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Safety of live attenuated herpes zoster vaccine in adults 70–79 years: A self-controlled case series analysis using primary care data from Australia's MedicineInsight program

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ABSTRACT

Background: Australia introduced a funded shingles vaccination program for older adults in November 2016, administered predominantly in primary care clinics. MedicineInsight, a nationally representative primary care database, was used to investigate the risk of pre-specified outcomes following live attenuated herpes zoster vaccine (ZVL) in Australia.

Methods: Individuals aged 70–79 years who received ZVL between 1 November 2016 and 31 July 2018 were identified from MedicineInsight. The self-controlled case series (SCCS) method was used to estimate the seasonally-adjusted relative incidence (RI) of seven pre-specified outcome events (injection site reaction (ISR) [positive control], burn [negative control], myocardial infarction (MI), stroke, rash, rash with an antiviral prescription, and clinical attendance) during a plausible post-vaccination at-risk window compared with times distant from vaccination. Sensitivity analyses examined the effect of common concomitant vaccinations and restriction to first outcome events.

Results: A total of 332,988 vaccination encounters among 150,054 individuals were identified during the study period; over 2 million clinical attendances were observed. There was an increased RI of ISR in the seven days following ZVL (RI = 77.4, 95% CI 48.1–124.6); the RI of clinical attendance (RI = 0.94, 95% CI 0.94–0.95) and stroke (RI = 0.58, 95% CI 0.44–0.78) were lower in the 42 days following administration of ZVL compared to control periods. There was no evidence of a change in the RI of MI (RI = 0.74, 95% CI 0.41–1.33), rash (RI = 0.97, 95% CI 0.88–1.08), or rash with antiviral prescription (RI = 0.83, 95% CI 0.62–1.10) in the 42 days following ZVL compared to control periods.

Conclusion: No new safety concerns were identified for ZVL in this study based on a novel, Australian primary care data source. An expected increased risk of ISR was identified; findings in relation to cardiovascular disease were reassuring but require confirmation using additional data, including hospital records.

1. Introduction

Herpes zoster (HZ) is a localized, painful, vesicular skin rash resulting from reactivation of varicella-zoster virus (VZV). The incidence increases with age to an average lifetime risk of around 30% [1]. Prior to implementation of immunization programs, the incidence of HZ in Australia was reported to be 10 per 1000 persons aged 50 years and older [2], similar to rates observed in Europe

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[3] and the United States (US) [4]. The risk of post-herpetic neuralgia (PHN), a chronic neuropathic pain syndrome which may complicate HZ, also increases with age [5]. Disseminated disease, often characterized by diffuse vesicular rash, can occur in people who are immunosuppressed.

Live attenuated herpes zoster vaccine (ZVL) was registered for use in Australia in 2006 for people aged over 50 years but was in limited supply until 2014; it is recommended for immunocompetent adults over 60 years of age [6]. In November 2016, ZVL was funded (making it free for patients) under Australia's National Immunisation Program (NIP) for the ongoing cohort of adults aged 70 years, with catch-up for those aged 71–79 years funded until October 2021. Influenza and pneumococcal vaccines are also NIP funded for adults 65 years and over [6]. Vaccines in this age group are predominantly administered in primary care, via general practice clinics.

ZVL was evaluated in large, pre-licensure clinical trials with no increased risk of serious adverse events (SAE), hospitalized adverse events or death identified [7–9]; the rate of injection site reactions (ISR) was higher in vaccine than placebo groups (48% compared to 16% in adults 60 years or older) [7,9,10]. Data from post-licensure surveillance, predominantly reports of adverse events (AE) via spontaneous reporting systems, have suggested a safety profile consistent with data from clinical trials, although with lower rates of ISR [11–13]. Most reports (93%) to the Merck, Sharp, & Dohme Corp (MSD) global safety database [13] and 96% of reports to the United States (US) Vaccine Adverse Events Reporting System (VAERS) [11] and Australian Therapeutic Goods Administration's (TGA) Adverse Events Management System database [12] were non-serious. In all three post-marketing surveillance systems, ISR was the most commonly reported AE (20.5% in the MSD database and 16% in the AEMS, with injection site erythema reported in 27% and injection site swelling in 17% within VAERS), followed by HZ and rash.

While cardiovascular events (stroke and myocardial infarction (MI)) have been associated with wild-type ZV infection [14,15], no significant increase in risk has been identified following ZVL [10,16]. Among serious AE reports to the TGA AEMS, one causally-related death from disseminated Oka vaccine strain VZV infection was reported in a 71-year-old immunocompromised male vaccinated despite a contraindication [17,18]. Another immunocompromised male also died from disseminated vaccine VZV disease in the United Kingdom [19].

While spontaneous post-marketing reporting systems can detect safety signals, they are limited by incompleteness, imperfect data quality and the potential for selective reporting [11]. In Australia, AusVaxSafety is a multiple component active vaccine safety system that aims to address these limitations. The first and major component of AusVaxSafety consists of active participant-based surveillance that monitors AEs solicited directly from vaccine recipients in the community via an automated text message [20,21]. During the first two years of the ZVL program, specific survey data did not identify any safety signals amongst 18,655 adults aged 70–79 years; 8.3% of vaccinated individuals reported an adverse event (most commonly an ISR) and 0.3% reported medical attendance within three to five days after vaccination (a proxy measure of seriousness) [22].

Another component of the AusVaxSafety program was established to analyze routinely extracted longitudinal primary care data from MedicineInsight, a national database developed and managed by NPS MedicineWise. MedicineInsight data is used to support the safe use of new medicines along with quality improvement activities in participating practices [23,24]. Both AusVaxSafety and MedicineInsight receive funding support from the Australian Government Department of Health.

To examine the risk of specific outcomes following ZVL, we aimed to conduct a novel analysis of MedicineInsight data, which has not previously been used for vaccine safety assessment. We used the self-controlled case series (SCCS) method, an approach which controls for unmeasured time-invariant confounders by allowing individuals to act as their own control [25]. This method was developed for vaccine safety evaluation [26–28] and has been previously used to examine ZVL safety using data from managed care cohorts in the US [16], but has not been used with Australian primary care data. The objective of this study was to explore the risk of pre-specified potential adverse outcomes following ZVL (including ISR, rash and cardiovascular outcomes) in the target NIP cohort using the nationally representative (in terms of age and gender) MedicineInsight data and to make comparisons with data on outcomes following influenza and pneumococcal vaccines.

2. Methods

2.1. Study setting

The MedicineInsight data set consists of longitudinal, de-identified, whole-of-practice data extracted from the electronic clinical information systems (CIS) of participating primary care practices across Australia [23]. These include practices in major cities and in rural and remote areas, similar to the distribution of the Australian population in these areas [29]. At October 2018, participating practices represented 10.7% of the Australian patient population. Data is routinely extracted on patient demographics, practice encounters (excluding progress notes), diagnoses, vaccinations, prescriptions, pathology tests and referrals. Practice encounters can include clinical (a medical or nursing appointment) or non-clinical (administrative) encounters. Within-site individual identifiers are used to identify records common to an individual.

2.2. Study population

The NIP target population for ZVL during the study period was individuals aged 70–79 years; all Australians over 65 years of age are also eligible for funded 23-valent pneumococcal (23vPPV) and influenza vaccines under the NIP. Although the primary vaccine of interest was ZVL, all individuals who had received 23vPPV and seasonal inactivated influenza vaccines were also included for two reasons: ZVL may be commonly co-administered with these two vaccines meaning that any outcome events identified might be attributable to these other vaccines; and to estimate the relative incidence (RI) of outcome events in other vaccines using the same data source and methods as comparators for the ZVL estimates. All MedicineInsight records were obtained for individuals 70–79 years of age who received ZVL, 23vPPV or influenza vaccine(s) between 1 November 2016 (the commencement of the funded ZVL program) and 31 July 2018.

Individuals with a history of stroke and MI were identified by a search of practice encounters and diagnoses related to these conditions using information from the diagnosis (medical history), reason for encounter, and reason for prescription fields, and included both coded and free-text data. Individuals with records for historical events of stroke and MI (occurring before the start of the study period) were excluded. Primary care records are not formally linked to hospitalization records in Australia, although general practitioners (GPs, primary care providers in Australia) may record hospitalization and new diagnoses in their CIS. Individuals who died were censored on 31 December of the preceding year because only the year of death was available.

2.3. Study design

We undertook a retrospective SCCS analysis of outcomes following ZVL using MedicineInsight data. The method estimates the relative incidence of an outcome event within a risk window following exposure (i.e. vaccination) compared to a control period distant from vaccination (Fig. 1) [30]. Only individuals who have experienced the outcome event of interest are included in the analysis and the design inherently controls for time-invariant confounders [25].

This study investigated the incidence of seven pre-specified outcome events: ISR [positive control], burn [negative control], MI, stroke, any rash, rash with a prescription for an antiviral medication within 2 days of the rash-related encounter, and any clinical attendance in a post-vaccination at-risk window compared with the incidence of these outcome events during control periods. ISR was included as a positive control given consistent evidence of an increased risk of ISR in pre-licensure and post-licensure studies. Burn was included as a negative control because of the absence of a plausible causal relationship with vaccination. Rash with antiviral prescription was specified because antivirals (e.g. valaciclovir) are prescribed to reduce the severity and duration of HZ infection [31]; prescription of an antiviral medication was considered to be a proxy for an HZ-like rash.

We defined an individual's observation period in terms of their record of activity at the site and recorded year of death (if applicable). An individual's observation start date was defined as the latest of 1 November 2016, or 365 days after their first recorded activity at the site (any encounter, diagnosis, or prescription). The lead time of 365 days from an individual's start of site activity was specified to ensure adequate patient follow-up was available to assess historical diagnoses. An individual's end date of observation was defined as 31 December in the year prior to their death for individuals who had year of death recorded, and 31 July 2018 for individuals who had no year of death recorded. Therefore, the maximum observation period for any individual was 638 days.

Exposure (vaccination) was defined as any record in the CIS immunization field for any of the three vaccines under study with a date of administration occurring within the individual's observation period. Vaccination prescriptions recorded only in the prescription field were excluded as these prescriptions may not have been filled at the time the prescription was provided. While some vaccines administered were clinically coded, others were free text entries; vaccination records for the study vaccines were identified via targeted, free-text search criteria (see Appendix A for search terms). The date of vaccination was set as the administration date specified in the immunization field. Individuals with multiple vaccination records for ZVL or 23vPPV during their observation period were excluded as these vaccines are generally recommended to be given as a single dose for older adults. We enforced a minimum time between influenza vaccinations of 126 days because a single dose is generally recommended each season. Any records occurring within 126 days of an individual's previous influenza vaccination were excluded to avoid overlapping risk windows (refer to Section 2.4). Any vaccines with the same recorded date of administration were assumed to be co-administered.

Except for clinical attendance, outcome events were identified using free-text regular expression searches of the reason for encounter, reason for diagnosis and reason for prescription fields (see Appendix A for search terms). In CIS software, the same event can be recorded in multiple locations on similar (but not necessarily identical) dates. Therefore, to ensure the earliest time point was selected for each event for each individual the following process was used: for each record matching an outcome event, we matched encounters, diagnoses, and prescriptions on their respective dates to identify likely-related events and then selected the date of first occurrence. Records of clinical attendance were identified as any site encounter excluding those identified to be non-clinical (administrative), which were identified by a free-text search of the encounter type and encounter reason fields for specific terms identified as administrative in nature (see Appendix A).

2.4. Definition of risk windows

At-risk windows were defined for all vaccine types based on biologically plausible windows supported by evidence. For ISR, the risk-window was 1–7 days post vaccination and for all other outcomes was 1–42 days post vaccination. The basis for the length of the risk window for systemic adverse events was the 42 day window used in pre-licensure clinical trials [7,9,10,32] and post-licensure studies [16,33]. This time period is also biologically plausible for MI and stroke events, which have been observed following wild-type VZV, particularly one to four weeks following infection [14,15], with viral replication in arterial walls the proposed mechanism for stroke [34]. Considering rash within 42 days was appropriate given that varicella-like rash more than 6 weeks after vaccination is more likely to represent primary wild-type VZV infection or reactivation of latent VZV as HZ (in older individuals), which remains possible due to modest vaccine efficacy for HZ [7,13]. The risk windows for burns (the negative control) and clinical attendance were chosen to be consistent with the risk window for systemic events. For ISR, the risk window was based on the short median time to ISR (~2 days) in the Shingles Prevention Study (SPS) and post-licensure surveillance [10,13] and the identification of a signal for cellulitis within 7 days in another post-licensure SCCS [16].

To account for the potential for medical events to negatively affect the likelihood of vaccination (healthy vaccinee bias) [25,35], a washout period of 42 days pre-vaccination was defined. A 42 day post-risk washout period was also included (except in the case of rash with an antiviral prescription) to minimize the potential for any risk attributable to vaccination carrying over into the control period (Fig. 1) [35]. For rash with an antiviral prescription, an indefinite post-risk period was specified to allow for exploration of the impact of vaccination on HZ; for this outcome event, only the first recorded influenza vaccination was considered for analysis to avoid overlapping risk periods.

Pre-exposure and post-risk washout periods were excluded from the control period. The day of vaccination (day 0) was excluded from all risk windows because only the date and not the time of clinical encounter, vaccination, nor medical event was recorded. As a result, we could not reliably distinguish vaccine

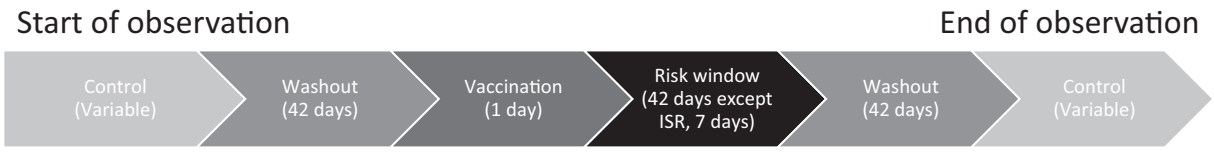

Fig. 1. Self-controlled case series design for the analysis of outcome events following administration of live attenuated herpes zoster vaccine to 70–79 year old adults using primary care data.

administration encounters from same-day encounters for medical events (occurring before or after vaccination) or unrelated reasons, including opportunistic coding. All other time periods an individual was under observation were allocated to their control period.

2.5. Statistical methods

Relative incidence estimates were obtained by the SCCS model using the windows defined in Section 2.4. The primary analysis modelled all vaccine exposures jointly; each outcome event was modelled independently and all outcome events occurring during the observation period contributed to the relative incidence estimates. Given that the study period spanned 1 November 2016 to 31 July 2018, we additionally specified fixed windows to adjust for seasonal effects by specifying cut-points: 1 December, 1 March, 1 June, and 1 September in each year. Weekly periodicity of events, such as regular GP attendances on the same day of the week noted for some patients, was accounted for indirectly by the specification of risk-windows in terms of full-week cycles.

Lack of independence of outcome events violates the Poisson assumption of the SCCS model and may bias estimates. Therefore, sensitivity analyses were undertaken which only included the first outcome event observed and assessed each vaccine independently, excluding co-administered vaccines.

The relative incidence and 95% confidence intervals for each outcome were estimated using conditional Poisson regression with the length of each window included as offset terms to account for the period of time under study. No adjustments were made for multiple comparisons. All analyses were conducted using R 3.5.1 [36] and the gnm package version 1.1–0 [37].

2.6. Ethical approval

The MedicineInsight program was approved through the Royal Australian College of General Practitioners National Research and Evaluation Ethics Committee (NREEC) in December 2017 (NREEC 17–017). Approval for use of MedicineInsight data in this study was received from the NPS MedicineWise external Data Governance Committee on 23 November 2016 and an amended version on 29 September 2017. This study was approved by the Sydney Children's Hospitals Network Human Research Ethics Committee (HREC/17/SCHN/159).

3. Results

3.1. Vaccinations and outcome events

A total of 337,294 vaccination records for 150,756 individuals from 456 MedicineInsight primary care practices were obtained. After excluding those with multiple ZVL or 23vPPV vaccinations or multiple influenza vaccinations within 126 days of each other, a total of 332,988 vaccination encounters (ZVL: 92,857; 23vPPV: 21,480; and influenza: 218,651) for 150,054 individuals were included. Most individuals (93%) were under observation for the entire study period, according to our pre-specified criteria.

ZVL vaccinations were clustered at the beginning of the study period following inclusion under the NIP. Weekly and seasonal fluctuations in vaccinations were observed for the three vaccines investigated (Fig. 2). The number of vaccination records declined with age, apart from a small increase in ZVL just prior to 79 years of age (the upper age limit of the catch-up cohort) (Fig. 3). Of ZVL doses, 82% were administered alone, 16% with influenza vaccine and 2% with 23vPPV. Of influenza vaccine doses, 89% were administered alone while 47% of 23vPPV doses were administered alone.

Over 2 million clinical attendances were observed among exposed individuals during their observation periods. The next most common outcome event was any rash, with 12,309 events observed. The least common outcome event was injection site reaction, with 177 events observed; 40% were recorded less than 8 days after vaccination. Vaccination centered event plots show

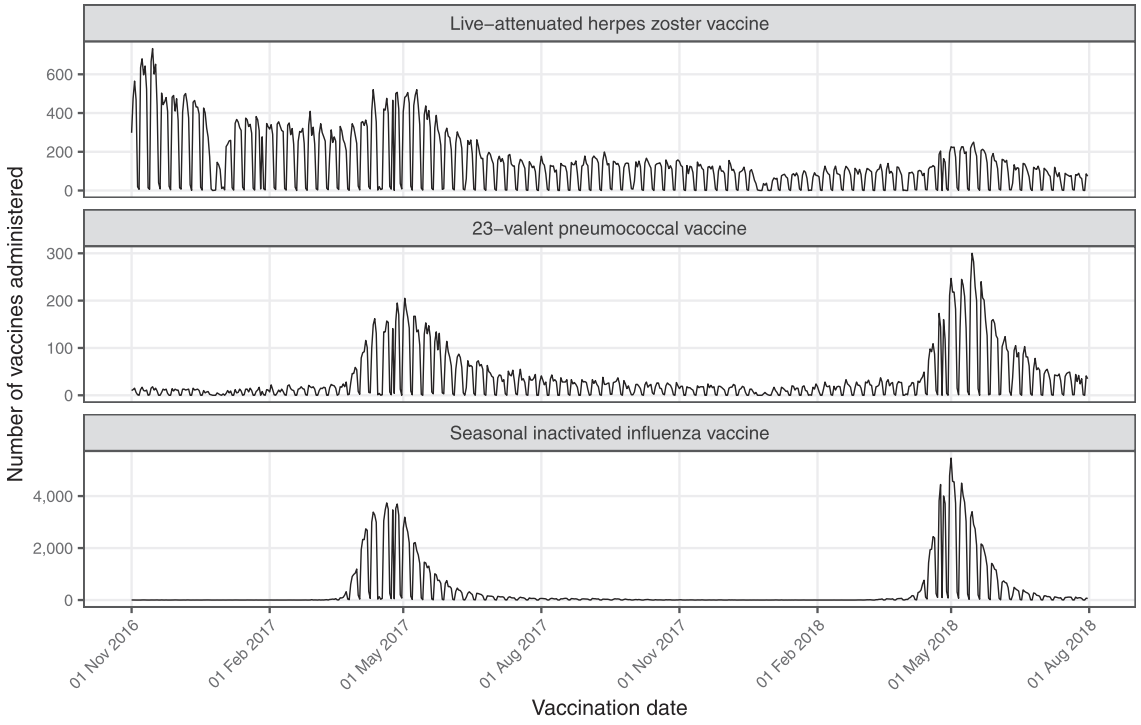

Fig. 2. Daily counts of vaccines administered to 70–79 year old adults in primary care between 1 November 2016 and 31 July 2018, by vaccine.

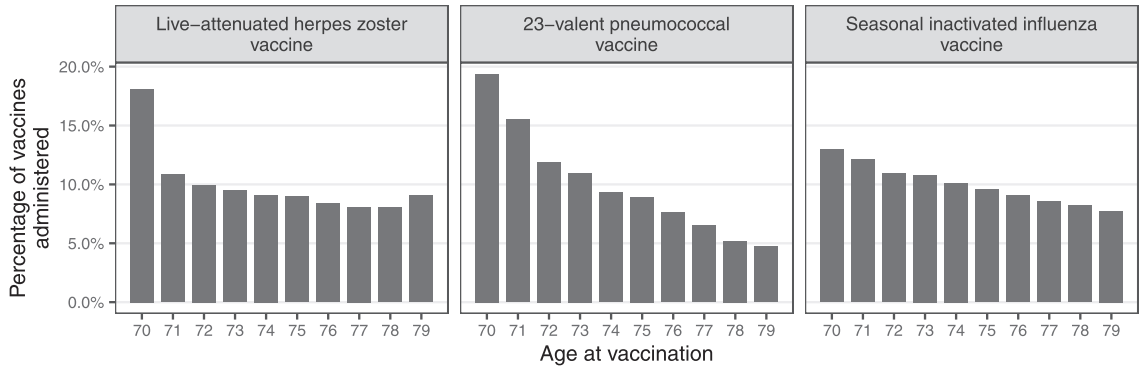

Fig. 3. Distribution of age of vaccination for vaccines administered to 70–79 year old adults in primary care between 1 November 2016 and 31 July 2018, by vaccine.

the number of events per-person days under observation for the positive control (ISR) peaks soon after ZVL vaccination, whereas for the other medical events, including the negative control (burns), there was no obvious elevation in the event rate in the 12 weeks after vaccination (Fig. 4).

3.2. Self-controlled case series analysis

3.2.1. Injection site reactions

An increase in the relative incidence of injection site reactions was observed in the 7-day risk window following all three vaccines in the main analysis (Table 1). Results of sensitivity analyses excluding co-administered vaccines were consistent (Table 2). The incidence of ISR remained elevated in the 42-day post-risk washout period following ZVL (RI = 3.42, 95% CI 1.81–6.49) (Appendix B); on further exploration, risk was elevated only in the early part of the post-risk washout period (8–14 days post-vaccination (RI = 16.2, 95% CI 6.77–38.7), before returning to control period levels (Appendix C).

3.2.2. Myocardial infarction (MI)

There was no evidence of an increased risk of MI in the 42-day risk window following any vaccine in the primary analysis (Table 1) or when including first events only as part of the sensitivity analysis (Table 2). There was evidence of an increased relative incidence of MI in the post-risk washout period (days 43–84 post exposure) for ZVL (RI = 1.68, 95% CI 1.11–2.54) (Appendix B). On further exploration, the increased relative incidence was observed in days 57–63 and 71–77 (Appendix D); small event numbers

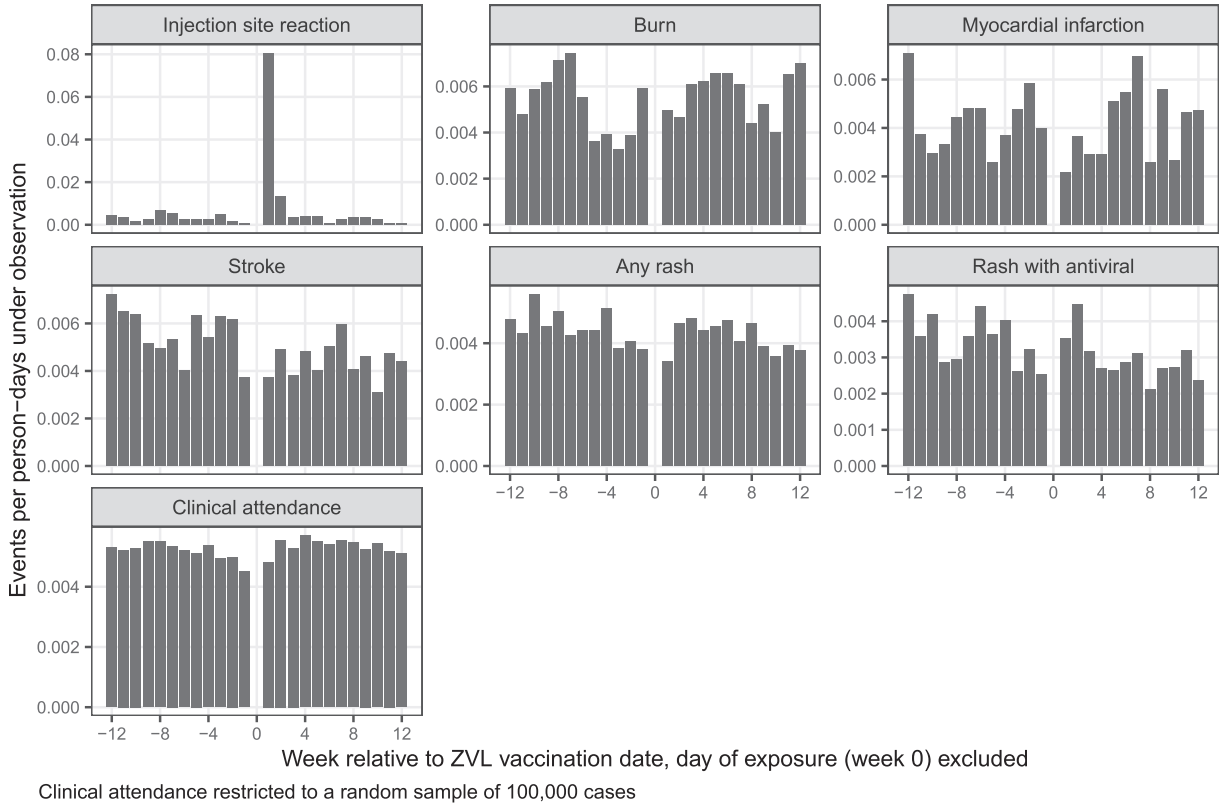

Fig. 4. Event rates by outcome relative to date of vaccination with live attenuated herpes zoster vaccine (ZVL), for vaccines administered to 70–79 year old adults in primary care between 1 November 2016 and 31 July 2018, by vaccine.

Table 1
Relative incidence (at-risk window versus control period)[a] of outcome events following vaccination of 70–79 year old adults in primary care between 1 November 2016 and 31 July 2018 (outcome events modelled independently with all vaccines included jointly, adjusted for season).

Outcome	Zoster vaccine			Pneumococcal vaccine			Influenza vaccine		
	At-risk n (PD)	Control n (PD)	RI (95% CI)	At-risk n (PD)	Control n (PD)	RI (95% CI)	At-risk n (RD)	Control n (PD)	RI (95% CI)
Injection site reaction	37 (833)	104 (96 876)	77.4 (48.1, 124.6)	30 (378)	138 (102,318)	65.0 (31.6, 133.6)	29 (1,071)	102 (84,934)	6.62 (3.42, 12.8)
Burn	72 (23,798)	1,282 (511,166)	1.23 (0.97, 1.57)	8 (5,259)	1,455 (564,087)	0.55 (0.27, 1.13)	145 (57,946)	1,036 (407,960)	0.93 (0.76, 1.14)
Myocardial infarction	12 (8,327)	436 (221,244)	0.74 (0.41, 1.33)	2 (2,729)	469 (237,376)	0.39 (0.09,1.59)	47 (23,226)	324 (176,808)	1.17 (0.82, 1.66)
Stroke	50 (35,113)	1,984 (793,445)	0.58 (0.44, 0.78)	15 (9,081)	2,132 (868,410)	0.72 (0.42, 1.21)	197 (88,397)	1,500 (633,321)	1.06 (0.89, 1.26)
Any rash	422 (228,311)	10,381 (4,990,170)	0.97 (0.88, 1.08)	115 (52,961)	11,959 (5,497,005)	1.01 (0.84, 1.23)	1,124 (564,634)	8,645 (3,982,480)	1.06 (0.98, 1.14)
Rash with antiviral	61 (33,800)	1,570 (856,854)	0. 83 (0.62, 1.10)	22 (10,571)	1,931 (1,099,845)	1.23 (0.77, 1.95)	104 (73,998)	917 (455,454)	0.78 (0.62, 0.97)
Clinical attendance	79,352 (3,726,764)	1,799,288 (79,138,828)	0.94 (0.94, 0.95)	19,616 (848,864)	2,032,393 (87,483,370)	1.06 (1.04, 1.07)	200,785 (8,840,389)	1,368,928 (63,862,675)	1.03 (1.02, 1.03)

CI: Confidence interval, n: number of events, PD: person days, RI: Relative incidence.
[a] At risk window is 42 days following vaccination except for injection site reaction (7 days). The control period is time periods an individual was under observation with the exception of the risk window, day of vaccination and 42-day washout periods before vaccination and following the at-risk window.

Table 2
Sensitivity analyses: Relative incidence (at-risk window versus control period[a]) of outcome events following vaccination with live attenuated herpes zoster vaccine (ZVL) in 70–79 year old adults in primary care between 1 November 2016 and 31 July 2018 (with and without concomitant vaccines (influenza and 23-valent pneumococcal polysaccharide vaccine vaccine) and considering all events or first events only).

	All vaccines modelled together, for all events	ZVL modelled independently (concomitant vaccines excluded), for all events	All vaccines modelled together, for first events only	ZVL modelled independently (concomitant vaccines excluded), for first events only
	RI (95% CI)	RI (95% CI)	RI (95% CI)	RI (95% CI)
Injection site reaction	77.4 (48.1, 124.6)	60.5 (37.4, 97.9)	71.2 (43.6, 116.1)	57.3 (34.8, 94.3)
Burn	1.23 (0.97, 1.57)	1.12 (0.86, 1.47)	1.08 (0.78, 1.50)	1.12 (0.80, 1.58)
Myocardial infarction	0.74 (0.41, 1.33)	0.70 (0.35, 1.36)	0.90 (0.49, 1.66)	0.80 (0.39, 1.64)
Stroke	0.58 (0.44, 0.78)	0.51 (0.37, 0.71)	0.54 (0.37, 0.77)	0.51 (0.34, 0.76)
Any rash	0.97 (0.88, 1.08)	0.96 (0.86, 1.07)	1.01 (0.90, 1.14)	1.01 (0.89, 1.14)
Rash with antiviral	0. 83 (0.62, 1.10)	0.67 (0.49, 0.92)	0.80 (0.59, 1.09)	0.64 (0.45, 0.90)
Clinical attendance	0.94 (0.94, 0.95)	0.94 (0.93, 0.94)	NA[b]	NA[b]

RI: Relative incidence, CI: Confidence interval.
[a] At risk window is 42 days following vaccination except for injection site reaction (7 days). The control period is time periods an individual was under observation with the exception of the risk window, day of vaccination and 42-day washout periods before vaccination and following the at-risk window.
[b] Clinical attendance was not considered sufficiently rare to conduct sensitivity analysis using first events only.

within this post-hoc analysis limited the ability to investigate these more granular patterns.

3.2.3. Stroke

A reduced relative incidence of stroke was observed in the 42-day window following ZVL but not following 23vPPV or influenza vaccine (Table 1). This persisted when including first events only as part of the sensitivity analysis (Table 2). This reduced incidence following ZVL persisted into the post-risk washout window (RI = 0.72, 95% CI 0.55–0.93) in the primary analysis (Appendix B).

3.2.4. Rash

There was no change in the relative incidence of rash or rash with antiviral prescription in the 42-day window following ZVL compared to the control period in the primary analysis (Table 1), although a reduced relative incidence was noted in the post-risk washout period compared to control-windows (RI = 0.67, 95% CI 0.54–0.83, for rash with antiviral prescription) (Appendix B). A reduced risk was observed in the at-risk window when ZVL was given alone (Table 2).

3.2.5. Clinical attendance

Compared to control periods, there was a small reduction in the risk of clinical attendance in the 42-day risk window following ZVL but not following 23vPPV or influenza vaccines (Table 1). The results of sensitivity analyses excluding concomitant vaccines was consistent for ZVL (Table 2).

3.2.6. Burn

No change in the incidence of burn, which was used as a negative control, was observed for any of the vaccines.

3.2.7. Pre-exposure risk

A reduced relative incidence of clinical attendance was observed for ZVL and influenza vaccines in the pre-exposure washout window (ZVL RI = 0.95, 95% CI 0.95–0.96; Influenza RI = 0.93, 95% CI 0.93–0.94) compared to control-windows in the primary analysis (Appendix B). A lower relative incidence of MI (RI = 0.44, 95% CI 0.21–0.94) and rash with antiviral prescription (RI = 0.69, 95% CI 0.51–0.94) were observed during the pre-exposure window compared to control period for ZVL (Appendix B).

4. Discussion

This analysis of outcome events following 332,988 eligible ZVL, influenza and 23vPPV vaccination encounters in 150,054 individuals in the Australian primary care setting found no evidence of an increase in the risk of serious outcomes in the pre-defined risk periods, while confirming an increase in ISR following ZVL and other vaccines. The risk of ISR following ZVL in the safety sub study [10] of the pivotal ZVL randomized controlled clinical trial was 48% in vaccine recipients compared to 16% in placebo recipients, with fewer than 1% reported as severe. Consistent with clinical trial data, the risk of ISR in our study was elevated both for ZVL alone and ZVL administered concomitantly with influenza vaccine [38]. While ISR occurred a median of 2.3 days following vaccination in the sub study [10], and has been observed a median of 2 days following vaccination in post-marketing surveillance [13], we observed an elevated incidence of ISR documented at primary care practices up to 14 days following ZVL, which likely relates to delay in reporting ISR to the GP.

The absence of any increase in clinical attendance following ZVL vaccination, identified in our study, is reassuring. Similarly, AusVaxSafety active surveillance data has demonstrated a low rate of reported medical attendance following ZVL [22]. A reduced relative incidence of clinical attendance in the pre-exposure period in this study provides evidence to support the healthy vaccinee effect, which was minimized by the use of the pre-exposure washout window. A reduced relative incidence of MI, but not stroke, was seen in the ZVL pre-exposure period.

Although wild-type VZV reactivation causing HZ has been associated with ischemic [14,15] and hemorrhagic stroke [15] and MI [14] in the one to four weeks following infection [34], the SPS [10] did not identify an increased risk for cardiovascular events. We identified a reduced relative incidence of stroke following ZVL; whether this is attributable to HZ vaccine efficacy and reduced risk of wild-type HZ associated complications requires further study. While death due to stroke and heart disease have been reported to post-marketing spontaneous reporting systems [11], some deaths from these causes would be expected in this age group irrespective of vaccination; no unusual pattern has been observed in surveillance data that would suggest a causal relationship to ZVL [11]. SCCS methodology aims to reduce confounding and other biases that may affect spontaneous reporting systems; other post-marketing studies (including SCCS) have not identified an increased risk of cardiovascular or cerebrovascular events following ZVL [16,33].

While no increase in the relative incidence of MI was observed in the pre-specified risk-window period, we observed a higher relative incidence of MI in the post-risk washout period (between 43- and 84-days following vaccination). On *post hoc* exploration an increased risk was not observed consistently during this period suggesting this may be a chance finding. Our findings may be affected by poor ascertainment of serious events like stroke and MI due to the use of primary care rather than hospital data; the study may not have been adequately powered for these rarer outcomes. Further investigation within emergency department and hospital data may provide greater sensitivity in identifying and validating cardiovascular and cerebrovascular outcome events.

While ascertainment of these serious events may be limited in the primary care setting, rash is common [39]. Rash has been considered a non-specific finding in post-marketing observational studies [16]; the pairing of rash with antiviral prescription is likely to be more specific for herpetiform, varicella- or zoster-like rashes. A reduced relative incidence of rash with antiviral prescription following ZVL was observed, which is most likely attributable to vaccine-induced effectiveness against HZ. The finding is reassuring given that a varicella-like rash in the days following vaccination may indicate disseminated infection with vaccine virus in immunocompromised patients [17]. In a recent survey of immunization providers in the US, family physicians report recommending ZVL to certain immunocompromised patients, despite a contraindication to ZVL vaccination [40]. Following the death of an Australian man from disseminated Oka vaccine VZV infection in 2016 [17] there was widespread education targeted toward GPs regarding vaccine contraindications and appropriate administration of ZVL [17,41].

There are limitations to the use of MedicineInsight data, in addition to those inherent in routinely collected data more generally, and the methods which could be applied in this study [23]. An assumption of the analysis is that an unbiased set of events occurring during an individuals' observation period have been ascertained. However, the quality of data used is dependent on GP data entry into the practice CIS, which is likely to vary by site; where an outcome was not recorded, it is not possible to know whether this reflected an absence of the outcome or failure of documentation, particularly for minor outcomes such as ISR. Outcomes such as stroke and MI would be more likely to present initially to an emergency department than to primary care; primary care data may be insufficiently sensitive to capture these events, without linkage to hospitalization data. For example, there was no reduced incidence of stroke identified in the pre-exposure period, which might have been expected if a healthy vaccinee effect is evident. Delayed coding of hospitalization information by GPs (due to delayed receipt of information such as hospital letters and laboratory test results) may also mean events that occurred in the pre-vaccination window are documented in the post-vaccination window. Inaccurate onset dates could also be reported for milder events, such as ISR, if they are recorded as a recent historical event during a routine primary care visit, which may explain the pronged period post vaccination over which ISR was observed. Due to lack of specific information on date of death, patients who died were censored on 31 December of the preceding year so that MI or stroke events occurring immediately prior to death may not have been captured.

The generalizability of the findings of this study are limited by the exclusion of patients with a past history of MI or stroke. In addition, it was not possible to determine an individual's level of immunocompromise due to the complexity of classifying the immune status of individual patients based on limited information; immune status may affect the experience of adverse events [17,42].

As not all MedicineInsight data were coded, exposures and outcome events were identified by regular expression searches of text strings, which were not validated. Additionally, individual identifiers were only available at the site level, meaning any individuals attending multiple practices, which can occur due to non-capitation of patients to a single primary care practice in the Australian context, were treated as distinct individuals. This meant that outcome events occurring at a site other than the practice attended for vaccination would not be ascertained. However, evidence suggests multiple practice attendance is low in older age groups, with only 12.9% of adults over 70 years of age reporting attending multiple practices in a recent survey [43].

The systematic exploration of the use of general practice data and the SCCS design in vaccine pharmacovigilance in this study is a critical step in moving beyond spontaneous reporting systems in Australia, given the inherent limitations of passive post-marketing adverse events surveillance. Although many Australian patients, especially older patients, see a regular GP and GPs are commonly the immunization provider, electronic primary care

data is rarely used for vaccine safety research in Australia; one proof of concept paper using a different (smaller) primary care database validated a safety signal of an increase in ISR with repeat 23vPPV vaccination, resulting in removal of a recommended vaccine dose [44]. There is significant scope to better utilize routinely collected primary care data for vaccine safety surveillance once the limitations and applications are more fully understood and further validation of the approach has been undertaken. For more severe adverse events, the application of SCCS to hospitalization data has been effective internationally [26,28]. Linkage with hospitalization data in Australia could make primary care data a richer source of information.

5. Conclusion

No new safety concerns were identified for ZVL in this study which used a novel data source and the SCCS design. Expected findings in relation to an increased risk of ISR following ZVL, influenza and pneumococcal vaccination support the validity of the SCCS in this setting, using primary care data. Findings in relation to MI and stroke were reassuring, but are subject to limitations including data completeness, delayed reporting and hospital presentation. Further work should focus on validation of identified exposures and outcomes and linkage with hospitalization data. The finding of reduced rash with antiviral prescription following ZVL suggests this data source could be examined to explore ZVL vaccine effectiveness in Australia, using a suitable study design.

Statement

This paper contains original unpublished work and is not being submitted for publication elsewhere. This work was submitted as a report to the Australian Government Department of Health.

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Author contributions

AP and JT contributed equally to the authorship of the manuscript. AP developed the study protocol, assisted with data interpretation and drafted and revised the manuscript; JT revised the study protocol, conducted the analysis and contributed to interpretation and revision of the manuscript; JM revised the study protocol and contributed to analysis and interpretation; CG, TS and KM provided input in the protocol, interpretation and manuscript; KC provided input into the protocol, provided the data and assisted with data interpretation and revision of the manuscript; all authors reviewed and approved the final manuscript.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Kendal Chidwick is an employee of NPS MedicineWise. The other authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Free text search criteria for vaccine and outcomes events, and to exclude non-clinical attendances, within NPS MedicineInsight data

Vaccine regular expression search terms[a]

Vaccine	Search Terms
Zoster	zost|herp|varic|shing
Pneumococcal	pn|ppv
Influenza	flu|ufl|quad|tetra|vaxig|intanza
Exclusions[b]	decl|ref|past|prev|not |priorix|no |quadracel|proquad|7 val|13 val

[a]The symbol|indicated 'or' within regular expression searches.[b]We generally undertook two regular expression searches: one to identify potential matches to the vaccine or condition of interest for inclusion; one to identify and exclude any matched records which were not of interest.

Outcome event regular expression search terms[a]

Outcome event		Search Criteria
Injection site reaction	Inclusions	(inje|vacc|admin|site|loca).*brui|(inje|vacc|admin|site|loca).*cell|(inje|vacc|admin|site|loca).*eryt|(inje|vacc|admin|site|loca).*indu|(inje|vacc|admin|site|loca).*infe|(inje|vacc|admin|site|loca).*infla|(inje|vacc|admin|site|loca).*nodu|(inje|vacc|admin|site|loca).*oede|(inje|vacc|admin|site|loca).*pain|(inje|vacc|a

(*continued on next page*)

Outcome event regular expression search terms (*continued*)

Outcome event		Search Criteria
		dmin|site|loca).*petech|(inje|vacc|admin|site|loca).*prur|(inje|vacc|admin|site|loca).*rash|(inje|vacc|admin|site|loca).*redn|(inje|vacc|admin|site|loca).*reac|(inje|vacc|admin|site|loca).*sore|(inje|vacc|admin|site|loca).*swel|(inje|vacc|admin|site|loca).*urti|post[p].*(inje|vacc|admin)
	Exclusions	zostavax injection|zostavax vaccn|shingle vaccination/|shingles vaccine/|zoster vaccine,|appointuit|postpone|pain clinic|parasite|fluvacc|knee - graze|vaccination,|vaccinations,|bee|sting|tick|bite|insect|incision site|concern of|carcinoma|spc site|catheter|(b12|b-12) injection|^shingles vaccination $|postpone vacc|travel |prolia|denosumab|vaccination//|vaccinations ,|vaccination ,|steroid +|re-vaccination
Burns	Inclusions	burn
	Exclusions	burning|craig
Myocardial infarction	Inclusions	^ami|ami$| ami myocar.*infar|posteri.*infar|anteri.*infar|septal.*infar|lateral.*infar|heart.*infar|heart.* attac
	Exclusions	fear|risk|lacunar|cortex|cerebell|1989|1999|1996|2008|transfer|undisplaced|amission|stopped|amiodarone|amiadarone|amiodorone|hypercholesterami|exported|family|prevent|fracture|aminoglycoside|tele|amiloid|renal|badami|cerebral|robyn|amine|amiodar|amioa|aminio|amigrai
Stroke	Inclusions	stroke|trans.*isch|^tia$\|^tia \| tia$| tia
	Exclusions	heat|sun|[pr]*event|family hist|\\?|week|risk|post |advice|protect|engage sms|engage email
Any rash	Inclusions	rash|shingles|zoster|vesic
	Exclusions	imm|vac|vax|injec|appointuit|letter|crash|water brash
Antiviral	Inclusions	acyclo|aciclo|famciclo|famvir|notaris

[a]The symbol | indicated 'or' within regular expression searches.

Free text encounter type and encounter reason terms used to exclude non-clinical records[a]

Encounter type	Encounter reason
access session|admin|admin notes|administration|administrative (clinical)|administrative procedure|allied health|clinical notes provided|closure|correspondence received|ctg registration|diabets educator|dietitian|ecc care coordination|ecc consultation|ecc family session|ecc outreach session|ecc phone intervention|ecc session|ecc tertiary liaison|engagement session|fax|infusion bay - nurse|intake|it testing|medical record transfer|medical records|medicare check|mhis|nh fax message|no consultation|non attendance/late cancellation warning|notes - patient not in attendance|nurse|nurse admin|nurse attendance|nurse consult|nurse consultation|nurse consultation|nurse encounter|nurse visit|nurse visit|nursing|nursing consult|nursing consultation|nursing staff consult|nursing visit|out of office|pathology recall by rn|patient consent|pcehr assisted registration|peer support|physio consultation|physiotherapy|practice admin|practice consultation|practice nurse|practice nurse|practice nurse consultation|practice nurse surgery consultation|psychology session|reception|reception colleen|registered nurse|sms|social worker|step session|surgery visit - nurse|treatment room - rn|tristar konnect|websterpak	^cc$\|^een$|^en$\|^fta$|aboriginal health work|administration office|administrative proced|ahpacc liason officer|ahpacc worker|ain|allied health assistan|care coordinator|chaperone|chart review|child health worker|chinese access support|clinical services mana|community health worke|counsellor|dermagen consultant|diabetes educator|did not attend|dietitian|een nurse|endorsed enrolled nurs|enrolled nurse|exercise physiologist|failed to attend|family services worker|file review|ips vocational worker|jven peer worker|left message|letter posted|letter written no consu|medical student|mental health nurse|midwife|non[ ]? urgent recall|notes and record|nurse|nurse assistant|nurse practitioner|nurse support of|nursing student|occupational therapis|on recall appoint|optomertrist|pap remind|pathology request|peer worker|phone result|phone[ ]?call|physiotherapist|podiatrist|practice manager|practice nurs|prescription no consul|prescription renewal|primary health worker|psychologist|recall|receptionist|record and notes|referral letter no con|registered nurse|reminder manage|repeat prescription no|research assist|researcher|review file no con|senior case manager|social worker|telephone|triage telephone|urgent recall|youth peer worker

[a]The symbol | indicated 'or' within regular expression searches.

Appendix B. Relative incidence (at-risk, pre-exposure and post-risk washout windows versus control period[a]) of outcome events following vaccination of 70–79 year old adults in primary care between 1 November 2016 and 31 July 2018 (all outcomes modelled independently with all vaccines included jointly, adjusted for season)

		Zoster vaccine (Exposures = 92,857)			Pneumococcal vaccine (Exposures = 21,480)			Influenza vaccine (Exposures = 218,651)		
Outcome	Risk period	n	PD	RI (95% CI)	n	PD	RI (95% CI)	n	PD	RI (95% CI)
Injection site reaction	Control	104	96,876	1.00	138	102,318	1.00	102	84,934	1.00
	At risk	37	833	77.4 (48.1, 124.6)	30	378	65.0 (31.6, 133.6)	29	1,701	6.62 (3.42, 12.8)
	Pre-exposure	6	4,472	2.05 (0.83, 5.08)	1	2,268	0.36 (0.04, 2.97)	11	10,206	0.60 (0.28, 1.32)
	Post-risk	15	4,978	3.42 (1.81, 6.49)	2	2,260	1.38 (0.30, 6.32)	17	10,194	1.11 (0.58, 2.12)
Burn	Control	1,282	511,166	1.00	1,455	564,087	1.00	1,036	407,960	1.00
	At risk	72	23,798	1.23 (0.97, 1.57)	8	5,259	0.55 (0.27, 1.13)	145	57,946	0.93 (0.76, 1.14)
	Pre-exposure	44	21,042	0.87 (0.64, 1.18)	6	5,296	0.42 (0.18, 0.95)	117	58,097	0.73 (0.58, 0.92)
	Post-risk	61	22,851	1.07 (0.82, 1.39)	6	4,661	0.47 (0.21, 1.07)	140	54,043	1.06 (0.85, 1.32)
Myocardial infarction	Control	436	221,244	1.00	469	237,376	1.00	324	176,808	1.00
	At risk	12	8,327	0.74 (0.41, 1.33)	2	2,729	0.39 (0.09,1.59)	47	23,226	1.17 (0.82, 1.66)
	Pre-exposure	7	7,618	0.44 (0.21, 0.94)	8	2,746	1.41 (0.67, 2.99)	55	23,310	1.50 (1.04, 2.14)
	Post-risk	26	7,892	1.68 (1.11, 2.54)	4	7,892	0.77 (0.28, 2.14)	42	21,383	0.90 (0.61, 1.32)
Stroke	Control	1,984	793,445	1.00	2,132	868,410	1.00	1,500	633,321	1.00
	At risk	50	35,113	0.58 (0.44, 0.78)	15	9,081	0.72 (0.42, 1.21)	197	88,397	1.06 (0.89, 1.26)
	Pre-exposure	72	31,886	0.90 (0.71, 1.15)	25	9,100	1.08 (0.72, 1.64)	217	88,990	1.19 (1.00, 1.42)
	Post-risk	60	33,674	0.72 (0.55, 0.93)	16	8,147	0.86 (0.52, 1.44)	184	82,132	0.97 (0.81, 1.16)
Any rash	Control	10,381	4,990,170	1.00	11,959	5,497,005	1.00	8,645	3,982,480	1.00
	At risk	422	228,311	0.97 (0.88, 1.08)	115	52,961	1.01 (0.84, 1.23)	1,124	564,634	1.06 (0.98, 1.14)
	Pre-exposure	392	209,613	0.97 (0.88, 1.08)	105	53,735	0.89 (0.73, 1.09)	1,09	567,207	1.08 (1.00, 1.17)
	Post-risk	346	217,586	0.85 (0.76, 0.95)	87	46,214	0.96 (0.77, 1.20)	1,018	523,365	1.01 (0.93, 1.09)
Rash with antiviral	Control	1,570	856,854	1.00	1,931	1,099,845	1.00	917	455,454	1.00
	At risk	61	33,800	0.83 (0.62, 1.10)	22	10,571	1.23 (0.77, 1.95)	104	73,998	0.78 (0.62, 0.97)
	Pre-exposure	48	31,811	0.69 (0.51, 0.94)	17	10,694	0.86 (0.51, 1.43)	134	74,279	1.03 (0.83, 1.27)
	Post-risk	371	254,613	0.67 (0.54, 0.83)	84	56,541	0.79 (0.56, 1.10)	891	572,406	0.82 (0.72, 0.94)
Clinical attendance	Control	1,799,288	79,138,828	1.00	2,032,393	87,483,370	1.00	1,368,928	63,862,675	1.00
	At risk	79,352	3,726,764	0.94 (0.94, 0.95)	19,616	848,864	1.06 (1.04, 1.07)	200,785	8,840,389	1.03 (1.02, 1.03)
	Pre-exposure	73,941	3,426,143	0.95 (0.95, 0.96)	20,795	863,058	1.02 (1.01, 1.04)	181,871	8,876,058	0.93 (0.93, 0.94)
	Post-risk	80,653	3,574,331	0.98 (0.97, 0.98)	16,586	739,952	1.01 (1.00, 1.03)	189,822	8,164,901	1.05 (1.04, 1.06)

CI: Confidence interval, n: number of events, PD: person days, RI: Relative incidence.

[a]At risk window is 42 days following vaccination except for injection site reaction (7 days); pre risk window is 42-days before vaccination; post risk window is 42-days following the at risk window; all other time periods an individual was under observation were allocated to the control period.

Appendix C. Relative incidence (at-risk, pre-exposure, post-risk washout and 7-day partitioned post-risk windows versus control period[a]) of injection site reaction following vaccination with live attenuated herpes zoster vaccine (ZVL) in 70–79 year old adults in primary care between 1 November 2016 and 31 July 2018 (adjusted for season)

Risk period	n	PD	RI (95% CI)
Control	104	96,876	1.00
Pre-exposure	6	4,472	1.92 (0.76, 4.87)
At risk (1–7 days)	37	833	86.2 (53.0, 140.3)
Post-risk (8 – 49 days)	15	4,978	3.42 (1.81, 6.49)
Post-exposure risk period: 7-day partition			
Post-risk (8–14 days)	6	833	16.2 (6.77, 38.7)
Post-risk (15–21 days)	2	833	3.88 (0.91, 16.6)
Post-risk (22–28 days)	3	833	3.32 (0.87, 12.7)
Post-risk (29–35 days)	3	833	3.06 (0.78, 12.0)
Post-risk (36–42 days)	0	826	0.00 (0.00, Inf)
Post-risk (43–49 days)	1	820	0.67 (0.08, 5.67)

CI: Confidence interval, n: number of events, PD: person days, RI: Relative incidence.

[a]At risk window is 7 days following vaccination; pre risk window is 42-days before vaccination; post risk window is 42-days following the at risk window; all other time periods an individual was under observation were allocated to the control period.

Appendix D. Relative incidence (at-risk, pre-exposure, post-risk washout and 7-day partitioned post-risk windows versus control period)[a] of myocardial infarction following vaccination with live attenuated herpes zoster vaccine (ZVL) in 70–79 year old adults in primary care between 1 November 2016 and 31 July 2018 (adjusted for season)[b]

Risk period	n	PD	RI (95% CI)
Control	436	221,244	1.00
Pre-exposure	7	7,618	0.44 (0.20, 0.93)
At risk (1–42 days)	12	8,327	0.74 (0.41, 1.32)
Post-risk (43–84 days)	26	7,892	1.68 (1.11, 2.54)
Post-exposure risk period: 7-day partition			
Post-risk (43–49 days)	3	1,351	1.00 (0.32, 3.17)
Post-risk (50–56 days)	2	1,349	0.81 (0.20, 3.28)
Post-risk (57–63 days)	8	1,330	3.15 (1.54, 6.46)
Post-risk (64–70 days)	3	1,310	1.27 (0.40, 3.99)
Post-risk (71–77 days)	7	1,288	2.96 (1.38, 6.35)
Post-risk (78–84 days)	3	1,264	1.10 (0.35, 3.47)

CI: Confidence interval, n: number of events, PD: person days, RI: Relative incidence.

[a]At risk window is 42 days following vaccination; pre risk window is 42-days before vaccination; post risk window is 42-days following the at risk window; all other time periods an individual was under observation were allocated to the control period.

[b]Changes to RI estimates compared to Table 2 are due to changing overlap of season and risk windows when using a different partition.

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