the seven-year study period corresponding to a case-fatality rate (CFR) of 0.3%. All deaths occurred in persons above 50 years of age, except for a single pediatric death. Additional five deaths (including 1 pediatric death) were identified within 30 days postdischarge that resulted in an overall CFR of 0.5% (n = 13). Of the 13 cases, varicella was listed as the primary diagnosis in 8 cases, and underlying conditions were present in eight patients.

During 2003–2012, a total of 4,021 persons were registered to have received 4,877 doses of varicella vaccine (on average 490 doses per year). One half of the vaccinated were children below one year of age (50.3%), and 87.6% were children <10 years of age. Linkage of immunization data with primary health care and hospital data indicated that a very few

varicella patients were vaccinated: 0.2% (n = 126) of all primary health care patients and 0.5% (n = 12) of hospitalized patients.

5.4 Burden of herpes zoster

Paper III describes epidemiology of HZ in Norway. During 2008–2014, 82,064 patients had HZ-associated diagnoses registered in primary and hospital care in Norway corresponding to an overall average annual incidence rate of 238 patients per 100,000 population. Of these patients, 95% were treated in primary healthcare, of which 5.9% referred to hospitals, and additional 4.6% of patients had no record in primary healthcare before being hospitalized. Average annual incidences were 227 patients per 100,000 in primary healthcare and 25 patients per 100,000 in hospitals. The hospitalization rate was 10.2 cases per 100,000 for inpatient cases and 13.7 cases per 100,000 for cases treated as outpatient.

The incidence increased in those 50 years of age: 230 per 100,000 in primary care and 20 per 100,000 in hospitalizations and peaked in patients >80 years to 775 per 100,000 and 151 per 100,000, respectively. The median age of the HZ patients was 61 years (IQR: 42–74) in primary healthcare, and 68 years (IQR: 52–80) in hospitalised patients. Women were significantly older in either primary healthcare (median age 62 years, IQR: 46–75 vs men: median age 59 years, IQR: 37–71) ($p<0.001$)) and in hospitals (median age 69 years, IQR: 53–81 vs men: median age 66 years, IQR: 48–77) ($p<0.001$)).

No records of vaccination against HZ were identified after linkage to the national immunization registry. We observed no seasonal pattern in the distribution of HZ-associated contacts in primary healthcare and hospitalizations.

A small proportion of HZ patients were children <10 years of age in primary healthcare (3%) and in hospitalizations (3%). Incidence rates of primary care ranged between 34 per100,000 in children aged 0–4 years to 109 per 100,000 in 10–14 year olds; hospitalization rates were 5.3 per 100,000 in 0–4 year olds, and 7.9 per 100,000 in 5–9 year olds.

During 2008–2014, of the 11,181 HZ-patients (26,224 visits) at primary healthcare registered annually, 59% were female. Similarly, more women (56%) were registered among 1,218 hospital patients (2,396 visits) per year with HZ-associated diagnosis.

HZ as primary diagnosis was reported in 93% of primary healthcare patients at their first contact and in 73% of hospitalizations.

Of all hospitalizations, the majority of patients (69%) were classified as outpatient, 27.2% as inpatient, and 3.9% as ambulatory care, and the rate of inpatient hospital contacts increased with age.

Complicated HZ as coded by ICD-10 codes B020–B023, B027, and B028 was reported in 47% of hospital patients. Uncomplicated HZ was assigned to 53.1% (ICD-10 codes: B029 and B02), including 23% of patients having uncomplicated HZ as the only diagnosis. Postherpetic neuralgia was reported in 9.3% of hospitalized HZ patients; of these, 59% were females who were marginally older (median age 70 years, IQR: 55–82) than men (median age 69 years, IQR: 55–79) ($p =0.047$). HZ in eye was the most frequent complication, reported in 26% of the HZ patients. A diagnosis of HZ encephalitis was made in 2.9% of the HZ patients and 0.7% had HZ meningitis.

Overall, 25% of the HZ patients had co-morbidities defined by the Charlson Comorbidity Index. Severe and very severe co-morbidities were reported in approximately 15% of all patients, and more than two-thirds were aged ≥60 years. In patients with immunodeficiency (8.7%), the majority had malignancies affecting the immune system (5.5%); HIV/AIDS was reported in 54 patients (0.6%). Ten women were pregnant at the time of their first HZ-associated hospital contact (0.1%) and four of them had HZ as the primary diagnosis.

Overall, 32,621 (3,758 patients) in-hospital days were associated with HZ. The overall median length of stay for HZ patients was 4 days (IQR: 2–9), whereas patients with zoster-related complications stayed one day longer. Several significant interactions (particularly between age and several diagnostic groups) were identified for patients with the following conditions: diabetes (15.2 days longer stay, 95% CI: 8.5–21.9), kidney disorders (11.1 days longer stay, 95% CI: 6.6–15.5) and stroke (15.7 days longer stay: 95% CI: 6.5–25.0).

During 1996–2012, overall 343 (annual range 8–27) deaths with HZ-associated ICD-codes listed as underlying (41%) or contributing cause of death (59%) were reported in Norway. All, except two deaths, occurred in persons aged ≥50 years. Considering all deaths with HZ-associated codes, a mortality rate as underlying cause of death was estimated at 0.18 deaths per 100,000 population per year (overall 0.43 per 100,000) with the highest mortality in adults aged ≥80 years, also in females.

The case-fatality-rate (CFR) among hospitalized zoster patients was 1.04% for in-hospital deaths (annual range 0.75% –1.45%) and 3.01% for combined in-hospital deaths and deaths occurring within 30 days post-discharge.

6 Discussion

Varicella-zoster virus is an important human pathogen with HZ being a major health issue in the aging and immunocompromised populations. However, varicella or chickenpox, poses a risk of serious complications and even death in previously healthy individuals, despite a general perception of the disease being benign. In addition, the neurotropic nature of the virus raises more questions on its effect on neurodegenerative or chronic diseases, which may occur between the episodes of varicella and herpes zoster such as giant cell arteritis, or multiple sclerosis [8, 131].

In this dissertation we examined VZV seroprevalence in overall and obstetric populations in Norway and estimated healthcare contact rates and deaths associated with varicella and HZ. Our results were comparable with findings from other countries without vaccination programs in place. We found low seroprevalence in a general population, but high varicella incidence in primary and hospital care, in particular in youngest children [132]. The incidence of varicella in primary and hospital care in Norway was low in adults compared to children, however more complications in hospitalized patients and deaths were reported in this group considerably increasing the burden of disease. For HZ, we found even higher rates of primary healthcare and hospitalizations, which demonstrate the substantial burden on the Norwegian healthcare system translating to significant economic impact [133].

6.1 Seroprevalence studies

6.1.1 Choice of epidemiological methods

For seroprevalence studies we applied a convenience sampling method. This method is the easiest, time-saving, and less expensive to implement, and is widely used for many studies across the world [134]. Furthermore, a proper choice of residual serological samples allows comparison of seroprevalence in different time periods [34]. However, it provides generalizability only to population studied and may have underrepresented sociodemographic subgroups providing insufficient power to detect differences between the groups [134], a limitation which we experienced in our seroprevalence studies. Varying quantity of specific antibodies in each sample may also lead to false results.

6.1.2 Choice of laboratory methods

The serological samples for our seroprevalence studies were tested by measuring IgG antibody levels using a commercial indirect enzyme-linked immunosorbent assay (ELISA). ELISA is one of the most popular and most accepted laboratory methods for varicella diagnostics used in Norway and other European countries [42]. Such popularity of this method allows comparison of the results between the countries. ELISA according to manufacturer has a very good sensitivity and specificity of 99.3% and 100%, respectively. Despite these good test characteristics, commercially available VZV IgG assays (ELISA) are not sensitive enough to detect seroconversion after vaccination [40]. Nevertheless, Norwegian population is mainly exposed to wild-type VZV, as very few varicella patients were vaccinated and few vaccine doses were distributed in Norway [117].

6.2 Burden of disease studies

6.2.1 Choice of the epidemiologic method and data source - registry data

This is the first registry-based study in Norway that employed a linkage of individual patient data across multiple national registries to quantify the health care burden of varicella and herpes zoster. As a very few patients in Norway were found to be vaccinated against varicella and HZ, our findings reflect epidemiology compatible with a circulation of a wild-type VZV.

We used information from the national health registries because these represent nearly complete population-based databases with a good level of detail regularly reported for several years, which represent unique data sources for conducting a comprehensive burden of disease assessment. The strengths of health registry data rely on specificity and detail level of the data, data validity, reporting coverage and timeliness, which are often associated with a type of registry and diseases. However, registry data provide limited information on community incidence and its acquisition is expensive and time consuming. Yet another limitation is comparability of the results. Healthcare rates associated with medically attended varicella and HZ, and related mortality and in-hospital CFRs established in our study were within reported European ranges, but Norwegian primary health care rates were lower for varicella [62]. Although, direct comparison of our findings with other countries is difficult, because of different study methods, coding practices at health care institutions and health care seeking patterns, our results were similar to those in other countries [33, 62, 63, 67, 68, 135].

The extraction criteria of the data also play an important role in research studies and should be taken into account during interpretation of results. Although we did not perform data

validation of registry data against clinical records (due to lack of time and resources), we believe these data captured the burden of varicella and HZ correctly.

Completeness of the Norwegian primary health care data, to our knowledge, has not been assessed, but we expect it to be high because these are used for reimbursement of all health care providers. In addition, data for varicella and HZ should be well represented due to specific codes (ICPC-2: A72 and S70), especially for cases presenting with typical symptoms. It is however possible that our results are underestimated because we used only varicella- and HZ-specific ICPC codes. A study from the Netherlands reported 27% lower incidence when only ICPC codes for varicella were used [58]. In addition, some cases may have been misdiagnosed, such as enteric zoster [2], or miscoded with nonspecific diagnoses, such as "localized skin rash" (ICPC-2 code: S06). These cases therefore would not be captured in our study.

The data from the Norwegian Patient Registry were previously validated with varying results that were affected by a particular disease studied [136, 137]. Completeness of reporting of a personal identification number to the registry varied between 98% and 35% across different regions in Norway, and this could have impacted our results because we used this number as the linkage key [136]. We did not perform a validation of varicella and herpes zoster discharge diagnoses against clinical records, but we believe that our hospital data capture the burden correctly. This is also supported by a recent Danish study that estimated a 74% sensitivity for varicella-related hospitalization rates reported at the National Patient Registry [125].

To reduce underestimation of hospitalization rates we included all patients with varicella and HZ diagnoses listed as primary or secondary diagnoses as has been done in some other studies [63, 64, 67, 68, 138], in contrary to studies which used only primary diagnosis of varicella and HZ [56, 139-141]. We found that varicella and HZ-specific codes were listed in the first three discharge diagnoses for almost all hospitalized patients (>90%). We acknowledge that there is a risk of overestimating the incidence of both diseases when using hospital registry data, because the diagnosis from a previous hospital experience may erroneously be carried over to subsequent unrelated visits to the hospital. We believe, however, that the number of such cases is low and this is seen mainly in patients with multiple visits. For example, only 3.5% of hospitalized varicella patients had three and more visits, whereas over 16% of such cases were reported among HZ patients. In addition, there might be some coding errors due to varying coding practices among clinicians. In the hospital registry data we captured some of the patients with both diagnoses assigned, especially in patients with multiple contacts. There is a possibility that some of such cases developed recurrent varicella, but it is difficult clinically and by laboratory testing to distinguish between primary VZV infection and VZV reactivation [142]. The use of varicella-specific and HZ-specific codes listed at any discharge diagnosis may be a useful tool to fully characterize the burden of these diseases.

Despite robust data coverage and completeness in the Norwegian Cause of Death Registry, the reporting of unspecific codes for the underlying cause of death remains high [143]. Moreover, the reported diagnosis on the death certificate may not always reflect the true underlying cause of death [143] due to different practices and misinterpretation of the WHO coding recommendations.

Varicella and HZ vaccines are not included in the Norwegian immunization program, thus very few individuals had records of varicella immunization and none had HZ in the immunization registry. Though it is possible that some patients were vaccinated but not reported to the national immunization registry, which only recently started to record immunizations with vaccines not included in the national immunization program with a patient consent [144].

Another limitation in our study was a lack of information about varicella and herpes zoster in immigrant population in Norway, this is because we had access only to anonymous data without country of birth. Despite a lower overall primary healthcare use by immigrant populations in Norway, there is a significantly 2% to 15% higher use of GP in this group compared to native population [145]. Given that immigration to Norway from tropical countries has increased in the past 20 years [146] that might have affected the epidemiology of VZV in Norway. Studies from other countries presented a lower VZV immunity in migrant populations: VZV susceptibility in refugees was from 7.9% in Canada to 18% in the US [147, 148], but in some groups in the US VZV seropositivity was unexpectedly high (92%–100%) and age and group dependent [149].

6.2.2 Real world evidence on the impact of varicella vaccination

The post-marketing evidence of universal varicella vaccination demonstrates a large public health impact in reducing the burden of disease and associated costs. A 74% reduction in varicella incidence has been reported by countries with one-dose varicella vaccination program, and reduction >90% by countries with two-dose vaccine program in place [135, 150-159].

Varicella hospitalization rates have been reported to decrease from 23% to 93% over a 4–14 year time period [159] and by 81%–88% in Uruguay, Canada and the US [150, 160-162]. Highest reduction in hospitalizations were reported in children 1–4 years of age with, e.g. a 62% reduction in Germany and 99% in the US [51, 159]. In addition, the US reported a decrease in varicella related deaths by 94% compared to pre-vaccine era with a significant reduction few years after vaccination implementation [154, 163]. In addition, the US has reported a reduced demand for VZV immunoglobulin [164], saving a considerable cost for post-exposure prophylaxis of primary VZV infection.

An upward shift in the age distribution of varicella has been suggested by the US as a result of childhood varicella vaccination programs. For example, surveillance data from Antelope Valley indicated a shift in varicella incidence peaks in children from 3 to 6 years (in 1995) to 9–11years of age (in 2004) [165]. These data prompted WHO to recommend higher vaccination coverage rates above 80%. However, incidence rates decreased in all age groups and age shift did not appear evident [159]. Nevertheless, some countries introduced catch-up vaccination for adolescents.

The effectiveness of varicella vaccine is indeed influenced by several factors, such as the number of administered doses, disease severity, and age at which the vaccine is administered [159]. The recent review studies found breakthrough varicella incidences ranging from 8% to 32% after single-dose varicella vaccine and 4% after two-doses [159].

6.2.3 Real world evidence on the impact of HZ vaccination

The aim of HZ vaccination is to reduce overall HZ incidence and reduce severity of the disease in older people. Vaccination could also reduce HZ-associated hospitalization rates in Norway, which causes a main burden of VZV infections.

Several countries have implemented publicly funded HZ vaccination with live attenuated zoster vaccine (UK, Greece, France and some regions in Germany and Italy, and in the US).

In the US, vaccine effectiveness of the live attenuated zoster vaccine in reducing the incidence of HZ in immunocompetent population was reported to decline gradually over time: 68.7% during year 1 and 49.5% during year 2; during years 3–6, values ranged from 39.1% to 32.9%; and 16.5% during year 7. Eight years after immunization, vaccine effectiveness was 4.2% and not statistically significant [166]. In addition, a case-control study in the US, reported overall 54% reduction in HZ incidence (which was dependant on age at vaccination: 67% when vaccinated before age 70 years and 38% if vaccinated at age ≥70 years), 58% reduction in prodromal HZ, and 70% in medically attended prodromal HZ [167]. Significant reduction of 61% was reported for PHN at 30 days after rash onset in the same case-control study [167]. In the UK vaccination of elderly with Zostavax resulted in HZ decrease by 62% and a reduction in PHN by 70%–88% in the first three years of vaccine use [103, 168]. In immunocompromised adults vaccine effectiveness was reported at 37%–39% against HZ [166]. Presumably higher decrease can be expected with implementation of Shingrix, which is recommended as a first choice vaccine in the US [109]. Given a high healthcare cost of HZ in Norway, HZ vaccination with either vaccine would be beneficiary.

6.2.4 Impact of universal varicella vaccination on HZ

The majority of the countries were reluctant to introduce universal varicella vaccination fearing a subsequent increase of HZ due to lack of natural external boosting, hypothesised by Hope Simpson in 1965 [13]. This hypothesis was already used in 2000 by Brisson et al. and in other modelling studies suggesting a temporary increase of HZ incidence after implementation of universal varicella vaccine in children [159, 169, 170]. Such an increase was predicted to occur ≥10 years following introduction of varicella vaccination [169, 171-173], which may depend on re-exposure episodes according to the progressive immunity model [174].

Increasing HZ incidence has been reported globally and in Europe, but most of the countries reported the increase already before implementation of universal varicella vaccination [15, 19, 170, 171]. For example, Germany, reported a continuous increase of hospitalization rates (from 8.8 in 1995 to 16.8 in 2012) which were significantly higher in the post-vaccination period (2005–2012) compared to the pre-vaccination period (1995–2003) [141]. Canada reported an overall 1.5-fold increase of HZ incidence over 16 years period (1997–2012), but a decrease in children 0–9 year old, which has started in pre-vaccine era [138]. Similar findings were reported by Australia [175], Japan [176, 177], and Taiwan [156, 178] with increasing HZ incidences before introduction of universal varicella programmes. Although Japan reported a significant increase of HZ in 20–49 years old adults right after introduction of varicella vaccine [179]. Some of the studies associate the HZ increase with varicella vaccination, while others claimed there was no direct association. Available real-world evidence however demonstrates that a rate of HZ in the United States has not increased over 60 years and in particular, no increase occurred in the post-vaccine era [180].

Independently of varicella immunization, HZ increase may be related to demographic and mixing changes in the population, especially in industrialized countries affected by migration and increasing proportion of the elderly [114, 181]. These changes have been taken into account by modellers in Germany, suggesting HZ incidence increase by 10% after universal varicella vaccination. They also suggested that HZ can be prevented with implementation of recombinant zoster vaccine [182]. In addition, recombinant zoster vaccine has shown optimistic modeling results in the UK and Norway [183, 184]. Economic model for the UK has predicted that use of recombinant zoster vaccine would avert almost four times more HZ and twice of PHN cases compared with live zoster vaccine [184]. Cost-effectiveness of HZ vaccination with either live attenuated or recombinant zoster vaccine, has suggested a substantial HZ incidence reduction with a gain from 16,338 to 38,546 quality-adjusted life years (QALYs), and an incremental from €1,423M to €1,490M in direct medical and vaccination costs and savings of €35M–€63M from indirect costs [185].

Therefore, in the light of the increasing elderly population and given the high healthcare burden in Norway, which is mainly driven by HZ hospitalizations, prevention strategies in Norway should be revised for both – varicella and HZ in children and adults.

In Norway, the first dose of MMR is administered at 15 months and a second dose at 11 years of age [82]. Thus, a suitable strategy would be to provide the first dose at 15 months of age either as monovalent varicella vaccine or as MMRV. The second varicella dose could be given through a school-based program at age 7 years when Norwegian children receive a booster dose of DTP-IPV.

6.3 Conclusions

Varicella and HZ pose a substantial healthcare burden in Norway, largely driven by HZ hospitalizations. The future introduction of varicella vaccination into the national immunization program may reduce the incidence of the disease in children and result in substantial economic benefits. Likewise, the implementation of HZ vaccination for adults may substantially reduce burden of disease and prevent an increase of HZ due to aging population. In view of available evidence, national vaccine recommendations for varicella and HZ should be urgently revised.

6.4 Future research priorities

We assessed the burden of varicella and HZ and provided baseline incidence of varicella- and HZ-associated healthcare visits in Norway, which is mainly driven by HZ hospitalizations. HZ vaccination has been demonstrated to be cost-effective in Germany [185]. For further research we recommend to prioritize cost-effectiveness analyses of different immunization strategies: varicella vaccination alone, HZ vaccination alone, and combined varicella and HZ vaccination.

Our study provides a knowledge base to support future efforts to assess the impact and effectiveness of varicella and HZ vaccination. To monitor the impact of immunization on both diseases, a suitable surveillance for varicella and HZ should be established for example by using the Norwegian Surveillance System for Communicable Diseases (MSIS). Surveillance of hospitalised cases may be a useful tool to monitor disease trends after vaccine introduction because hospitalization may reflect the severe disease which would be impacted by the immunization program. Alternatively, sentinel surveillance or use of registry data could be

also considered, however in Germany the reporting of complicated cases became insufficient and was stopped few years later, following a decrease of varicella cases [141].

We identified groups of individuals mostly affected by varicella or HZ. An improvement of VZV screening practices for pregnant women especially for women originating from tropical and subtropical countries should be considered. The management of pregnant women with primary varicella-zoster virus infection depends on the knowledge of the healthcare workers. In France, the consequences of VZV primary infection during pregnancy were poorly known, and management was diverse among healthcare workers [186]. It is of interest to evaluate such knowledge of midwifes and other healthcare workers in Norway. In addition, non-immune women planning to become pregnant should get varicella vaccine before getting pregnant.

We suggest to examine parents and physicians' attitudes towards disease and vaccination to improve vaccine communication, reduce vaccine hesitancy and increase vaccination uptake. High vaccination coverage for varicella is crucial for the change of varicella epidemiology.

Despite the well accessible Norwegian healthcare system, there should be an improvement of adult immunisation status by establishing a separate immunization program for adults. This will help to reach elderly as a target population and address the problems of the increasingly aging population.

Further research on use of antimicrobial medicines among varicella and herpes zoster patients is advisable by assessment of antibiotic prescription rates in primary healthcare. Vaccination against varicella and HZ may reduce the use of antibiotics, likely reducing antibiotic resistance.

7 References

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RESEARCH ARTICLE Open Access

Varicella-zoster virus susceptibility and primary healthcare consultations in Norway

Grazina Rimseliene*, Kirsti Vainio, Moustafa Gibory, Beatriz Valcarcel Salamanca and Elmira Flem

Abstract

Background: Currently Norway does not recommend universal varicella vaccination for healthy children. This study assessed susceptibility to varicella-zoster virus (VZV) in the Norwegian population for the first time.

Methods: A national convenience sample of residual sera was tested for anti-VZV IgG by ELISA. We estimated age-specific seropositivity to VZV, controlling for sex and geographical distribution. We assessed differences between the proportions using the chi-square test and multivariable logistic regression. Seroprevalence data were compared to the varicella and herpes zoster-associated consultation rates in patients attending primary healthcare.

Results: Although 73.2 % ($n = 1,540$) of all samples were positive for VZV, only 11.2 % of samples collected from 1-year-olds were seropositive. There was a sharp increase in the proportion of seropositive in 3- and 5-year-olds (40.2 % and 65.4 %, respectively). By the school entry age of 6 years, 69.8 % of children were seropositive. The age-specific annual consultation rate for varicella in primary healthcare peaked in 1-year-olds, with 2,627 cases per 100,000 population. The profile of varicella-related consultations in primary healthcare mirrored the VZV seropositivity profile. The herpes zoster-related consultations in primary healthcare peaked in people over 70 years of age (702 cases per 100,000 population).

Conclusions: VZV seroprevalence in Norway was somewhat lower than in some other European countries. The age-specific varicella–related consultation rates in primary healthcare mirrored the age profile of VZV seroprevalence.

Background

Varicella-zoster virus (VZV) is a ubiquitous DNA virus that belongs to the Herpesviridae family. The virus spreads via airborne droplets and direct contact [1] and causes varicella (chickenpox) and herpes zoster (shingles; HZ) [1]. Varicella is a contagious childhood disease that is usually benign [1]. However, an estimated 2–6 % of varicella cases that seek care from a clinician develop complications such as bacterial superinfections or neurologic or pulmonary disorders [1, 2]. Although such complications can occur in previously healthy children, the risk is higher for adults [1]. The virus also establishes latency in the neurons of sensory ganglia [3] and later, in association with diminished VZV-specific cell-mediated immunity, may reactivate causing HZ [4]. The lifetime risk for HZ from natural infection is estimated to be 25 %, with most cases occurring in people over 50 years of age and in immunocompromised individuals [5].

Safe and effective varicella vaccines have been available since the 1970s [6], and vaccine against HZ is available since 2006 [7]. Recently, a new candidate vaccine against HZ has been developed as well [8]. However, despite recommendations from the World Health Organization (WHO) [9, 10] and the European Working Group on Varicella [11], only some European countries have integrated the varicella vaccine into national immunization programs [12, 13]. There is a concern that universal varicella vaccination may result in an increased incidence of HZ due to the possible decline of exogenous boosting following a reduced circulation of the wild type virus [14]. In addition, high vaccination coverage is needed to avoid shifting varicella morbidity to older age groups [10]. In Norway, varicella vaccine is not currently offered through the national immunization program, but it is recommended for non-immune individuals [15] and is fully reimbursed for those who are at risk of

* Correspondence: Grazina.Rimseliene@fhi.no
Norwegian Institute of Public Health, Infection Control and Environmental Health, PO Box 4404, NO-0403, Oslo, Norway

complications, such as people with immunodeficiencies and stem cell transplantation patients [16]. Otherwise, the vaccine is available at a cost per dose of 465 Norwegian kroner (NOK) [17], which is roughly equivalent to $57 USD. Based on the National Immunization Registry SYSVAK, approximately 550 doses of varicella vaccines are given to 450 individuals annually in Norway, with a birth cohort of 60,000 children per year. There is currently no national recommendation regarding the use of the HZ vaccine [18]. This vaccine has been licensed in Norway since 2006 and is available at a cost of 1,748 NOK or roughly $220 USD per dose; approximately 100 doses have been sold since its licensure.

The availability of the varicella and HZ vaccines highlights the urgent need to assess the public health burden of these diseases in Norway in order to inform national vaccine policy decisions. Such an evaluation should be supported by the assessment of VZV seroprevalence in the population to understand the age-dependent dynamics of the infection and to identify susceptible groups. In Norway, few data about VZV seroepidemiology are available. All earlier studies focused on subsets of the population, such as patients with multiple sclerosis, infectious encephalitis, or pregnant women of foreign descent [19–21]. Therefore, we examined the anti-VZV antibody levels in different age groups in a sample of the Norwegian population and identified population groups with the lowest immunity against VZV. We also compared seropositivity proportions with the age-specific consultations rates for varicella and HZ in patients attending primary healthcare.

Methods

Study design and data sources

This was a cross-sectional seroprevalence study conducted using anonymized residual sera collected from patients of all ages who sought either primary or hospital care in Norway. Because all samples were anonymized, reasons for healthcare visits and associated sample collection are unknown. Laboratories however exclude samples from known HIV and hepatitis cases. Sera specimens are collected from all 19 counties throughout Norway during a 5-week period each year, usually in July–August. This study used residual sera obtained in 2006, 2007, 2008, 2011, and 2014 and excluded samples collected during the influenza pandemic of 2009–2010. The following information was available for each sample: patient birth year, sex, county of residence, sample collection date, and laboratory name.

The sample size in the study for each age group was calculated using a 95 % confidence interval (95 % CI) with a 10 % margin of error. As a result, roughly 100 samples were selected for each of the following age groups: 1-year bands between 0 and 9 years; 5-year bands between 10 and 49 years; 10-year bands between 50 and 69 years; and 100 samples from those 70 years old and older. These age groups were chosen to allow comparisons with data from other European countries.

The sera were stored at −20 °C at the Norwegian Institute of Public Health where the testing was performed. IgG antibody levels were measured using a commercial indirect enzyme-linked immunosorbent assay (ELISA); Enzygnost anti-VZV-IgG Virus/IgG, Siemens Healthcare Diagnostics AS, Erlangen, Germany) with the automated EVOLIS™ System from Bio-Rad and the DS2 Processing System from DYNEX. According to the manufacturer, the sensitivity of this method is 99.3 % and the specificity is 100 %. The assay was run in accordance with the manufacturer's instructions. The positive and negative controls from the kit were used to validate the assay and results. We had no kit independent controls available. The cut-off for qualitative evaluation of positivity was a corrected optical density (OD) >0.2 at 450 nm. Samples with ODs <0.1 were counted as negative, and samples with ODs between 0.1 and 0.2 were considered equivocal. Equivocal samples were not re-tested.

The rates of primary healthcare consultations associated with varicella and HZ were measured using health reimbursement data from 2008–2012 extracted from the Norwegian Health Economics Administration database. The database includes individual reimbursement claims from all primary care providers in Norway. The extracted data included all consultations that had varicella or HZ at any diagnostic position, coded as A72 and S70, respectively, according to the International Classification of Primary Care, Second Edition (ICPC-2). The age- and sex-specific rates per 100,000 population were calculated using the number of primary care patients registered with varicella and herpes zoster diagnoses for the first time during 2008–2012 as the nominator and population data for the same time period as the denominator [22].

Data analysis

VZV seropositivity was estimated as a proportion with the corresponding 95 % CI. We used the chi-square test to examine differences in seropositivity by age, sex and geographical regions. We also performed multivariable logistic regression analysis to assess the association between VZV seroprevalence, which was classified as positive or negative, and a set of explanatory variables (sex, age, geographic region). We assessed the fit of the different models using likelihood ratio tests. Statistical significance was set at a P-value <0.05. All analyses were performed using the statistical software STATA, version SE13 (StataCorp LP, College Station, TX, USA).

Results

A total of 2,103 samples from patients aged 0 to 92 years were included in the study, 51.9 % ($n = 1,093$) of which were from males. Overall, 73.2 % ($n = 1,540$) of the samples were seropositive for VZV (Table 1). The proportions of seropositive males and females were similar, 50.6 % and 49.4 %, respectively. The seropositivity proportion in children under 1 year of age was 58.9 %. This decreased to 11.2 % at the age of 1 year, likely reflecting a short-lived immunity conferred by maternal antibodies [23, 24]. The proportion of seropositive individuals increased to 40.2 % and 65.4 % at 3 and 5 years of age, respectively. By school entry age, which is 6 or 7 years old, 69.8 % and 71.4 % of children, respectively, were immune to varicella. The proportion of immune children increased further to 81.4 % by age 10–14 years (Fig. 1). By age 20 years, 86.4 % of the Norwegian population had acquired natural varicella immunity, and by age 35–39 years, 95.7 % of subjects had detectable anti-VZV antibodies.

Females of childbearing age, defined as those aged 15 to 49 years old [25], accounted for 34 % of all samples collected from women (343/1,010) and for 16.3 % of all tested samples. Of these samples, the overall seropositivity proportion was 88.6 %. The average proportion of seronegative females in this age group was 5.3 %. The proportion of non-immune women was highest, 13 %, in young adulthood (20–24 years); this proportion declined in the older age groups.

We also assessed the VZV seroprevalence in seven geographic regions defined by the population density [22]. The seropositivity proportions ranged from 59 % in sparsely populated central Norway to 86 % in densely populated Southeast Norway. However, multivariable analysis indicated that age group was the only explanatory variable that was significantly associated with VZV seropositivity (Additional files 1 and 2).

From 2008–2012, there were a total of 73,065 varicella-related primary healthcare consultations by 56,134 persons in Norway, corresponding to an average annual consultation rate of 231 cases per 100,000 population. The highest consultation rate, 2,627 cases per 100,000 population, was observed in children aged 1 year; the lowest consultation rate was found in patients ≥70 years old. The varicella consultation rate in primary healthcare mirrored the VZV seroprevalence profile (Fig. 2), with children under 10 years old accounting for 79.3 % of all varicella cases. The majority of varicella patients (80 %) had only

Table 1 Age-specific varicella-zoster virus seroprevalence (%, 95 % CI) among a subset of Norwegian population ($n = 2,103$)

Age group	Positive		Negative		Equivocal	
	% (No of samples)	95 % CI	% (No of samples)	95 % CI	% (No of samples)	95 % CI
0 y	58.9 (56)	48.8–68.4	29.5 (28)	21.1–39.4	11.6 (11)	6.5–19.8
1 y	11.2 (12)	6.5–18.8	86.9 (93)	79.1–92.1	1.9 (2)	0.5–7.2
2 y	16.3 (17)	10.4–24.8	77.9 (81)	68.9–84.9	5.8 (6)	2.6–12.3
3 y	40.2 (41)	31.1–50.0	55.9 (57)	46.1–65.2	3.9 (4)	1.5–10.0
4 y	48.5 (49)	38.9–58.2	50.5 (51)	40.8–60.2	1.0 (1)	0.1–6.8
5 y	65.3 (66)	55.5–74.0	33.7 (34)	25.1–43.5	1.0 (1)	0.1–6.8
6 y	69.8 (67)	59.8–78.2	26.0 (25)	18.2–35.8	4.2 (4)	1.6–10.6
7 y	71.4 (70)	61.7–79.5	24.5 (24)	17.0–34.0	4.1 (4)	1.5–10.4
8 y	82.8 (82)	74.0–89.1	15.2 (15)	9.3–23.7	2.0 (2)	0.5–7.8
9 y	78.1 (75)	68.7–85.3	16.7 (16)	10.4–25.5	5.2 (5)	2.2–12.0
10–14 y	81.4 (118)	74.2–86.9	11.7 (17)	7.4–18.1	6.9 (10)	3.7–12.4
15–19 y	89.5 (94)	82.0–94.1	4.8 (5)	2.0–11.0	5.7 (6)	2.6–12.2
20–24 y	86.4 (89)	78.3–91.8	8.7 (9)	4.6–16.0	4.9 (5)	2.0–11.2
25–29 y	90.0 (81)	81.8–94.7	10.0 (9)	5.3–18.2	0 (0)	-
30–34 y	91.9 (79)	83.8–96.1	2.3 (2)	0.6–8.9	5.8 (5)	2.4–13.3
35–39 y	95.7 (90)	89.1–98.4	1.1 (1)	0.1–7.2	3.2 (3)	1.0–9.5
40–44 y	91.8 (89)	84.3–95.8	1.0 (1)	0.1–7.0	7.2 (7)	3.5–14.4
45–49 y	94.8 (91)	88.0–97.8	3.1 (3)	1.0–9.3	2.1 (2)	0.5–8.0
50–59 y	95.9 (94)	89.6–98.5	3.1 (3)	1.0–9.1	1.0 (1)	0.1–7.0
60–69 y	95.8 (91)	89.3–98.4	3.2 (3)	1.0–9.4	1.1 (1)	0.1–7.2
70+ y	93.7 (89)	86.6–97.1	1.1 (1)	0.1–7.2	5.3 (5)	2.2–12.1
Total	73.2 (1540)	71.3–75.1	22.7 (478)	21.0–24.6	4.0 (85)	3.3–5.0

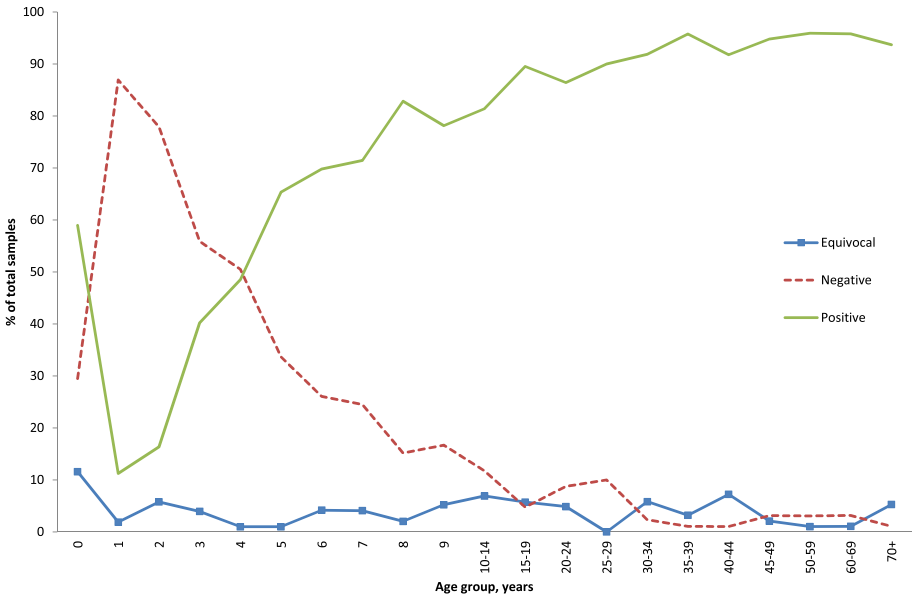

Fig. 1 Age-specific varicella-zoster virus seroprevalence as measured by serum IgG antibodies among a subset of Norwegian population ($n = 2{,}103$)

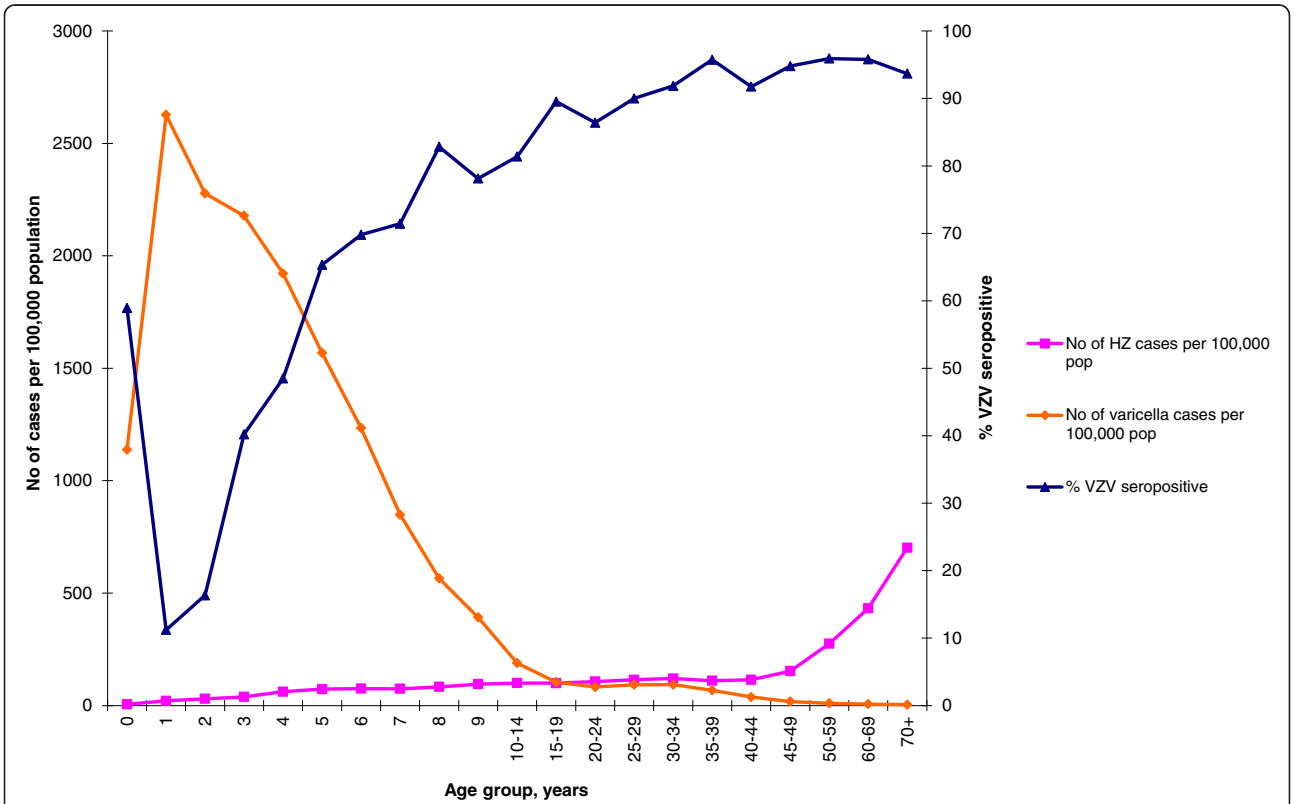

Fig. 2 Age-specific varicella-zoster virus seropositivity (serum IgG antibodies) and age-specific consultation rate (cases per 100,000 population) of varicella and herpes zoster as first encounter with primary healthcare in Norway 2008–2012. The blue line represents percent of VZV seropositive individuals as measured by serum IgG antibodies in a subset of Norwegian population ($n = 2013$). Orange line shows the number of varicella cases per 100,000 population measured as first encounter with primary healthcare in Norway, 2008–2012 ($n = 56{,}126$). The pink line represents number of herpes zoster cases per 100,000 population, measured as first encounter with primary healthcare in Norway, 2008–2012 (KUHR)

one encounter in a primary healthcare setting, mostly with GP (75 %). In 2008–2012, there were 124,139 HZ consultations by 54,094 persons in Norway, translating to an average annual rate of 223 cases per 100,000 population. The highest HZ consultation rate was observed in patients ≥70 years old (702 cases per 100,000 population), and the lowest rate was found in children in their first year of life (5.6 cases per 100,000 population). Most HZ patients had one or two encounters (76 %) with primary healthcare, and the majority (80 %) were GP consultations.

Discussion

This is the first study to describe the age-specific seroprevalence of anti-VZV antibodies in different age groups in a Norwegian population. Because the varicella vaccine is currently used infrequently in Norway, we documented the pre-vaccine seroepidemiology of VZV and the use of primary healthcare associated with varicella and HZ. Overall, 73.2 % of the Norwegian population has natural immunity against varicella, with the highest seropositivity, 95.7 %, found in adults 35–39 years of age, suggesting almost universal transmission of VZV infection. Varicella-related consultation rates in primary healthcare mirrored VZV seroprevalence, with a peak in children aged 1 year. This pattern suggests a possible correlation between these different measures of varicella occurrence. For HZ, the opposite pattern was observed, prompting further investigation of the factors that influence the occurrence of this disease in Norway.

Similar to other European countries, varicella immunity in Norway is acquired gradually, starting in early childhood and showing a sharp increase around age 3–5 years. By this age, 90 % of Norwegian children have entered organized childcare [26], thereby increasing their opportunities for varicella exposure. By the school entry age of 6 years, 7 of 10 children are already immune, and an additional 10 % acquire natural immunity by age 10 years. The latter is somewhat lower than findings in other Nordic countries. For comparison, 91 % of children are reported to be seropositive by age 10 years in Finland [27], and in Sweden, 98 % of 9–12-year-olds are immune to varicella [28]. This is higher than the 78 % found in the same age group in our study, and there is no clear explanation for the difference. The 12 % of susceptible individuals aged 10–14 years in Norway is higher than the 8.3 % found in the same age group in Spain [27] or in Poland, where 82 % are seropositive by the age of 10 years [29]. We also found somewhat higher proportions of susceptibility in young children and adolescents compared to other countries, e.g. England and Wales, Belgium, Israel, Ireland, Netherlands, Slovakia [27], and Poland [29]. In Europe, VZV seroprevalence differs by country. Although, a standardized VZV seroprevalence study in 11 European countries demonstrated that over 90 % of children are VZV seropositive by age 15 years in most of the countries [27], for 5-year-old children, the lowest proportions of seropositive individuals were found in Italy (38 %) [27] and Poland (48 %) [29], and the highest proportion was found in the Netherlands (95–97 %) [30].

In our study, the proportion of susceptible adults aged 20–29 years was 9.5 %, whereas in most other European countries, this proportion is less than 5 %, except in Italy (11.5 %), the UK (7.1 %), Spain (6.9 %), and Ireland (6.2 %) [27]. Among females of childbearing age (15–49 years) in Norway, the proportion of non-immune subjects was 5.3 %. Nardone et al. reported such proportion to be less than 5 % in most European countries, except for Ireland (5.4 %) and Italy (12.5 %) [27]. The results of Nardone et al. are not directly comparable to our findings due to their use of a slightly different age group (15–39 years). It is difficult to compare our results with countries that were not included in the study by Nardone et al. due to methodological differences and variations in the age groups.

The level of IgG antibodies in a single sample may vary in different assays. A high percentage of equivocal samples detected in young adults in our study may therefore partly be due to the assay chosen for the study, for which international standards were not used.

Differences in VZV seropositivity levels in different European countries can be explained in part by varying population densities and social mixing patterns in the countries and perhaps by climate differences. However, it is surprising that VZV seropositivity in the children and adults in our study was somewhat lower than in reports from other Nordic countries with comparable populations and climates. It is possible that our results were somewhat affected by the convenience sampling used in the study. Such sampling is subject to selection bias because residual samples are collected from people seeking medical help, limiting the generalizability of the results. Despite these limitations, this method is often preferred in seroepidemiological studies over more generalizable population-based probability sampling. Convenience sampling is less costly and time-consuming, and the samples are easier to obtain [31]. Moreover, the VZV seroprevalence as estimated by convenience sampling is shown to be similar to the results of studies that use population-based cluster sampling [32]. To increase study validity, we collected samples from all geographic regions in the country and selected sera only from large microbiological laboratories that test patients who receive both primary and hospital healthcare. All residents in Norway have universal access to healthcare, so it is possible that our data included individuals who visited a healthcare provider for prophylactic purposes.

We found high seropositivity in infants (58.9 %), but this dropped sharply to 11.2 % by age 1 year, which may be explained by waning maternal antibodies [23, 24, 33]. In children aged one year, the proportion of seropositive subjects in our study was similar to the proportions in Finland, Italy, and Spain. However, in the majority of other European countries, the proportions are higher, varying between 20 % and 40 % [27]. Nevertheless, the actual age at sample collection in our study was not available; thus, the year of birth was subtracted from the year of sample collection, which could have affected the results for children under one year of age. Given that samples are collected in July–August of each year, the age group that was under one year of age in our sample was composed of children aged 0 to 8 months, whereas the one-year age group included children aged 7 to 20 months. This age distribution could result in overestimation of seropositivity in those under one year of age and underestimation of seropositivity in those older than one year. With increasing age, this difference would not have such a dramatic effect on seropositive proportions. However, this could be only verified if the actual age was reported rather than just the year of birth.

Our sample size was estimated to allow a detailed assessment of seroprevalence in children because we expected high seropositivity in adults. Although the total number of samples in our study ($n = 2{,}103$) was similar to the number of samples used in other European studies, we had fewer samples per age group in adults compared to, for example, the study by Nardone et al. (100 vs. 200 samples per 5-year age band) [27, 34]. Since we used anonymized sera, we cannot determine the number of samples that were collected from people who originate from tropical and subtropical countries, where lower varicella immunity in adolescents and young adults is established [35]. Since the 1990s, the estimated proportion of people of foreign descent in Norway has increased to 13 %, of which about one-third (26 %) originate from Asia [22]. A similar pattern is reported in Sweden [36] but not in Finland (3 %) [37], suggesting that the higher seroprevalence among Swedish children compared to our findings could be due to the timing of sample collection. Samples in Sweden as well as in Finland were collected in 1997–1998 when the proportion of immigrants was considerably lower than in 2006 and later when there were higher proportions of people of foreign descent in Norway. Therefore, the probability of samples being collected from people originating from settings that have shown differences in their varicella epidemiology may be higher in Norway than in other Nordic countries. In the Netherlands, being a foreign national was associated with lower VZV seropositivity in children under 6 years old [30], and more seronegative adults were found to originate from tropical and subtropical countries [35, 38]. Since ethnicity data were not available for this study, this hypothesis requires further research.

The differences between geographical regions found in our study should be interpreted with caution. Sampling bias may minimize the study's power to find differences since the study was designed primarily to measure VSV seroprevalence in different age groups on the national level, not on the regional level. We found that 5.3 % of women of childbearing age were susceptible to VZV. This proportion was even higher in those aged 20–24 (13 %) and 25–29 years old (11 %). This is a potential concern because women in these age groups give birth to 45 % of the infants born annually in Norway. VZV infection during pregnancy can lead to serious complications, such as maternal pneumonia and congenital varicella syndrome [1]. However, these findings should also be interpreted with caution because they, too, could be affected by sampling bias. Since women born outside of Norway may lack immunity to varicella, more evidence is needed to define the groups for pregnancy screening in order to reduce the risk of potential VZV complications.

Overall, the primary healthcare consultation rate of both varicella and HZ was lower in Norway than in other European countries [34]. However, a direct comparison with other studies is very difficult due to differences in methodology as well as varying VZV epidemiology from country to country. We found a similar varicella consultation rate in Canada in a study by Brisson et al. [39] that use a similar data source (the physician billing claims); however, that study used data from 1979–1997. The consultation rate in our study was calculated using information on reimbursement claims from primary care providers. It is thus unlikely that the consultation rate was greatly underestimated because healthcare is generally easily accessible to all Norwegian residents. However, it may be somewhat underestimated, as patients with mild symptoms, and for example additional family members with infection may not seek medical help. In addition, the disease could be misclassified due to atypical presentation. We observed a peak in the consultation rate of varicella-related primary care consultations around 1 year of age. This is the age at which children are likely to be susceptible due to loss of protection conferred by maternal antibodies, and this is supported by our seroprevalence curve. However, it is difficult to determine whether this increase represents a true increase in the varicella incidence in the general population or whether this peak reflects an increase in more severe cases that have complications requiring medical help. It is also possible that the increase is affected by healthcare-seeking behavior since parents may be more likely to seek medical help when a young child contracts varicella.

A high proportion of susceptibles in certain age groups detected in our study underlines a need to revise Norwegian varicella vaccine recommendations such as expanding current recommendations to include adolescents aged 10–15 years without a positive history of varicella. There is also a need to consider varicella screening in pregnancy to identify non-immune women to be targeted for vaccination after giving birth. Such recommendations may potentially reduce the proportion of susceptible individuals at older ages and reduce the risk of complications.

Conclusions

The VZV seroprevalence in Norway was somewhat lower than in some other European countries. The age-specific varicella-related consultation rates in primary healthcare mirrored the age profile of VZV seroprevalence. These data lay the ground for further research to quantify the disease burden of varicella and HZ and predict the impact of potential vaccination programs through mathematical modeling.

Additional files

Additional file 1: Univariate and multivariable analysis of varicella-zoster virus seropositivity by sex (reference: female), age group and region (reference: Oslo and Akershus) in Norway (odds ratios (OR), 95 % confidence intervals (95 % CI), and p-value). (XLSX 12 kb)

Additional file 2: Model fitting information (Likelihood ratios and 95 % confidence intervals (CI)). (S: Sex; R: region; A: age groups. Df: the number of parameters that differ between the two nested models; AIC: Akaike information criterion). (XLSX 10 kb)

Abbreviations

ELISA, enzyme-linked immunosorbent assay; HZ, Herpes zoster; IgG, immunoglobulin G; VZV, varicella-zoster virus

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Availability of data and materials

The dataset supporting the conclusions of this article cannot be shared per national data protection legislation.

Authors' contributions

GR conducted data analysis and drafted the manuscript. MG implemented sample testing. BVS contributed to the statistical analysis and helped to draft the manuscript. EF and KV conceived and designed the study and drafted the manuscript. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

Not applicable.

Ethics approval and consent to participate

The study was approved by the Regional Committee for Medical and Health Research Ethics, Oslo, Norway, as well as an exemption from patient's consent to use residual sera. The de-identified samples were obtained from the biobank at the Norwegian Institute of Public Health following the internal procedures and approval from the Regional Committee for Medical and Health Research Ethics, Oslo, Norway.

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III

The burden of herpes zoster disease in Norway

Grazina Mirinaviciute[1], Else Quist-Paulsen[2], Arne Broch Brantsæter[3], Elmira Flem[1,4]

1 Department of Infectious Diseases Epidemiology and Modeling, Infection Control and Environmental Health, Norwegian Institute of Public Health, PO Box 222 Skøyen, N-0213 Oslo, Norway

2 Department of Infectious Diseases, Oslo University Hospital, Ullevaal and Institute of Clinical Medicine, University of Oslo, Norway

3 Department of Infectious Diseases and Department of Acute Medicine, Oslo University Hospital, PO Box 4956 Nydalen, N-0424 Oslo, Norway

4 Current affiliation: MSD Norway, Associated Director Medical Affairs Vaccines

Abstract

Background

No national vaccination program against herpes zoster (HZ) is currently in place in Norway. We aimed to quantify the burden of medically attended HZ to assess the need for a vaccination program.

Methods

We linked data from several health registries to identify medically attended HZ cases during 2008–2014 and HZ-associated deaths during1996–2012 in the entire population of Norway. We calculated HZ incidence and rates for primary and hospital care by age, sex, type of encounter, vaccination status, and co-morbidities among hospitalized patients. We also estimated HZ-associated mortality and case-fatality rates.

Results

The study included 82,064 patients with HZ-associated diagnoses, which were not reported as vaccinated against HZ. The crude annual HZ incidence rates were 227.1 cases per 100,000 in primary healthcare and 24.8 per 100,000 in hospitals. HZ incidence rates were higher in adults aged ≥50 years (461 per 100,000 in primary care and 56 per 100,000 in hospitals). Most zoster patients were females: 267 per 100,000 in primary healthcare vs 188 per 100,000 in males, and 28 hospitalizations per 100,000 vs 22 per 100,000 in males. Among hospitalized patients 47% had assigned codes of complicated HZ and 25% of patients had comorbidities, according to Charlson comorbidity index. The median hospital stay (4 days) increased with the severity of comorbidities. The estimated mortality rate was 0.18 deaths per 100,000 for HZ as underlying cause of death; the in-hospital case-fatality rate was 1.04%.

Conclusions

Medically attended HZ poses substantial burden on the Norwegian healthcare with a highest burden in the hospital sector. Most hospitalized zoster cases occurred among adults aged ≥50 years. Vaccination should be considered to reduce the disease burden.

Keywords: herpes zoster, shingles, postherpetic neuralgia, burden, registries, Norway, primary healthcare, hospitalizations, deaths

Background

Herpes zoster (HZ) (shingles) is a painful disease characterized by a blistering skin rash and caused by reactivated varicella zoster virus (VZV)[1]. Usually self-limiting, HZ may result in severe complications such as postherpetic neuralgia (PHN) in 10%–50% of patients [2] and zoster ophthalmicus in 5%–14% [3, 4]. Defined as persisting pain occurring ≥30 or ≥90 days after the onset of HZ, PHN is a particularly debilitating condition that leads to ≥30% of patients experiencing persistent pain for more than one year [4] and more than five years in 2% of patients [2]. Reactivation of VZV may also cause several neurological complications, including encephalitis, meningitis, and myelitis [5], and has been associated with an increased risk of stroke [6]. HZ and associated complications can significantly impact the quality of life and result in multiple healthcare visits, hospitalizations, and deaths [7]. The lifetime risk of HZ is estimated to be 23%–30% [8]. The age-related decrease of VZV-specific cell-mediated immunity increases the risk of disease at ages ≥50 years and the risk peaks at ages ≥80 years [9-11]. Higher HZ risk is also reported in individuals with immunosuppression due to cancer, HIV infection, or organ transplantation [12].

Several studies have previously assessed the burden of medically attended HZ disease in different countries. In the US, General Practitioner (GP) consultation rates associated with HZ were 3.2 cases per 1,000 person-years with a peak of 10.9 cases per 1,000 person-years among persons ≥80 years of age [12]. In North America and Asia, the HZ-associated hospitalization rates ranged from two to 25 per 100,000 person-years, with even higher rates reported in the elderly [4]. In Western Europe, HZ-associated rates of GP consultations and hospitalizations also gradually escalate from one to two cases per 1,000 person-years in children <10 years of age to seven to eight cases in adults ≥50 years of age, with a peak at 10–11 cases per 1,000 person-years among 80-year-olds [8, 13]. Higher incidence rates are reported in women [8, 12, 14].

Sweden and Denmark reported hospitalization rates for HZ to 13 cases per 100,000 with a predominance in women [15, 16]. HZ associated mortality in Sweden reported in patients ≥50 years of age varied between 0.67 per 100,000 in women and 0.26 per 100,000 in men [16]. An overall standardized mortality rate of 1.8 per 100,000 was found in Denmark [15].
Considering the magnitude of HZ disease burden and an increasing proportion of elderly in the population in Europe [17], vaccination may be a viable strategy to reduce the impact of disease on both the individual and society. Currently two vaccines are available: a live-attenuated vaccine Zostavax® (Merck Sharp & Dohme Corporation, USA) and a subunit recombinant vaccine Shingrix® (GlaxoSmithKline, Rixensart, Belgium). Zostavax®, available in Europe since 2006, has an established efficacy and safety profile, albeit reports of waning vaccine protection with age [18]. Shingrix®, licensed in Europe in 2018, demonstrated a promising short-term efficacy above 90% against HZ in persons aged ≥50 years, and 89% efficacy against PHN in individuals aged ≥70 years [19, 20]. Both vaccines are licensed for prevention of shingles and PHN in adults ≥50 years of age.
At present, vaccination against HZ or varicella is not included in the national immunization program in Norway. The need to introduce national zoster immunization was not assessed before due a lack of estimates of the national burden of disease. However, 95% of Norwegian

adults aged ≥50 years were reported to have detectable VZV-specific antibodies in their blood [21], and about 1.8 million are estimated to be in the target age group for HZ vaccination [22]. Despite Zostavax® being available on the Norwegian market since 2006, few doses were distributed due to lack of endorsed national recommendations and also because of a limited vaccine supply. Thus, the aim of this study was to quantify the burden of medically attended HZ in Norway in order to assess the need for the national policy decision.

Materials and Methods

Study design

We conducted a national registry-based study to estimate the use of healthcare resources and mortality in patients with HZ-associated diagnoses. Given a universal access to healthcare and because children can also develop HZ, we included the entire population of Norway (5.3 million in 2018) in the study [22]. We used individual patient data from the following national registries: the Norwegian Immunization Registry (HZ and varicella vaccinations), the Norwegian Health Economics Administration (HZ-coded primary healthcare consultations), the Norwegian Patient Registry (NPR, HZ-coded hospital contacts), and the Cause of Death Registry (CDR, HZ-coded deaths). Data were extracted for the period of 2008–2014 except for data from the CDR, which covered the period of 1996–2012. Data from each source were extracted based on specified criteria, details of which are provided in the Supplementary file 1. We linked primary care and hospital data using a unique patient identifier to determine the number of patients consulting both primary and hospital care. We also linked these data to vaccination records to ascertain individual immunization status of each patient.

Data analysis

We calculated the annual age- and sex-specific incidence rates per 100,000 population for HZ-associated diagnoses in primary and hospital care. Incidence rates were calculated using the first record with a HZ-associated diagnosis for each patient registered during 2008–2014. Individual patient identifier allowed us to select each patient with all registered diagnoses and determine a number of HZ-associated episodes for each individual patient. Incidence rates were estimated separately for each type of primary (GP or emergency) and hospital (inpatient, outpatient, ambulatory) care. The population data by age, sex, and year were obtained from Statistics Norway [23]. We compared age-specific differences by sex in different patient groups by performing a Kruskal-Wallis H test.

For patients with HZ-related diagnoses in hospitals, registration of HZ as the primary or secondary diagnosis was recorded. In addition, other accompanying diagnoses were categorized as coded by the International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10) (Supplementary file 2) for descriptive purposes. The categorization was performed by two infectious disease specialists. We assessed the presence and severity of underlying conditions in patients with HZ-associated diagnosed by applying the Charlson comorbidity index (CCI). The CCI categorized patients into the following groups: no comorbidity (score 0), moderate (score 1), severe (score 2), and very severe comorbidity (score ≥3). Nineteen diseases are weighted in this index according to the strength of their association with mortality [15].

To examine the association between the length of hospital stay by age, sex, and a diagnostic category, we used multivariable regression analysis. We tested associations for interactions for the same factors and calculated regression coefficients for significant interactions.

To estimate HZ-associated mortality, we estimated age- and sex-standardized mortality rates per 100,000 using the World Health Organization's population data for Scandinavian countries [24]. We used Poisson regression analysis to assess seasonal trends in the number of HZ patients in primary healthcare, hospitals, and HZ-associated deaths.

In addition, we estimated the case-fatality-rate (CFR) among hospitalized HZ patients, calculating CFR separately for in-hospital deaths, and deaths occurring within 30 days post discharge.

Results

During 2008–2014, 82,064 patients were registered with a HZ-associated diagnosis in primary and hospital care in Norway, corresponding to an average annual incidence rate of 238.1 per 100,000 population. No records of vaccination against HZ were identified for these patients after linkage to the national immunization registry.

Ninety-five percent of patients were treated in primary healthcare, of which 5.9% referred to hospitals. An additional 4.6% of the patients had no record of contact with primary healthcare before being hospitalized.

Primary healthcare

During the study period, an average of 11,181 patients with a HZ-associated diagnosis (range: 10,030–12,304) attended annually primary healthcare corresponding to an average annual incidence rate of 227.1 patients per 100,000 population (Figure 1). These cases had a mean of 26,224 healthcare encounters each year. Of these patients, 59% were female. The median age was 61 years (IQR: 42, 74). Women were significantly older (median age 62 years, IQR: 46, 75) than men (median age 59 years, IQR: 37, 71) (p<0.001). Incidence rates of herpes zoster cases in primary healthcare increased from 230.4 per 100,000 for those aged 50–54 years to a peak of 774.7 per 100,000 in patients aged 80–84 years. Incidence rates in children ranged between 33.9 per 100,000 in 0–4 year olds to 108.8 per 100,000 in 10–14 year olds, with children <10 years of age accounting for 3.2% of all cases. We observed no seasonal pattern in the distribution of HZ-associated contacts in primary healthcare.

The majority of contacts in primary healthcare were GP consultations (88.5%), but 10.7% of the patients visited emergency primary care clinics, mostly outside the ordinary working hours of GPs. In 93% of patients, HZ was the main diagnosis at the first contact. More than a half the HZ patients had only one contact with primary healthcare, the remaining patients had two or more (range 1–152 per patient).

Hospital care

During the study period 2008–2014, an average of 1,218 patients (range: 1,001–1,393) with a HZ-associated diagnosis were treated in Norwegian hospitals annually, resulting in 2,396 hospitals encounters per year. Herpes zoster was listed as primary diagnosis in 73.4% of patients at their first hospital contact; 90% of patients had less than three contacts with a hospital. Among hospital cases, 68.9% were treated as outpatient, 27.2% as inpatient, and 3.9% received ambulatory care. Considering all cases with HZ-related codes on primary and secondary discharge diagnoses, the overall hospitalization rate was 24.8 per 100,000 population per year. The hospitalization rate was 10.2 cases per 100,000 for inpatient cases and 13.7 cases per 100,000 for cases treated as outpatient (Figure 2). The rate of HZ cases treated as inpatient increased with age (Figure 3). Fifty-six per cent of patients were female,

and the median age was 68 years (IQR: 52–80). The lowest hospitalization rate (5.3 per 100,000) was in children 0–4 years of age, with a slight increase to 7.9 per 100,000 in those aged 5–9 years. The incidence steadily increased and reached 19.9 per 100,000 in adults 50–54 years of age with a peak of 151.1 cases per 100,000 at 85–89 years of age (151.1 per 100,000). The hospitalization rate in adults aged ≥50 years was 56 per 100,000 when all cases with HZ-related codes on primary and secondary discharge diagnoses were included. We did not observe clear seasonal pattern in the distribution of HZ hospital cases.

Complicated HZ as coded by ICD-10 codes B020–B023, B027, and B028 was reported in 46.9% of hospital patients. Uncomplicated HZ was assigned to 53.1% (ICD-10 codes: B029 and B02), including 22.8% of patients having uncomplicated HZ as the only diagnosis (Table 1). Postherpetic neuralgia was reported in 9.3% of hospitalized HZ patients (Table 1); of these, 59% were females who were marginally older (median age 70 years, IQR: 55, 82) than men (median age 69 years, IQR: 55, 79) (p =0.047). HZ in eye was the most frequent complication, reported in 26% of the HZ patients. A diagnosis of HZ encephalitis was made in 2.9% of the HZ patients and 0.7% had HZ meningitis (Table 1).

Table 1 Number and proportion of patients at first contact with hospital with herpes zoster listed at any diagnosis, as primary or as secondary diagnosis by selected diagnostic groups; and length of hospital stay in days (coefficient, 95%CI)(n=3,758), Norway, 2008-2014.

*Coefficient represents the length of hospital stay (days) adjusted for age and sex, estimated using a multivariable linear regression.

We also found 0.67% (n=552) of patients had both varicella and HZ codes listed as their discharge diagnosis.

Overall, 25% of the HZ patients had co-morbidities defined by the CCI. Severe and very severe co-morbidities were reported in approximately 15% of all patients, of which more than two-thirds were aged ≥60 years (Table 2). In patients with immunodeficiency (8.7%), the majority had malignancies affecting the immune system (5.5%); HIV/AIDS was reported in 54 patients (0.6%) (Table1). Ten women were pregnant at the time of their first HZ-associated hospital contact (0.1%) and four of them had HZ as the primary diagnosis.

Table 2 The proportion (%) of comorbidities among hospital patients with HZ-related ICD-10 codes on discharge diagnoses according to the Charlson comorbidity index by age (years), severity, and difference in the length of hospital stay (days), Norway, 2008–2014.

*Coefficients in the table are estimates of differences in length of hospital stay in days for moderate, severe, and very severe co-morbidities which were estimated using multivariable linear regression and adjusted for age and sex.

The median length of stay for HZ patients was 4 (IQR: 2, 9) days and the mean was 7.1 days (SD: 9.709, range 1 - 242). The median length of hospital stay for patients with uncomplicated HZ was 4 days and 5 days 1.3 (0.2–6.1) days longer for those with zoster-related complications. The patients with complicated HZ stayed in hospital longer compared with patients with other HZ-associated diagnoses (Table 1). Several significant interactions (particularly between age and several diagnostic groups) were identified for patients with the following conditions: diabetes (15.2 days longer stay [95% CI: 8.5 - 21.9]), kidney disorders

(11.1 days longer stay [95% CI: 6.6 – 15.5]) and stroke (15.7 days longer stay: 95% CI: 6.5 – 25.0).

HZ-associated mortality and case-fatality rate

During 1996–2012, overall 343 (annual range 8–27) deaths with HZ-associated ICD-codes listed as underlying (41%) or contributing cause of death (59%) were reported in Norway. All, except two deaths, occurred in persons aged ≥50 years. Considering all deaths with HZ-associated codes, a mortality rate as underlying cause of death was estimated at 0.18 deaths per 100,000 population per year (overall 0.43 per 100,000) with the highest mortality in adults aged ≥80 years, also in females (Table 3).

Table 3 Crude and age- and sex-adjusted mortality rates associated with herpes zoster diagnosis (ICD-10) as underlying or contributing cause of death, Norway, 1996–2012.

	Crude HZ mortality per 100,000			Standardized HZ mortality per 100,000		
Age group (years)	Total	HZ as underlying cause of death	HZ as contributing cause of death	Total	HZ as underlying cause of death	HZ as contributing cause of death
<50	0.00	0.00	0.00	0.00	0.00	0.00
50–59	0.08	0.01	0.07	0.01	0.00	0.01
60–69	0.19	0.04	0.14	0.02	0.00	0.01
70–79	0.71	0.27	0.44	0.04	0.01	0.02
≥80	8.13	3.48	4.65	0.16	0.07	0.09
Sex						
Female	0.56	0.26	0.30	0.28	0.13	0.15
Male	0.31	0.10	0.21	0.15	0.05	0.10

The case-fatality-rate (CFR) among hospitalized zoster patients was 1.04% for in-hospital deaths (annual range 0.75% –1.45%) and 3.01% for combined in-hospital deaths and deaths occurring within 30 days post-discharge.

Discussion

This is the first study to estimate a pre-vaccine burden of medically attended HZ in Norway. The disease results in 11,181 patients being treated in primary care, and 1,218 patients admitted to hospitals each year. The majority of cases and highest incidences occur in adults aged ≥50 years, in line with reports from other European countries [8, 15, 16, 25], which may be related to a decline in VZV-specific cell-mediated immunity with age [10, 26]. We also observed a higher disease incidence in women, even though cell-mediated immunity is not believed to differ by sex. It is possible that lifestyle habits, psychosocial factors and healthcare seeking behavior unique to women play a role [26].

Despite differences in methodology and data used, our incidence estimates were within the range of reported rates in primary healthcare [8] and hospitals from other developed countries [16, 27-31]. Although an overall hospitalization rate in Norway was higher (24 per 100,000), the rate of inpatient admissions (10.2 per 100,000) was similar to those reported by Denmark and Sweden [15, 16]. Moreover, 73% of hospitalized Norwegian patients had HZ listed as their primary discharge diagnosis, similarly to a 72% proportion reported by Denmark [15].

In our study, HZ patients spent on average of 7.1 days in the hospital, similarly to the findings in Denmark and Sweden [15, 16]. However, the hospital stay with a HZ-related diagnosis was longer (9.2 days) in England despite a comparable age distribution [14]. Differences in study methods and hospital discharge practices may explain these variations in the length of hospitalization.

None of the patients in our study had records of HZ immunization. This is not surprising, given a low number of HZ vaccine doses distributed since its licensure in Norway (approximately 200 doses during 2006–2014, unpublished data). It is however possible that some patients were vaccinated but not reported to the national immunization registry, which only recently started to record immunizations with vaccines not included in the national immunization program [32].

The estimated HZ-associated mortality rate in our study was 0.18 per 100,000 population, whereas the case-fatality-rate among hospitalized patients was 1.04% when counting only in-hospital deaths. Both estimates fall within the ranges reported from other European countries [14-16, 33]. However, our mortality estimates should be interpreted with caution. Despite a robust data coverage and completeness in the Norwegian Cause of Death Registry, reporting of unspecific codes for the underlying cause of death remains high [34]. Moreover, the reported diagnosis on the death certificate may not always reflect the true underlying cause of death [34]. It is also debatable if deaths where HZ is listed as contributing cause of death can be indeed attributable to the disease.

To assess the burden of HZ in primary healthcare, we used administrative claims by primary care physicians. As a primary healthcare providers in Norway are reimbursed through this system, we assume a high data completeness. Nonetheless, not all HZ patients would be captured in our data, as some may be assigned non-specific diagnoses such as “localized skin rash”. It is also possible that some patients with mild HZ do not seek medical help either because they feel well enough to work or use their right to a short-term sick leave, which in Norway can be granted without providing a certificate from a healthcare practitioner.

Another limitation of the registry data is the potential misclassification of diagnoses, which were not validated against clinical records in our study. The reported completeness of individual records in the Norwegian Patient Registry has been estimated to vary between 35% and 98% across different regions and for different diagnoses [35]. There might be some errors due to varying coding practices among clinicians, leading to underestimation of the proportion of HZ diagnoses in the registry. For this reason, we included all patients with HZ listed in any diagnostic field. There is also a risk of overestimating the incidence of HZ when using hospital data because the diagnosis from a previous hospital stay may erroneously be carried over to subsequent unrelated hospital stays.

Several patients in our study, in particular those with multiple healthcare encounters, had both varicella and herpes zoster diagnoses, which partly may be explained by coding errors. However, clinically, it might sometimes be difficult to distinguish between primary VZV infection (varicella) and reactivation of the virus (herpes zoster) or recurrent disease [36]. We found that a small proportion (3.3%) of HZ-associated diagnoses assigned in the hospital were in children under 10 years of age. It was impossible to verify if these children had a true HZ disease or if these were misclassified varicella cases. Although pediatric HZ is not common [8], the risk of developing HZ within the next four years is higher for children who acquire varicella in early childhood [37]. It is important to document the proportion of pediatric HZ cases while varicella vaccination is not universally used in Norway as recent studies suggest a decline in pediatric HZ rates after the introduction of varicella vaccination program [38].

We also assessed the role of VZV among patients with viral infections of the central nervous system (CNS). Almost 3% of HZ patients in hospital settings were diagnosed with HZ encephalitis, and this is consistent with findings from Denmark and Sweden [15, 16]. According to our previous study, VZV was the third most frequent virus among Norwegian patients with viral CNS infections, which were mostly detected in adults ≥50 years of age [39]. However, only 79.9% of these patients were assigned diagnoses involving CNS in the hospital registry, indicating that there might be more patients with neurological HZ complications than coded in the registry [39].

We found that 25% of hospitalized HZ patients had severe to very severe comorbidities, resulting in longer hospital stays than other HZ patients. This proportion might be larger as the diagnostic groups presented in our study represent only a handful of diagnostic codes. It is possible that more complex comorbidities could be missed, including complications caused by VZV reactivation, which may increase the HZ burden substantially. Although, the majority of hospitalized HZ patients in our study could be classified as immunocompetent and thus could be protected by zoster vaccination.

A recent mathematical modelling study projected some reduction in the HZ incidence after the introduction of a vaccination program with a live zoster vaccine in Norway [40]. A program using a new recombinant zoster vaccine was predicted to result in a larger reduction, depending on different assumptions for vaccine efficacy and the duration of vaccine-derived protection [40]. Further research should assess the cost-effectiveness of different vaccination strategies in Norway to inform policy decision on the use of zoster vaccination.

Conclusions

In Norway, HZ causes a substantial burden in the healthcare sector, with the majority of cases occurring in primary healthcare and among immunocompetent adults older than 50 years of age. Immunization against HZ may be a viable strategy to reduce the associated burden.

Abbreviations

CCI – the Charlson comorbidity index

CDR – the Cause of Death Registry

CFR – case-fatality-rate

CI – confidence interval

CNS – the central nervous system

GP – General Practitioner

HIV/AIDS – Human immunodeficiency virus infection and acquired immune deficiency syndrome

HZ – herpes zoster

ICD-10 – the International Statistical Classification of Diseases and Related Health Problems, 10th revision

IQR – interquartile range

NPR – the Norwegian Patient Registry

p – p-value

PHN – postherpetic neuralgia

SD – standard deviation

US – the United States of America

VZV – Varicella zoster virus

Disclaimer

Data from the Norwegian Patient Registry has been used in this publication. The interpretation and reporting of these data are the sole responsibility of the authors, and no endorsement by the Norwegian Patient Registry is intended nor should be inferred.

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Conflict of interests

The authors declare no conflict of interests.

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Figure 1 Annual rates in primary healthcare (first contact) for herpes zoster per 100,000 population by age and sex, Norway 2008–2014.

Figure 2 Annual rates in hospital care (first contact) for herpes zoster per 100,000 population by age and sex, Norway 2008–2014.

Figure 3 Annual contact rate (first contact) in hospital care of herpes zoster per 100,000 population by age and hospital care level, Norway, 2008-2014.

Table 1 Number and proportion of patients at first contact with hospital with herpes zoster listed at any diagnosis, as primary or as secondary diagnosis by selected diagnostic groups; and stay in hospital in days of hospitalized patients (coefficient, 95%CI)(n=3,758), Norway, 2008-2014.

*Coefficient represents the length of hospital stay (days) adjusted for age and sex, estimated using a multivariable linear regression.

	Herpes zoster at any diagnostic field		Herpes zoster as primary diagnosis		Herpes zoster as secondary diagnosis		Difference of length of hospital stay (days)			
Diagnostic group	Number of patients	%	Number of patients	%	Number of patients	%	Coefficient *	95%CI		p-value
HERPES ZOSTER patients	8529	100	6256	100	2273	100	ref	ref	ref	ref
UNCOMPLICATED HERPES ZOSTER (B029 and B02)	4525	53.1	3072	49.1	1453	63.9	-1.3	-1.8	-0.7	<0.000
Herpes zoster (B02)	27	0.3	23	0.4	4	0.18	na	na	na	na
Uncomplicated herpes zoster (B029)	4498	52.7	3049	48.7	1449	63.8	-1.3	-1.8	-0.7	<0.000
COMPLICATED HERPES ZOSTER	4004	46.9	3184	50.9	820	36.1	1.3	0.7	1.8	<0.001
HZ encephalitis, HZ meningoencephalitis (B020)	243	2.9	187	3.0	56	2.5	6.1	1.0	11.2	0.020
HZ meningitis (B021)	61	0.7	54	0.9	7	0.3	0.2	-1.9	2.3	0.851
Postherpetic neuralgia (B022)	790	9.3	573	9.2	217	9.6	0.7	-0.2	1.5	0.112
HZ in eye (B023)	2219	26.0	1914	30.6	305	13.4	-0.2	-1.1	0.7	0.682
HZ disseminated (B027)	120	1.4	86	1.4	34	1.5	4.0	1.9	6.0	<0.001
HZ with other complications (B028)	663	7.8	450	7.2	213	9.4	1.2	0.3	2.1	0.006
COMORBIDITIES AND OTHER CONDITIONS**	1434	16.8	634	10.1	809	35.6	3.4	2.8	4.0	<0.001
IMMUNODEFICIENCY	715	8.4	331	5.3	384	16.9	3.3	2.5	4.0	<0.001
Malignancies affecting immune system	466	5.5	211	3.4	255	11.2	2.9	2.1	3.8	<0.001
HIV/AIDS	54	0.6	18	0.3	36	1.6	0.4	-2.9	3.7	0.821
Organ transplantation	131	1.5	81	1.3	50	2.2	3.3	1.7	4.8	<0.001
Conditions affecting immune system	161	1.9	59	0.9	102	4.5	5.2	3.8	6.7	<0.001
Primary immunodeficiency	38	0.5	18	0.3	20	0.9	8.9	5.7	12.0	<0.001
AUTOIMMUNE DISEASES	432	5.1	209	3.3	223	9.8	1.7	0.7	2.7	0.001
Hematological system	8	0.1	4	0.06	4	0.2	1.8	-4.2	7.9	0.55
Endocrine system	3	0.04	3	0.05	0	0	2.3	-7.2	11.8	0.631
Central nervous / neuromuscular system	19	0.2	12	0.2	7	0.3	-1.2	-5.0	2.7	0.551

Gastrointestinal / hepatobiliary system	52	0.6	28	0.5	24	1.1	1.3	-1.2	3.8	0.295
Skin	64	0.8	25	0.4	39	1.7	3.7	0.9	6.6	0.009
Rheumatoid arthritis	102	1.2	49	0.8	53	2.3	1.0	-0.8	2.9	0.277
Juvenile rheumatoid arthritis	3	0.04	3	0.05	0	0	-2.6	-13.6	8.5	0.648
Ankylosing spondylitis	17	0.2	5	0.08	12	0.5	3.1	-2.1	8.4	0.244
Systemic lupus erythematosus	29	0.3	16	0.3	13	0.6	2.2	-1.7	6.0	0.265
Mixed connective tissue diseases	1	0.01	1	0.02	0	0	-3.3	-12.8	6.3	0.503
Sjögren´s syndrome	14	0.2	4	0.06	10	0.4	-0.9	-8.7	6.8	0.813
Sarcoidosis	12	0.2	4	0.06	8	0.4	8.9	3.1	14.6	0.002
Vascular diseases	64	0.8	31	0.5	33	1.5	0.8	-1.5	3.2	0.487
Ocular diseases	56	0.7	33	0.5	23	1.0	1.0	-4.6	6.5	0.736
Pulmonary system	12	0.1	5	0.08	7	0.3	2.2	-3.1	7.5	0.415
Diabetes	321	3.8	156	2.5	165	7.3	2.3	1.3	3.3	<0.001
Kidney disorders	380	4.4	160	2.6	220	9.7	3.3	2.3	4.2	<0.001
Dialysis	29	0.3	10	0.2	19	0.8	8.8	5.7	11.7	<0.001
Pregnancy	10	0.1	4	0.06	6	0.3	-3.2	-9.0	2.6	0.279
Neurological conditions	321	3.8	182	2.9	139	6.1	1.6	0.6	2.5	0.002
Other malignancies	453	5.3	154	2.5	299	13.2	3.0	2.1	3.9	<0.001
Liver disorders	18	0.2	5	0.08	13	0.6	3.6	-0.3	7.4	0.067
Stroke	162	1.9	62	1.0	100	4.4	3.9	2.5	5.3	<0.001

*Coefficients in the table are estimates of differences in length of hospital stay in days for moderate, severe, and very severe co-morbidities which were estimated using multivariable linear regression and adjusted for age and sex.

Table 2 The proportion (%) of comorbidities among hospital patients with HZ-related ICD-10 codes on discharge diagnoses according to the Charlson comorbidity index by age (years), severity, and difference in the length of hospital stay (days), Norway, 2008–2014.
**The category includes ICD-10 codes registered on hospital discharge diagnoses for patients with HZ diagnosis.

Age group (years)	Total		0–19y		20–49y		50–59y		60–69y		70–79y		80y+					
Comorbidity Severity	No. of patients	%	No. of patients	%	No. of patients	%	No. of patients	%	No. of patients	%	No. of patients	%	No. of patients	%	Coeff.*	95% CI		p-value
None	6373	74.7	440	5.2	1260	14.8	849	10.0	1174	13.8	1263	14.8	1387	16.3	Ref	Ref	Ref	Ref
Moderate	878	10.3	10	0.1	31	0.4	54	0.6	122	1.4	252	3.0	409	4.8	2.5	1.8	3.3	<0.001
Severe	1062	12.5	90	1.1	69	0.8	126	1.5	224	2.6	244	2.9	309	3.6	4.3	3.6	5.0	<0.001
Very severe	216	2.5	9	0.1	35	0.4	36	0.4	66	0.8	41	0.5	29	0.3	4.8	3.5	6.1	<0.001
Total	8529	100	549	6.4	1395	16.4	1065	12.5	1586	18.6	1800	21.1	2134	25.0				

Figure 1 Annual rates in primary healthcare (first contact) for herpes zoster per 100,000 population by age and sex, Norway 2008–2014

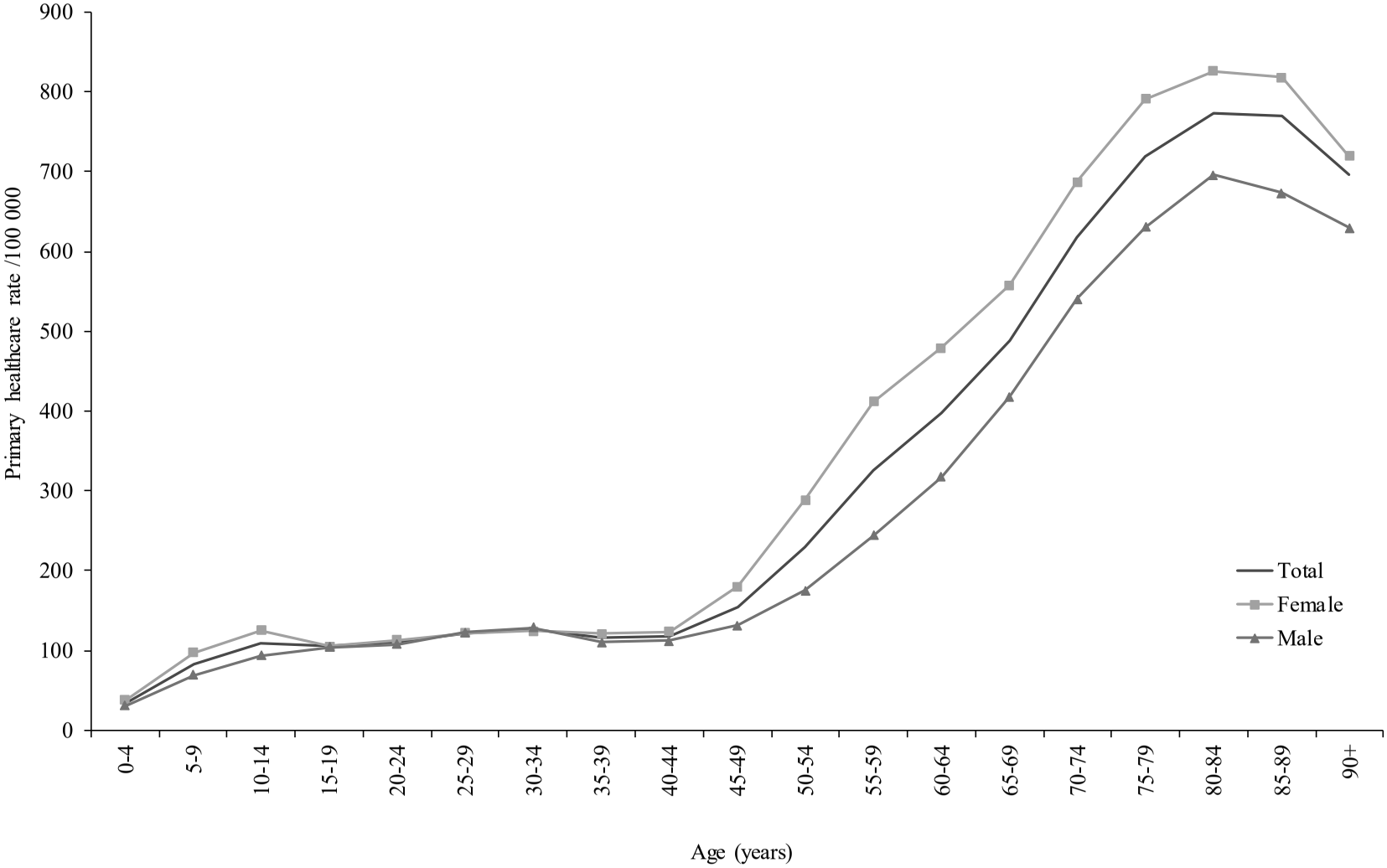


Figure 2. Annual rates in hospital care (first contact) for herpes zoster per 100,000 population by age and sex, Norway 2008–2014

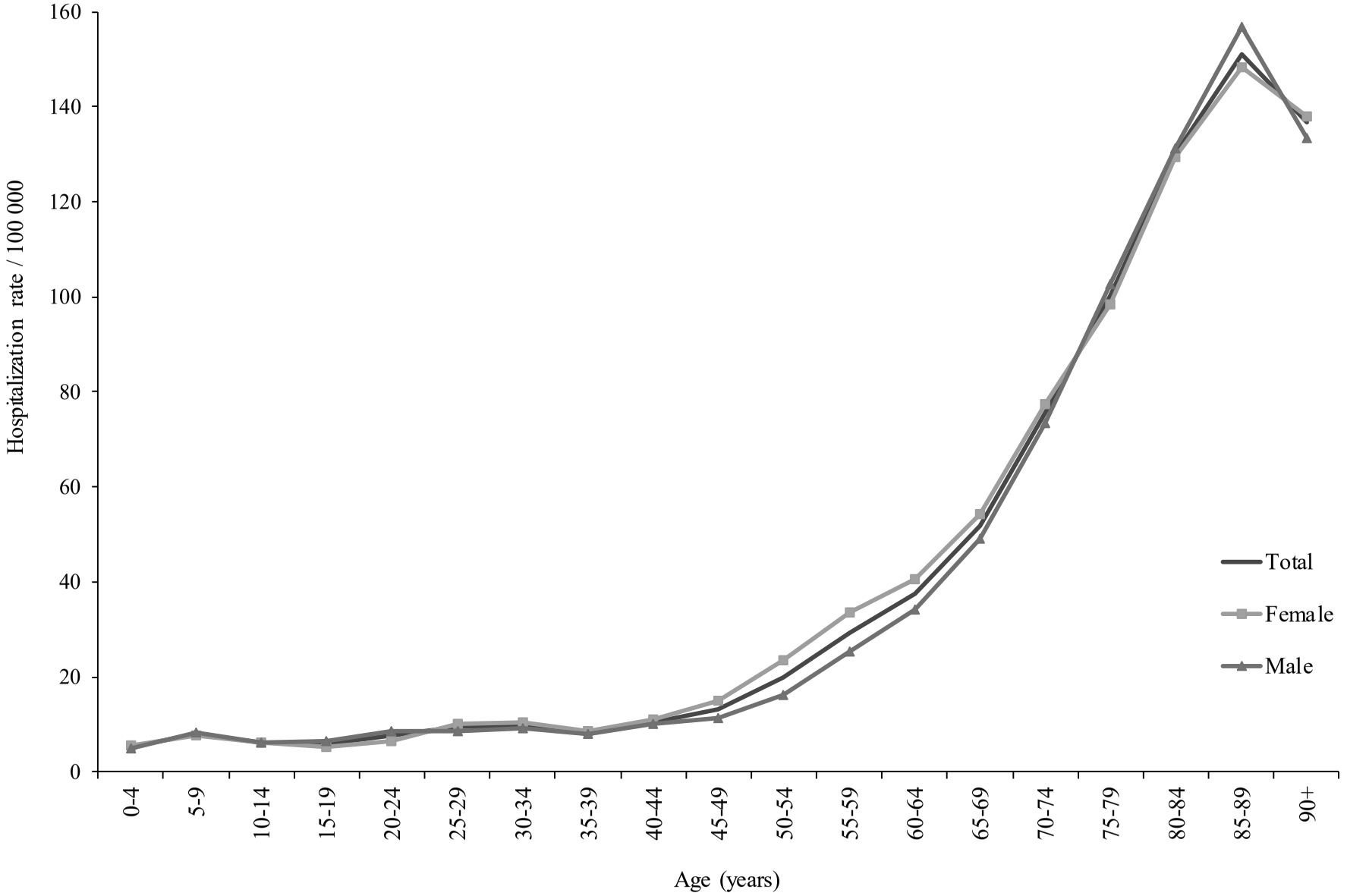
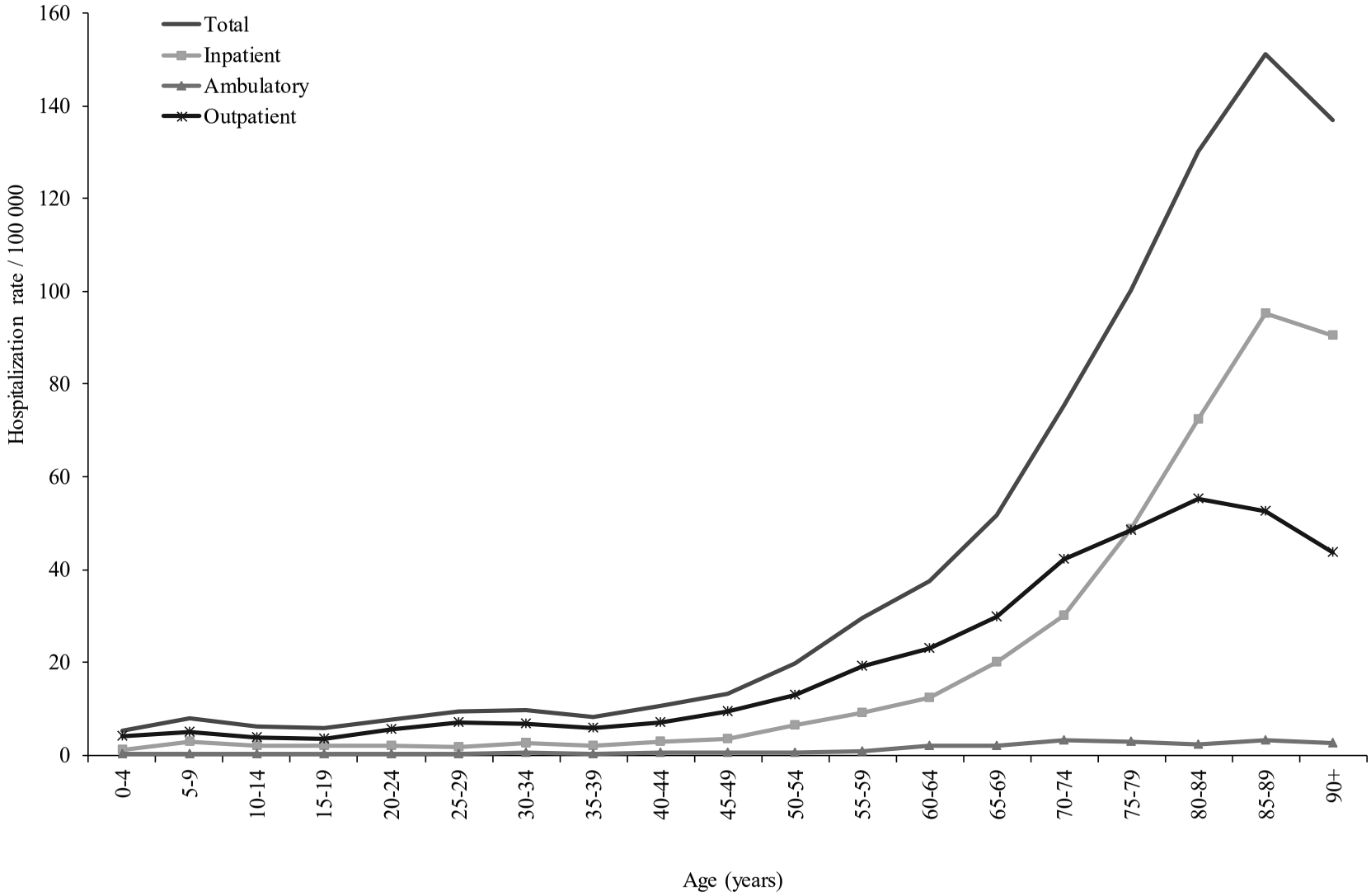


Figure 3. Annual contact rate (first contact) in hospital care of herpes zoster per 100,000 population by age and hospital care level, Norway, 2008-2014



Supplemental file 1. Data sources and type of data extracted for herpes zoster (HZ).

Data type	Data source	Period of data extraction	Extraction criteria	Extracted variables
Vaccinations against herpes zoster	National Immunization Registry	2003–2012	All registered herpes zoster vaccinations	Patient ID, age, sex, type of vaccine, a date of vaccination for each received dose
Primary healthcare contacts	Norwegian Health Economics Administration	2008–2014	All registered contacts as coded by herpes zoster code S70 by the International Classification for Primary Care, Second edition (ICPC-2)	Patient ID, age, sex, information on care provider (General Practitioner, emergency clinic), and type of diagnosis (primary, secondary)
Hospital contacts	Norwegian Patient Registry	2008–2014	All registered contacts as coded by varicella codes B02—B029 by the International Classification of Diseases - tenth edition (ICD-10)	Patient ID, age, sex, date of admission and discharge, type of hospital care (inpatient, outpatient, and ambulatory care)*, outcome of hospital stay, accompanying non-herpes zoster diagnoses coded by the ICD-10 codes.
Deaths	Cause of Death Registry	1996–2012	All registered deaths with herpes zoster codes B02—B029 by the International Classification of Diseases - tenth edition (ICD-10)	Anonymous data with age, sex, date of death and accompanying non-herpes zoster diagnoses
Viral infections of CNS	Norwegian Surveillance System for Communicable Diseases	1997–2012	All reported viral infections of CNS, including those caused by varicella zoster virus.	Patient ID, age, sex, sample type (e.g. cerebrospinal fluid), date of sampling, laboratory method (polymerase chain reaction (PCR), culture), etiologic agent, the name of the laboratory where the sample was tested, and type of report (clinician and/or laboratory-based report).

*inpatient – is a patient who stayed at the hospital more than 5 hours; outpatient – a patient who stayed at the hospital less than 5 hours; ambulatory care – a care that requires more resources than in outpatient, but patient does not overnight in the hospital.

Supplemental file 2. Diagnostic groups and associated ICD-10 codes registered on hospital discharge diagnoses for patients with HZ diagnosis.

Diagnostic group	ICD-10code
UNCOMPLICATED HERPES ZOSTER	B029, B02
Herpes zoster (B02)	B02 (if in combination with complicated HZ, the case is included in complicated HZ only)
Uncomplicated herpes zoster; Herpes zoster other (B029)	B029 (if in combination with complicated HZ, the case is included in complicated HZ only)
COMPLICATED HERPES ZOSTER	B020, B021, B022, B023, B027, B028
HZ encephalitis, HZ meningoencephalitis (B020)	B020
HZ meningitis (B021)	B021
Postherpetic neuralgia (B022)	B022
HZ in eye (B023)	B023
HZ disseminated (B027)	B027
HZ with other complications (B028)	B028
COMORBIDITIES AND OTHER CONDITIONS*	
IMMUNODEFICIENCY	
Malignancies affecting immune system	C81-C85.9, C88-C88.9, C90-C96.9
HIV/AIDS	B20-B24.9, Z21, R75, F024
Organ transplantation	Z94-Z94.9, Y830, N165, T824, T861, T862, T863, T864
AUTOIMMUNE DISEASES	
Hematological system	D590, D591, D693
Endocrine system	E050, E063, E271, E10
Central nervous/ neuromuscular system	G35, G700
Gastrointestinal/ hepatobiliary system	D510, K50-K51.9, K743, K900, M074, M075, K523

Skin	L20-L20.9, L100, L101, L102, L104L120, L129, L130, L40-L40.9, L80, L88, L93-L93.2, M070, M071, M072, M073, O264
Rheumatoid arthritis	M05-M06.9, I528
Juvenile rheumatoid arthritis	M08-M08.9
Ankylosing spondylitis	M45, H221
Systemic lupus erythematosus	M32-M33.9, G058, L931, L932
Systemic scleroderma	M34-M34.9
Mixed connective tissue disease	M351
Sjögren´s syndrome	M350
Sarcoidosis	D86-D86.9, G532, M633
Vascular diseases	D690, I776, L95-L95.9, M30-M31.9, M353, M356
Ocular diseases	H200, H201
Pulmonary system	J841
Diabetes	E10, E11, E12, E13, E14, H360, N083, O244, O249
Kidney disorders	N00-N08, N10-N16, N17-N19, N20-N23, N25-N29.8
Dialysis	Z49-Z49.2, Z992,T824, Y602, Y612, Y622, Y841
Pregnancy	Z321, Z33, Z34-Z37.9, Z390, O20-O29.9
Neurological conditions	F050, F058, F059, F060, G040, G048, G049, G458, G459, G500, G501, G530, R202, R260, R261, R560
Other malignancies	C00-C75, C97, Z08-Z08.9, Z511, Z85-Z85.9
Liver disorders	K70-K77
Stroke	I60-I69

*The category includes ICD-10 codes registered on hospital discharge diagnoses for patients with HZ diagnosis.

IV

PLOS ONE

RESEARCH ARTICLE

Immunity to varicella zoster virus among pregnant women in the Norwegian Mother and Child Cohort Study

Grazina Mirinaviciute[1]*, Regine Barlinn[2], Susanne Gjeruldsen Dudman[2,3], Elmira Flem[1]

1 Department of Infectious Diseases Epidemiology and Modeling, Infection Control and Environmental Health, Norwegian Institute of Public Health, Oslo, Norway, **2** Department of Microbiology, Oslo University Hospital, Oslo, Norway, **3** Institute of Clinical Medicine, University of Oslo, Oslo, Norway

* grazina.mirinaviciute@gmail.com

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Data Availability Statement: Data cannot be made publicly available because it contains sensitive participant information. Additionally, participants did not give consent for data to be made publicly available in a repository. Interested researchers can request access to the relevant datasets via request to: datatilgang@fhi.no. The request will require approval from an ethics committee and formal contract with Norwegian Mother and Child Cohort study (MoBa).

Abstract

Introduction

Infection with varicella zoster virus (VZV) in pregnancy may lead to serious outcomes both for the mother and the newborn. Targeted screening and vaccination of non-immune women during reproductive age could prevent varicella infection in pregnancy. Currently, no universal varicella screening of pregnant women is implemented in Norway, but serological testing in pregnancy is recommended in particular situations. We examined seroprevalence of VZV in a national pregnancy cohort in order to help assess a need for VZV screening of women during reproductive age.

Methods

We determined the susceptibility to VZV and the reliability of self-reported history of VZV infection in the Norwegian obstetric population by using a random sample of 1,184 pregnant women from the Norwegian Mother and Child Cohort study (MoBa). The MoBa study included approximately 95,200 pregnant women in Norway between 1998 and 2009. Blood samples taken at gestational week 17–18 were analysed using a commercial enzyme immunoassay for specific IgG antibodies to Varicella-Zoster virus. Second sample taken at birth was tested if the first sample result was negative or equivocal.

Results

Of the 1,184 pregnant women, 98.6% (n = 1,167) were seropositive, 0.83% (n = 10) remained seronegative, and four women (0.34%) seroconverted during their pregnancy. No significant associations were found between serological status and women's age at birth, gestational age, women's country of birth and year of child's birth. One woman reported prior history of varicella, whereas 143 (12.1%) women reported a household exposure to childhood diseases with fever and rash, of which 25 reported exposure to varicella, of which all were seropositive.

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Competing interests: The authors have declared that no competing interests exist.

Conclusions

The findings support antenatal screening recommendations in Norway advising testing for VZV in pregnant women with unknown immunity to VZV. Further studies are however needed to better identify target groups for screening and vaccination.

Introduction

Varicella infection in pregnancy, especially during the first 20 weeks, may cause serious complications in pregnancy including spontaneous abortion, premature delivery, and stillbirth [1–3]. Various studies estimate the risk of primary maternal VZV infection to be 0.5–3 cases per 1,000 pregnancies [1, 4]. The most frequent maternal complication is VZV-associated pneumonia which occurs in 10%–20% of pregnant women infected with varicella, 40% of these patients may require mechanical ventilation [3, 5]. In offspring, varicella infection manifests as neonatal varicella (infection within the first 10 days of life) [6] or congenital varicella syndrome (CVS) [1, 7, 8]. CVS is a severe condition affecting about 2%, it affects multiple organs causing limb hypoplasia, skin lesions, neurological abnormalities, and eye damage, and has an estimated mortality of 30% [3, 7, 9]. The risk of severe neonatal varicella is from 20% to 50% if mother acquired infection five days antepartum to two days postpartum [10], and the estimated risk of CVS is at 0.8 per 100,000 live births [11]. CVS usually does not occur after herpes zoster (HZ) during pregnancy [3].

VZV-associated immunity in pregnancy can be detected through antenatal screening whereas the infection can be prevented by vaccinating susceptible women before conception. Antenatal varicella screening combined with post-partum vaccination may be a cost-effective strategy to prevent occurrence of VZV in the next pregnancy and reduce the risk of complications [12]. Information about VZV-associated immunity can be obtained by serological testing or through a self-reported history of varicella or herpes zoster disease. Currently, pregnant women in Norway are offered universal screening for hepatitis B, human immunodeficiency virus, and syphilis; varicella screening is recommended only if a woman with no verified varicella infection history has been exposed during pregnancy[13].

In Norway, non-immune pregnant women exposed to varicella during pregnancy are offered varicella zoster-immunoglobulin (VZIG) within 96 hours of exposure, mainly to protect the woman from a severe course of infection and complications [13]. In addition, infants born to seronegative women who developed varicella close to delivery, especially four days before and two days after the delivery, and preterm infants exposed to varicella, are also recommended to receive VZIG due to a high risk of severe disease [13]. VZIG in Norway can be obtained from three manufacturers: Varicellon P (CSL Behring, King of Prussia, Pennsylvania, USA), Varizig (Emergent Biosolutions, Rockville, Maryland, USA) and Varitec CP (Biotest Pharma GmbH, Dreieich, HE, Germany).

Susceptibility to VZV varies by geographic regions and women born in tropical and subtropical regions have lower rates of childhood exposure and immunity to varicella [14–17]. Such women may remain susceptible during reproductive age and thus may have a higher probability of being infected with varicella during pregnancy. This may lead to increased risk of disease and complications in this particular group.

Previously, no population-based study has been conducted in Norway to assess the prevalence of VZV-associated infections in pregnancy. A single study assessed the VZV-associated immunity among pregnant women of Pakistani origin in Norway, reporting that 7% were

seronegative [16]. However, the study size (n = 206) and its design does not allow generalization of the findings to the entire Norwegian population. Of approximately 58,500 Norwegian babies born per year, about 26% had mothers with a foreign background, of which mostly were from Asia and Africa (2011–2018 data)[18]. Additionally, a recent national study reported that 25 pregnant women with varicella-associated diagnoses and ten patients with CVS were hospitalized during 2008–2014 and 46 varicella related deaths were reported (26 reported as underlying condition) during 1996–2012 [19]. Moreover, a recent seroepidemiological study of Norwegian population demonstrated that only 88.6% of Norwegian women of reproductive age (15–49 years), regardless of their pregnancy status, were immune against varicella, whereas 5.3% were seronegative [20]. In comparison, a higher seroprevalence of 96.2% to 98.5% among Finnish pregnant women was found [21, 22].

In Norway, no universal varicella or herpes zoster vaccination programme is currently implemented. Several live varicella vaccines with a good safety profile are available on the Norwegian market. These vaccines have an estimated effectiveness of 70%–90% for one dose and 98% for two doses [23]. Varicella vaccination can be initiated from 9 months of age, and is recommended in Norway for non-immune adolescents and adults, including women of reproductive age, and persons in defined risk groups [24]. Varicella vaccination is contraindicated during pregnancy, but vaccine can be administered after delivery to prevent infection during the subsequent pregnancies.

The objectives of our study were to 1) determine VZV seroprevalence and seroconversion rates in a national cohort of pregnant women, 2) to evaluate association between a self-reported history of VZV infection and VZV immunity status, and 3) to explore associations between serological status and mothers age, gestational age, year of child's birth and women's country of birth. This is in order to assess a need for antenatal varicella screening and inform policy decision on varicella immunization of women of reproductive age.

Methods

Ethics statement

The current study was approved by The Regional Committee for Medical Research Ethics in South-Eastern Norway (2013/2071/REK sør-øst B) and relies on maternal and paternal consent. All data and samples were fully anonymized before the study group accessed them.

The establishment and data collection in MoBa was previously based on a permission from the Norwegian Data protection agency and approval from The Regional Committee for Medical Research Ethics and it is in compliance with regulations in the Norwegian Health Registry Act.

Study design

This was a cross-sectional seroprevalence study of pregnant women in Norway nested within the Norwegian Mother and Child Cohort (MoBa) study. The MoBa study is an ongoing population-based pregnancy cohort study conducted by the Norwegian Institute of Public Health. Study participants were recruited from all over Norway from 1999–2008. The women consented to participation in 41% of the pregnancies. The cohort now includes 114,500 children, 95,200 mothers and 75,200 fathers [25, 26]. The participants completed several questionnaires administered at different time points during pregnancy and after delivery. In addition, blood samples were obtained from both parents during pregnancy and from mothers and children (umbilical cord) at birth. Details about the MoBa cohort are provided elsewhere [26].

The current study is based on the version 10 of the quality-assured study files released for research on October 17, 2018. The enrolment of study participants occurred during 2001–

2009. In the study, we used blood samples paired with data from selected MoBa questionnaires coupled with information from the Norwegian Medical Birth Registry (MBR). We obtained paired serum samples from pregnant women. The samples were collected at pregnancy week 17–18 and during delivery. Testing was performed in 2017–2018.

During the course of the MoBa study, the participants filled out seven questionnaires administered at pregnancy weeks 17 and 30, and when the child was 6 months, 18months, 36 months, 5 and 7 years of age. Details about questionnaires are available elsewhere [27].

For our study, we obtained data from four questionnaires administered at pregnancy week 17 and 30, at delivery, and when a child turned 6 months of age. The questionnaires included information about self-reported exposure to varicella, information on the number of children in a household, daycare attendance, and disease history of the mother and a child. In addition, questionnaire data were coupled with information from MBR about prenatal health, pregnancy complications, birth outcomes, and neonatal morbidity. The study has received ethical approval and relies on maternal and paternal consent.

Study sample

The study sample included 1,350 mother-infant pairs, assuming 2% pregnant women being seronegative for VZV based on the literature [28]. The sample size was expected to provide results with confidence intervals' total widths of about 1.5% [29]. The 1,350 women were randomly selected to form a control group in a separate case-control study nested within the MoBa cohort [30, 31]. This control group was included in the above mentioned study where their plasma samples were tested for cytomegalovirus, and parvovirus B19. Of these, 1,184 women had sufficient sample volume to allow examination of IgG antibodies for VZV, and thus were included in our study (Fig 1).

Serological examination

Plasma samples were stored at -20˚C until testing was performed at the Norwegian Institute of Public Health. The samples were analysed using a commercial enzyme immunoassay for specific IgG antibodies to Varicella-Zoster virus (VZV) Enzygnost, Anti-VZV/IgG (Siemens, Healthcare Diagnostics AS, Erlangen, Germany), following manufacturer's instructions. Enzygnost has shown a sensitivity of 99.3% and specificity of 100%, according to a manufacturer. IgG cut-off levels were set in accordance with manufacturer's recommendation. Equivocal sample were retested in duplicate. If a sample collected at week 17–18 was negative, the second maternal sample taken at delivery was examined for the presence of IgG. Detection of IgG in the sample taken at delivery indicated seroconversion, suggesting that VZV infection was acquired during pregnancy.

Data analysis

We used descriptive analysis and logistic regression analyses to compare the proportions of seropositive and seronegative, as well as seroconverted women. Exposure variables were mother's age, child's gestational age, year of child's birth and mother's country of birth. Categorical data were analysed using Pearson's chi-square test and Fisher's exact test. One-way analysis of variance (ANOVA) was used for continuous variables.

We used stratified analysis to explore associations between mean values of optical density (of VZV IgG antibodies), number of children in the household and day care attendance. Additionally, we estimated Spearman's rank correlation coefficient (r_S).

Data were analysed with the statistical software STATA 14 (StataCorp LP).

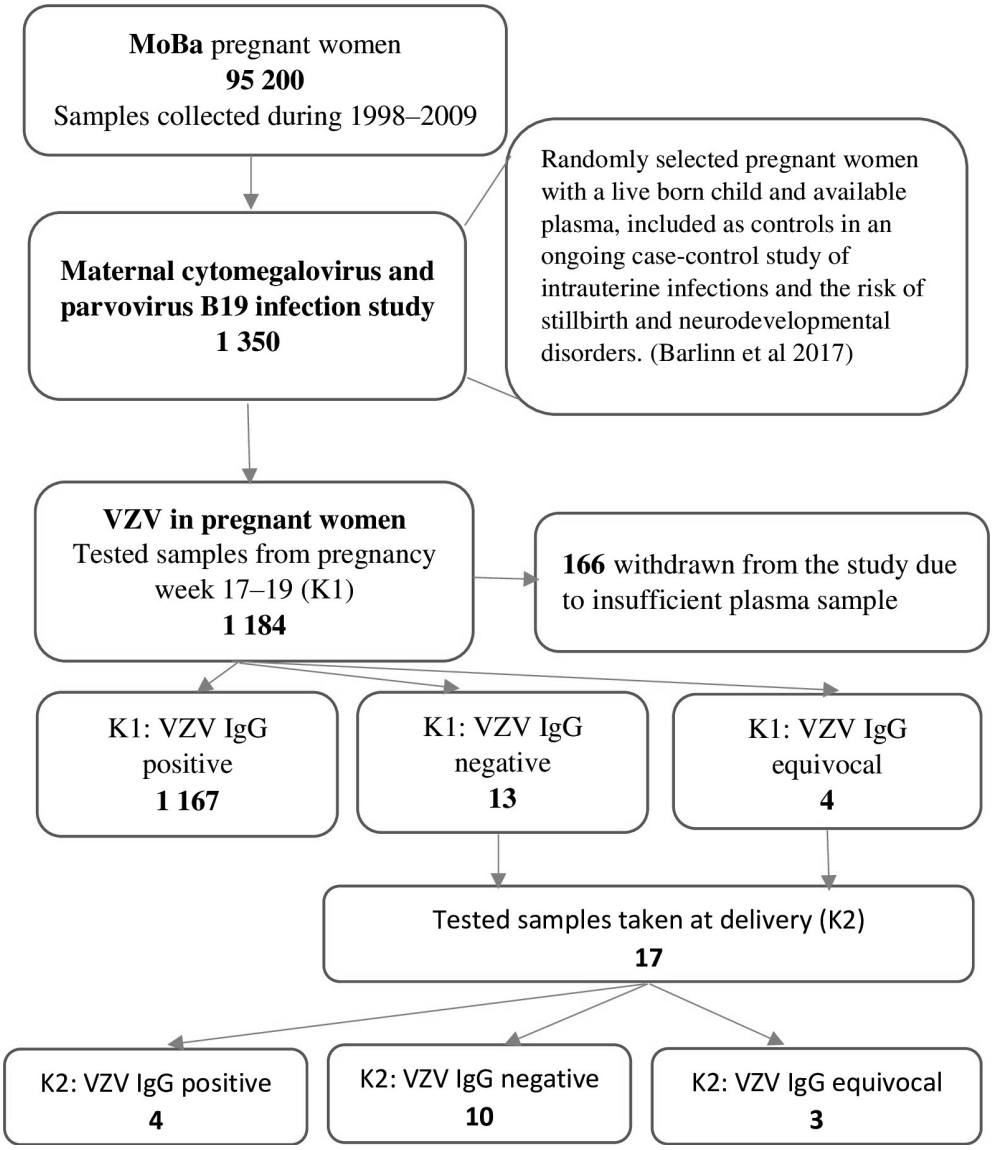

Fig 1. Selection of the study samples and study results by sample: First sample taken in pregnancy week 17–19 (K1), and second sample taken at birth (K2), Norway, 2001–2009.

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Results

Seroprevalence

Of the 1,184 tested women, 98.58% (n = 1,167) were VZV-IgG positive, 14 VZV-IgG negative and 3 VZ-IgG equivocal in the first sample taken at pregnancy week 17–18. After second testing of blood samples taken at delivery, 0.83% (n = 10) were still seronegative, while 0.34% (n = 4) seroconverted during pregnancy, and three (0.25%) women had an equivocal test results. Overall, 14 (1.2%) women were considered susceptible to varicella. The mean age was 30 years (SD: 4.381, range: 18–45 years) and all women gave birth to one child per birth with 91% of babies born between gestational weeks 38–42. The majority of women (92%)were born

in Norway. Among women born abroad, only one seroconverted and another one tested seronegative in both samples. Both women indicated a different mother tongue than Norwegian.

History of varicella and herpes zoster

Among study participants, one woman reported a history of varicella prior to pregnancy. No women reported having had varicella or herpes zoster during pregnancy and no cases of congenital varicella syndrome were registered among study participants. Overall, 143 (12.1%) women reported having a household exposure to different childhood diseases during their pregnancies. Of these, 25 women indicated exposure to varicella in the beginning of their pregnancies, 23 of which were living together with children aged <6 years at the time. All were VZV-seropositive. In addition, almost half (533) of the women reported having children aged 0–18 years.

Birth defects among infants born to study participants were reported for 44 (3.7%) woman, all of them were VZV-seropositive. None reported being vaccinated against varicella.

Statistical analysis

Women who seroconverted during pregnancy (n = 4) and seropositive women did not differ by their country of birth, age at delivery, child's gestational age, and child's year of birth. Further, there were no differences in these parameters between seropositive and seronegative women.

We did not find significant associations between the VZV susceptibility status (seropositive vs seronegative and seropositive vs seroconverted) and mother's age, year of child's birth, and mother's country of birth. The Spearman's rank correlation coefficient was insignificant and showed no linear relationship between optical density and the number of children in the household (r_S = -0.04; p = 0.3), or the number of children attending daycare (r_S = -0.04; p = 0.4).

Discussion

Our study is the first to examine the immunity to VZV in a large national pregnancy cohort in Norway. Nearly all women (98.6%) in our study were immune to varicella prior to becoming pregnant but a small proportion (1.2%) was still susceptible during pregnancy, whereas four women (28% of susceptible) seroconverted during pregnancy similar to findings from other studies across Europe [32]. As the information about self-reported history of varicella and herpes zoster was limited, it was impossible to assess the reliability of prior exposure or disease in determining the woman's immune status.

The strength of this study is coupling of data from serological testing with health information collected in a large national cohort study including over 1,000 Norwegian women. Most of the similar studies among pregnant women in Europe included between 500 and 1,000 participants [14, 21, 22, 33], except the Irish study with 7,980 pregnant women of which 11.3% were susceptible to varicella [34]. The proportion of susceptible women in this study varied depending on the nationality between 6.9% in Irish-born women and 21.7% in women born in sub-Saharan Africa [34].

For serological testing, we used a commercial test kit with a high sensitivity of 99.3%, and specificity of 100% to detect antibodies to VZV. Using this assay made our results more comparable to similar seroprevalence studies utilising the same kit.

We were not able to evaluate the association between the women's immune status and a self-reported history of varicella or herpes zoster before pregnancy, since only one woman

reported varicella before pregnancy. This is partly because the study questionnaire was not designed to capture specifically exposure to VZV.

Ninety two percent of women in our study were born in Norway and the remaining proportion was born in other western countries. Given that 14% of Norwegian population are of foreign descent, of which 47% are from Asian and African countries [35], it is likely that women born outside westernized settings with a different varicella epidemiology were not represented in our data[36]. Thus, we may have overestimated the proportion of seropositive subjects, because higher levels of susceptibility to VZV (7%–10%) in pregnancy are reported from tropical and subtropical countries [14, 15, 17, 34, 37]. In addition, a seroprevalence below 90% was demonstrated among women of reproductive age in other studies in several European countries, including Norway where a seroprevalence of 88.6% in this population was found [20, 38]. As information about the birth country was limited in our study, a further research examining immunity to varicella among women originating from countries outside Western Europe is warranted. Such information would help better define risk groups eligible for antenatal screening of varicella susceptibility.

We compared age at birth among study participants with general population in the same period. Overall, both groups were comparable, but a higher proportion (75%) of study participants was aged 25–34 years compared to women in general (66%). Proportions of our study reflect the age distribution of mothers in MoBa where younger women were underrepresented [36]. Therefore, it is possible that a higher seropositivity among women in our study is related to a higher proportion giving birth at older age compared to the general female population [20].

Although no CVS cases were reported in this study sample, we found ten CVS cases reported during a seven-year period (2008–2014) in a national registry-based study of varicella burden [19]. In view of these observations, we believe that there are more non-immune women of reproductive age in Norway and that the risk of neonatal and congenital varicella cannot be ruled out.

According to current Norwegian recommendations, varicella screening should be considered only for pregnant women with no history of varicella infection or varicella vaccination prior to their pregnancy [13]. Similar recommendations exist in other countries such as the UK and Australia [39, 40]. However, ideally women with unknown VZV immune status should be counselled before pregnancy planning. Most women with spontaneous pregnancies seek antenatal care either when they suspect being pregnant or after the pregnancy is confirmed, which makes such counselling difficult to implement in healthcare practice. However, women who undergo assisted reproduction are easier to access by healthcare professionals and therefore, it may be more feasible to offer counselling to this group, which comprises three to four per cent of the annual birth cohort in Norway [41]. Another group to be considered for counselling and selective screening include healthcare workers and women employed in childcare, which may be exposed to varicella at work. This may be a rather small group in the population, but healthcare providers should be aware of VZV history among such women when assessing the risk of infection and need for vaccination or passive immunization with VZV immunoglobulin [17, 42].

Varicella zoster immunoglobulin is indicated for non-immune pregnant woman and should be administered within 96 hours of exposure to varicella virus. However, not all women may know their exposure status and some women may develop only subclinical disease, which still can cause CVS [43]. Thus, serological testing may be a useful tool to identify women in need for passive immunization and other prophylactic measures. Prophylactic measures would contribute to minimise the risk of CVS in Norway where up to three cases annually have been reported during 2008–2014 [19].

The evidence from our study supports the current Norwegian recommendations on selective screening for varicella in pregnancy [13]. Serological testing is recommended if a woman was exposed to varicella during pregnancy and if the disease history is unclear. In addition, varicella counselling should be included as a part of antenatal care for all women of reproductive age and a need for serological testing and potential vaccination should be reviewed for women employed in settings with a high probability of exposure to varicella zoster virus.

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Author Contributions

Conceptualization: Susanne Gjeruldsen Dudman, Elmira Flem.

Data curation: Grazina Mirinaviciute, Regine Barlinn.

Formal analysis: Grazina Mirinaviciute.

Funding acquisition: Elmira Flem.

Supervision: Elmira Flem.

Writing – original draft: Grazina Mirinaviciute.

Writing – review & editing: Grazina Mirinaviciute, Regine Barlinn, Susanne Gjeruldsen Dudman, Elmira Flem.

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