Effectiveness of the herpes zoster vaccine Zostavax® in Stockholm County, Sweden

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ABSTRACT

Objective: The objective of this study was to estimate the effectiveness of the herpes zoster vaccine Zostavax in a cohort of vaccinated individuals in Sweden.

Methods: The study is a retrospective population-based matched cohort study conducted with data from health care registers in Stockholm Country. Primary endpoints were new diagnosis of HZ after administration of Zostavax. Individuals above the age of 50 years and living in Stockholm County in 2013 were included into the study. Ten non-vaccinated individuals per vaccinated were included and randomized into the cohort. The non-vaccinated were matched on age at index date and gender.

Results: Zostavax had an overall effectiveness (VE) of 34% (HR = 0.66, 95% CI: 0.55–0.78). When stratifying by age, 61–75 years was the only age group that showed a reduced risk of HZ (HR = 0.57; CI 0.44–0.73) compared to those that were non-vaccinated. As compared to the unvaccinated group, the VE was significant at days 180–359 (HR = 0.53; 95% CI 0.33–0.88), 360–539 (HR = 0.46; 95% CI 0.27–0.80) and at days 540–719 (HR = 0.56; 95% CI 0.35–0.90) after vaccination.

Conclusion: This is the first population-based study in Sweden studying the effectiveness of HZ vaccination. Our findings are well in-line with previous studies, however studies addressing the longitudinal efficacy and effectiveness of Zostavax are still required.

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1. Introduction

1.1. Background

Varicella-zoster virus (VZV) is a human herpesvirus that causes varicella (chickenpox) as a primary infection. After the primary infection is cleared, a variable period of latency follows, where the VZV remains within dorsal root or cranial nerve ganglia. Reactivation of latent VZV usually occurs later in life and causes herpes zoster (shingles). Herpes zoster (HZ) is associated with numerous complications, such as acute and chronic pain, meningitis, encephalitis, myelitis, post-herpetic neuralgia (PHN) and possibly stroke [1–3]. The complications of the disease can interfere with daily functioning and lowers health-related quality of life [4–6]. The lifetime risk of VZV reactivation is 20–30% [7] and the incidence and duration of HZ caused pain and PHN gradually increases after the age of 50 years and peaks in individuals over age 80 years [8–10]. Vaccination against VZV is not included in the Swedish immunization program for children, thus at least 95% of all Swedish children are infected with VZV during childhood [11].

The incidence of herpes zoster in Sweden is approximately 0.3% (3 per 1000 person years) for any herpes zoster related diagnosis for all ages, which corresponds to around 6000 new cases in Stockholm County per year [12–14]. The live-attenuated herpes zoster vaccine (HZV), Zostavax (Merck & Co. Inc., Kenilworth, NJ, USA), has been approved in the EU since 2006 for the prevention of HZ and PHN in adults aged > 50 years [15]. Primary analyses of clinical trials have demonstrated a reduced incidence of HZ after administration of Zostavax [16,17]. The effectiveness of Zostavax in real-world settings has been demonstrated in a number of studies [18–20] where Zostavax significantly reduced the risk of HZ in immunocompetent or immunosuppressed adults [18,21,22].

The aim of this study was to use registers to prospectively estimate the effectiveness (VE) and protection provided by the live-attenuated herpes-zoster vaccine (Zostavax) in a cohort of vaccinated individuals in Sweden.

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2. Methods

2.1. Study design

The study was a retrospective population-based matched cohort study conducted with data from health care registers in Stockholm County.

2.2. Study population/settings

The study participants in this study were identified from a previous nested case control study [23] where vaccination status was our outcome. In the current study we took advantage of the previous study set up converting the study into a cohort study. Thus, vaccination status became the vaccination and diagnosis of HZ the outcome.

In detail, individuals above the age of 50 years living in Stockholm County in September 2013 to November 2014 were included in the study. Since following the whole population above 50 years would not increase statistical power, 10 non-vaccinated individuals for each vaccinated individual were included and randomized as controls into the cohort. The non-vaccinated controls were matched on age at index date and gender. The index is date of vaccination. The controls were selected from the total population register (described in data sources), selection and randomization was carried out by Statistics Sweden.

Zostavax is incorporated in the vaccination schedules of several European countries, while it has not been incorporated in the Swedish vaccinations schedule since November 2014. Zostavax was included in the Swedish national pharmaceutical benefit scheme between September 2013 and November 2014, which is a high-cost protection for medicines and applies to most prescription drugs [24]. After November 2014, the herpes zoster vaccine was removed from the national pharmaceutical benefit scheme and individuals were then expected to pay the total cost for the vaccine themselves. This means that between September 2013 and November 2014, people above 50 years of age were able to get the vaccine prescribed. When the prescriptions are dispensed at pharmacy, it is automatically registered in the Prescribed Drug Register, which allowed us to identify 9046 individuals that picked up the vaccine during the described time period.

2.3. Variables

Primary endpoint in this study was new diagnosis of HZ at least 35 days after vaccination, using ICD-10 codes for HZ (all codes starting with B02). Prescription of analgesics in combination with ICD-10 for HZ was used as a proxy for PHN (ACT codes N06AX21, N06AA09, N03AX16, N03AX12, N01BX04) [14]. Prescription of antivirals in combination with ICD-10 codes for herpes zoster were also used as a proxy for HZ (ATC codes: J05B01, J05B09, J05B11).

The study participants were followed until the first occurrence of HZ, death or end of the observation period (December 31, 2016). An unvaccinated individual that became vaccinated during the study period, contributed with person-time in the vaccinated cohort instead of the unvaccinated cohort at the date of vaccination.

2.4. Data sources

Data was collected through the Swedish health care registers described, linked on an individual level by the use of personal identification numbers (PINs) [25].

2.5. The prescribed drug register

Vaccination was identified from the Prescribes Drug Register (PDR). The PDR was established in July 2005 and is maintained by the National Board of Health and Welfare [26]. The PDR contains information on all prescriptions dispensed at pharmacies in Sweden. Over the counter drugs and drugs administered at hospitals are not included in the PDR. We identified individuals who had a dispensation of the Zostavax (cases) during the study period, using the Anatomical Therapeutic Chemical Classification system (ATC) code J07BK02, [27].

2.6. Stockholm County VAL database

HZ diagnosis (ICD-10 B02) was identified from VAL database, which collects regional administrative healthcare data in Stockholm County and includes information on all consultations and diagnoses in primary care (since 2003), inpatient and outpatient specialist care (since 1997) [28].

2.7. The National patient register

The National Patient Register (NPR) was established in the 1960's by the National Board of Health and Welfare and contains information on secondary care (inpatient care and outpatient specialist care). In 1987, the NPR started coverage on a national level with outpatient data also being added from 1997 (systematically nationalized in 2001) [26]. The International Classification of Diseases (ICD) with the 10th revision of ICD has been in use for diagnoses in Sweden since 1997 [29].

2.8. Total population register

The Total Population Register (TPR) was used to identify the "control" population. TPR was established in 1968 and is held at Statistics Sweden. This register includes real-time information on all people born in Sweden and those who immigrate into the country and has data on demographics e.g. age, gender and immigration/emigration status [24]. Statistics Sweden did the control selection, randomization and matching for the controls.

2.9. Longitudinal integration database for health insurance and labor market studies (LISA)

Socioeconomic/sociodemographic information including education, income, immigration status (individuals born outside of Sweden are defined as immigrants) and marital status were collected from LISA maintained by Statistics Sweden [30]. LISA is a register that integrates existing data from various sources including the labor market, social and educational sectors. LISA is annually updated since 1990 and contains information on all Swedish residents aged over 16 years.

2.10. Statistical analysis methods

Cox proportional hazard models were used to estimate the hazard ratios (HRs) for HZ among vaccinated versus unvaccinated individuals, where the time scale of our interest was the time since vaccination. Adjustment was made for age at entry, educational level (categorized as: high = college or university studies; middle = attended high school; low = only secondary school; and missing); civil status (single or not), birth country (Sweden, EU or other); and five-year CCI since entry to the study. To examine the influence of age at entry, we conducted the stratified analysis stratified on age at entry. To examine the influence of time since vaccination, we conducted stratified analysis on time since

vaccination. In all Cox models, the proportional hazards assumption was checked graphically and by Schoenfeld's partial residuals; neither of them revealed any indication of violation of this assumption. Two-tailed 95% confidence intervals and p-values were given, with $p < 0.05$ regarded as significant. The statistical software package SAS 9.2 (SAS Institute Inc., Cary, NC) was used for all analyses.

A wash-out period of 35 days after the date of vaccination was imposed to allow the vaccine to become efficacious (following methods used in clinical trials) but also to allow time from dispensation to administration of the vaccine. Hence entry to the study was the date of vaccination, or the matching date in the unvaccinated group, plus 35 days. During the wash-out period, 1135 unvaccinated individuals took the vaccine and 374 of these were excluded from the analysis.

The study analyses were conducted on one dose of Zostavax. Since the prescription date of the vaccine may not always be equivalent to the vaccination date, different time cut offs after the prescription date were used in different sensitivity analysis. The vaccinated and matched unvaccinated groups were described according to their baseline characteristics. Incidence rates of HZ in vaccinated and unvaccinated individuals were calculated and compared for measurement of vaccine effectiveness.

The Charlson Comorbidity Index (CCI) reflects general health status and is generated from NPR. CCI was used to represent individuals who had a higher risk of one-year death based comorbid conditions at hospitalization, where 22 conditions are taken into account including heart disease and cancer [31].

3. Results

3.1. Participants

A total of 100,111 individuals were diagnosed with HZ during the study period September 2013 and November 2014. After exclusions (described in detail in Fig. 1), 99,189 individuals remained in the cohort among which 9046 were vaccinated and 90,143 were unvaccinated (Fig. 1).

3.2. Descriptive data

Table 1 describes demographic variables commonly associated with vaccination. These have been studied in more detail in Fogelberg et al. [32]. Briefly, 66% of the vaccinated persons were observed in the age group 61–75 years. Less than 9% of vaccinated
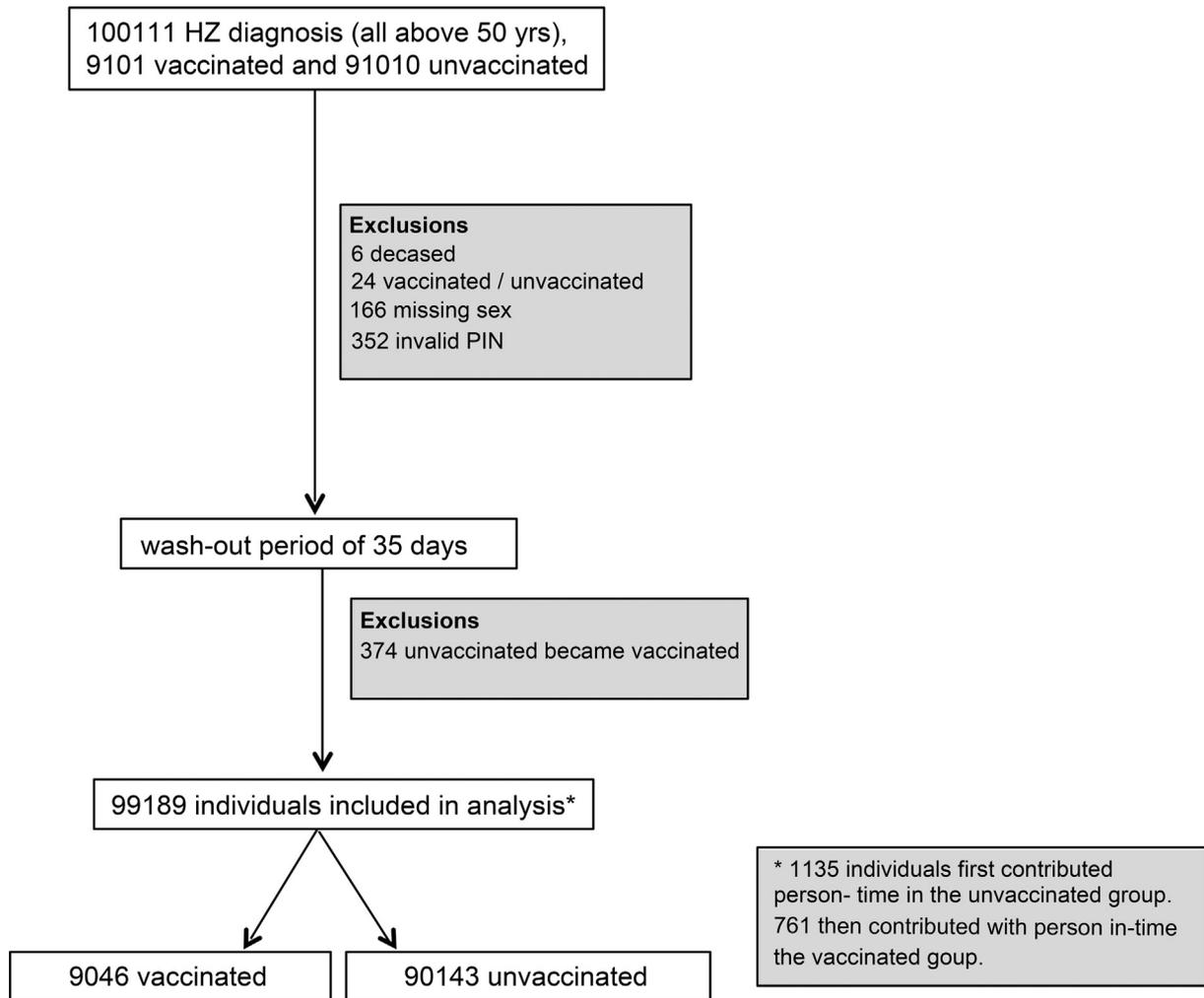

Fig. 1. A flow-chart describing the inclusion and exclusion process of the study. 100,111 individuals, 9101 vaccinated and 91,010 unvaccinated, over 50 years with a diagnosis of HZ were included in the cohort between September 2013 and November 2014. 12 individuals were excluded because they were identified both as vaccinated and unvaccinated, 6 individuals deceased, 166 individuals were excluded due to missing sex, 196 individuals were excluded due to inconsistent date of birth, 352 individuals were excluded due to invalid PINs. This study included a wash-out period of 35 days after the date of vaccination to allow the vaccine to become efficacious, and to allow time from dispensation to administration of Zostavax. 1135 unvaccinated individuals took the vaccine and 374 of these were excluded from the analysis during the wash-out period of 35 days. 99,189 individuals, 9046 vaccinated and 90,143 unvaccinated, were left in the cohort after exclusions and wash-out period.

Table 1
Sociodemographic characteristics, including income, education and immigration status. Numbers describe frequency in vaccinated and unvaccinated populations, included in the study between September 2013 and November 2014.

	Vaccinated		Unvaccinated	
	Frequency	(%)	Frequency	(%)
	9046		90,143	
Gender				
Male	3003	33.2	29,966	33.2
Female	6043	66.8	60,177	66.8
Age				
50–60	796	8.8	8015	8.9
61–75	5998	66.3	59,809	66.4
75-	2252	24.9	22,319	24.8
Civilian status				
Married	5367	59.3	46,223	51.3
Unmarried	3679	40.7	43,920	48.7
Education				
High	4646	51.4	31,986	35.5
Mid	3288	36.4	36,045	40.0
Low	1051	11.6	20,577	22.8
Missing	61	0.7	1535	1.70
Income (in 100 Euro)				
0–20	1269	14.0	22,938	25.5
21–40	1572	17.4	20,823	23.1
41–60	1904	21.1	17,079	19.0
61–80	2029	22.4	15,886	17.6
81-	2272	25.1	13,417	14.8
Country of birth				
Sweden	8081	89.3	71,284	79.1
EU	798	8.8	13,382	14.9
Other	167	1.9	5377	6.1

persons were below the age of 60, and 67% of the vaccinated persons were female. Higher education was more common among the vaccinated persons than among unvaccinated persons (51.4% vs 35.5%) and received a higher income in all quintiles. Vaccinated persons were more likely to be married (59.3%) than unvaccinated persons (51.3%). People born in Sweden were more likely to be vaccinated (89.3%) than people born in other countries (79.1%). Furthermore, people in other EU countries were less likely to be vaccinated (8.8%) than unvaccinated (14.9%). This was also the case for people born outside of EU, where a larger percent of people was unvaccinated (6%) than vaccinated (2%).

3.3. Zostavax vaccine effectiveness

Overall, the vaccine effectiveness (VE) was 34% (HR = 0.66, 95% CI: 0.55–0.78) in vaccinated persons (Table 2). When stratifying by age, VE was increased in all groups, however it was not statistically significant for the age group 50–60 (HR = 0.53, 95% CI: 0.21–1.30) and in persons above 75 years (HR = 0.93, 95% CI: 0.68–1.26) (Table 2).

In addition, VE was slightly increased at the time directly after vaccination, at days 0–179 (HR = 0.88, CI: 0.61–1.28), however it was not statistically significant. VE of Zostavax was significantly increased at days 180–359 (HR = 0.53; 95% CI 0.33–0.88), 360–539 (HR = 0.46; 95% CI 0.27–0.80) and at days 540–719 (HR = 0.56; 95% CI 0.35–0.90) (Table 3) after vaccination. VE decreased days 720–899 (HR = 0.77, 95% CI: 0.49–1.20) and at days 900+ (HR = 0.82, 95% CI: 0.48–1.40) after vaccination (Table 3).

4. Discussion

4.1. Main findings

In this retrospective population-based study, we investigated the VE of the Zostavax vaccine in a cohort of vaccinated persons between September 2013 and December 2016 in Stockholm, Sweden. This is to our knowledge the first study showing the VE of Zostavax or any other HZV in Sweden. Our major findings were that vaccination with Zostavax had an overall VE of 34% (HR = 0.66,

Table 2
Primary analysis: crude incidence rate (95% CI) and adjusted hazard ratio (95% CI) comparing exposed to unexposed populations vaccinated to unvaccinated populations.

	Diagnosis HZ (n)	Follow up (days)	Incidence rate * 100000 (95% CI)	Hazard Ratio (95% CI)
Overall				
vaccinated	1694	231400.7	732.0 (698.0, 767.8)	0.66 (0.55, 0.78)
unvaccinated	119	23909.4	497.7 (415.86, 595.68)	1 (ref)
Stratified on age				
50–60 vaccinated	5	2097.5	238.4 (99.2, 572.7)	0.53 (0.21, 1.30)
50–60 unvaccinated	91	20965.3	434.1 (353.4, 533.1)	1 (ref)
61–75 vaccinated	68	15924.0	427.0 (336.7, 541.6)	0.57 (0.44, 0.73)
61–75 unvaccinated	1141	155008.4	736.1 (694.6, 780.1)	1 (ref)
75- vaccinated	46	5888.0	781.3 (585.2, 1043.0)	0.93 (0.68, 1.26)
75- unvaccinated	462	55427.1	833.5 (760.9, 913.1)	1 (ref)

Table 3
Primary analysis: crude incidence rate (95% CI) and adjusted hazard ratio (95% CI) comparing exposed to unexposed populations over exposure periods in days.

	Diagnosis HZ (n)	Follow up (days)	Incidence rate * 100000 95% CI	Hazard Ratio 95%CI
Days from vaccination				
0–179 vaccinated	31	4444.1	697.5 (490.6, 991.9)	0.88 (0.61, 1.28)
0–179 unvaccinated	322	43924.7	733.1 (657.2, 817.7)	1 (ref)
180–359 vaccinated	19	4420.9	429.8 (274.1, 673.8)	0.53 (0.33, 0.8)
180–359 unvaccinated	334	43082.9	775.3 (696.4, 863.0)	1 (ref)
360–539 vaccinated	14	4391.6	318.8 (188.8, 538.3)	0.46 (0.27, 0.80)
360–539 unvaccinated	286	42423.5	674.2 (600.4, 757.0)	1 (ref)
540–719 vaccinated	19	4359.4	435.8 (278.0, 683.3)	0.56 (0.35, 0.90)
540–719 unvaccinated	315	41902.7	751.7 (673.1, 839.5)	1 (ref)
720–899 vaccinated	21	3702.8	567.1 (369.8, 869.8)	0.77 (0.49, 1.20)
720–899 unvaccinated	261	35423.1	736.8 (652.6, 831.8)	1 (ref)
900 + vaccinated	15	2590.7	579.0 (349.1, 960.4)	0.82 (0.48, 1.40)
900 + unvaccinated	176	24643.9	714.2 (616.1, 827.9)	1 (ref)

95% CI 0.55–0.78), and was greatest in persons between 61 and 75 years of age (HR = 0.57, 95% CI: 0.44–0.73). VE decreased with age, and vaccination at the age of 75 and above showed a VE of 7%. An increased VE wasobserved from 6 months to 2 years after vaccination. VE decreased 2 years after vaccination. However, the number of vaccinated persons in this analysis is low due to the relatively short follow-up time during the study period (2013–2016).

4.2. Limitations

The major strength of this study was the population-based setting, allowing for inclusion of all people in Stockholm Country that had a prescription of Zostavax during the study period. Limitations to the study include short duration of the follow-up, and that we do not have access to the exact date of vaccination (but instead date of dispensation at pharmacy). Furthermore, we are not able to confirm administration of the vaccine, which could misclassify some unvaccinated individuals in vaccinated individuals and potentially underestimate the effectiveness. However, because Zostavax was recommended and reimbursed for persons at 50 years and above during 2013–2014, we expect that people that had a prescription for Zostavax and a delivery at pharmacy level, received the vaccine. Known limitations that are associated with observation studies compared to randomized trials, may be applied in this study. For example, higher socioeconomic status is more prevalent in the vaccinated persons, thus presenting a possible bias in this population. However, this possible bias was handled by covariate adjustment for the most well-known factors in the statistical analysis (age at entry, educational level, civil status birth country). Another limitation was our small study population and short follow-up time, that did not allow us to study the VE for specific HZ complications, such as PHN.

4.3. Interpretation

We observed an increased VE of Zostavax in all age groups, and the VE is highest in the age group 61–75 years. VE was increased in the age group 50–60 years, however it was not statistically significant; most likely due to a low number of individuals in this group (n = 5). Further investigations including more individuals are required to determine the vaccine effectiveness in this particular age group. We show that VE decrease with age, and similar findings have been presented in other population based community studies [18–20]. For example, another retrospective register-based study show that VE of Zostavax increase in all ages from 65 years and up, but wanes over time [33] In a large retrospective cohort study in the US (including data from the Kaiser Permanente Southern California health plan from January 2007 to December 2009), Zostavax significantly reduced the risk of HZ in immunocompetent adults with 55% compared with unvaccinated immunocompetent adults [21]. Additionally, Zostavax reduce the risk of HZ by 44% in immunocompetent or immunosuppressed adults [18].

Data from this study are similar to that observed in controlled clinical trial settings. The Shingles Prevention Study (SPS), showed that Zostavax reduced the burden of illness due to HZ by 61% and reduced the incidence of HZ by 51% [17]. Another clinical trial, the Zostavax Efficacy and Safety Trial (ZEST), showed a reduced incidence of HZ by nearly 70% in individuals aged 50–59 years [16]. The estimated VE of Zostavax in the age group 50–59 years in the ZEST study (70%), was close to that observed in individuals aged 60–69 years (63.9%) in the SPS study. Both reports show a greater VE in age groups 50–59 and 60–69 years, as compared to older individuals (>70 years). Our community-based data from this study support earlier data from controlled clinical trial settings, that VE declines with age.

In our cohort we found an overall lower VE than compared to other studies [16,17]. One explanation may be that the vaccinated individuals were more likely to have had a previous zoster infection than the control group, and thus more prone to reactivation of the virus to due risk factor that could not be measured in this study.

Time after vaccination appears to be an important factor for the VE of Zostavax. Herein, we present a significant effectiveness between 6 months to 2 years after vaccination. The VE wanes gradually after this time and this may be to a longitudinal gradual loss of immunity to disease, or to the relatively short follow up time in the cohort. There are previous reports showing that both antibodies [34] and cellular immunity decreases [35] over time. Furthermore, the immune responses could not be emphasized or improved with two doses of the vaccine [34]. The same results were shown with a booster dose at a later stage in life [35].

4.4. Generalizability

Epidemiological studies addressing the long-term trend of HZ over the last six decades found that incidence of HZ increased over four times in all age groups and in both genders [9,36,37]. An increase of HZ may result in affected vaccine acceptance in a population. The estimated societal costs of HZ are high, given the complications and relatively high lifetime risk of reactivation of varicella virus [12,38,39]. One approach to prevent HZ in older adults, would be to supplement the varicella program with HZ vaccination. This should be considered for future policy making [40,41]. In particular, with the potential for an increasing number of children receiving VZV vaccine in the future (and potential debate regarding its inclusion into the childhood vaccination program in Sweden). The VZV vaccine is not currently part of the childhood vaccination program in Sweden. However should this change, it brings the question whether herpes zoster vaccine should be reimbursed or partially reimbursed again in the future, as it was during the study period.

This is the first report showing reduced risk of HZ in vaccinated individuals in Sweden. However, further studies addressing the long-term effects, as well as on other populations, will be needed to increase the understanding of the efficacy, effectiveness and protection of Zostavax.

Contributors

Design of study (LAD), Data analyses (LY), Drafted manuscript (KB, LAD, LY), Prepared manuscript for submission (KB), Interpretation of results (KB, LAD, LY), Guarantor of the study (LAD).

Ethics approval

Regional Ethical Review Board of Stockholm, Sweden.

Funding

Data availability statement

The data underlying the findings is applied to access restrictions according to Swedish law, thus the authors are not able to make the dataset publicly available. The data used in this study are owned by Statistics Sweden (SCB), the Swedish National Board of Health and

Welfare (Socialstyrelsen), and the Stockholm County. Any researchers, including international researchers, who are interested in obtaining the data can contact SCB via information@scb.se, Socialstyrelsen via registerservice@socialstyrelsen.se, and http://www.gups.sll.se/val/atkomst_till_val.htm. One can also visit https://www.scb.se/sv_/Vara-tjanster/Bestalla-mikrodata/ (SCB) and http://www.socialstyrelsen.se/register/bestalladatastatistik/bestallaindividuppgifterforforskningsandamal (Socialstyrelsen)) for detailed information about how to apply for access to register data for research purposes.

Declaration of Competing Interest

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