**Abstract** (300 allowed; currently 309)

*Objective* To investigate the risk of pre-specific adverse events following live attenuated herpes zoster vaccine (ZVL) in older adults attending primary care providers in Australia.

*Methods* Individuals aged 70 to 79 years who received ZVL between 1 November 2016 and 31 July 2018 were identified within a nationally representative primary care database. The self-controlled case series (SCCS) method was used to compare the seasonally-adjusted relative incidence (RI) of seven pre-specified outcome events (injection site reaction (ISR), burn [negative control], myocardial infarction (MI), stroke, any rash, rash with a prescription for an antiviral within 2 days of the rash-related encounter, and clinical attendance) in a post-vaccination, at-risk window with the incidence at a time distant to vaccination. Sensitivity analyses examined the effect of concomitant vaccination (influenza and 23-valent pneumococcal vaccination) and restriction to first outcome event.

*Results* A total of 332,988 vaccination encounters in 150,054 individuals were identified during the study period. The most common outcome event was clinical attendance (over 2 million) followed by rash (12,309 events); ISR was the rarest outcome event (177 events). There was an increased RI of ISR in the 7-days following ZVL (RI=77.39, 95% CI 48.06 to 124.62). No change to the RI of MI (RI = 0.74, 95% CI 0.41 to 1.33), rash (RI = 0.97, 95% CI 0.8 to 1.08), or rash with antiviral (RI = 0. 83, 95% CI 0.62 to 1.10) were identified in the 42 days following ZVL. The RI of clinical attendance (RI = 0.94, 95% CI 0.94 to 0.95) and stoke (RI=0.6, 95% CI 0.4 to 0.8) were lower in the 42 days following administration of ZVL.

*Conclusions* No new safety concerns were identified for ZVL in this study based on a novel primary care data source using a SCCS design. An expected increased risk of ISR was identified; findings in relation to cardiovascular disease were reassuring.

Word count: 5000 allowed; currently around 3500. References: 50 allowed; currently 31

**Keywords (max 6)**

1. **Introduction**

Herpes zoster (HZ) is a localised, painful, vesicular skin rash resulting from reactivation of varicella-zoster virus. The average lifetime risk is around 30% but increases with age.[1] Prior to implementation of vaccination 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[3] and the United States (US).[4] The risk of post-herpetic neuralgia, a chronic neuropathic pain syndrome, also increases with age.[5] Disseminated disease can occur in people who are immunosuppressed.

Live attenuated varicella-zoster vaccine (ZVL) was registered in Australia for use in Australia in 2006 and available from 2014 for people aged over 50 years. It is recommended for immunocompetent adults over 60 years of age. In November 2016, a funded ZVL immunisation program commenced under the Australian National Immunisation Program (NIP) for adults aged 70 years with catch-up for those aged 71–79 years also funded until October 2021.

ZVL was evaluated in large pre-licensure clinical trials with no increased risk of serious adverse events (SAE), hospitalized adverse events or death.[6-8] The rate of injection site reactions (ISR) was higher in vaccine than placebo groups.[6, 8] A post-licensure clinical trial demonstrated a similar safety profile, with no statistically significant difference in the rate of SAE up to 182 days following vaccination.[9] Post-licensure passive surveillance has been consistent with clinical trials. Of 23,556 reports submitted by healthcare providers to the Merck, Sharp, & Dohme Corp (MSD) Adverse Event (AE) global safety database between May 2006 and May 2016, 93% of reports were non-serious, with ISR the most commonly reported AE (20.5%), followed by HZ (8.6%) and rash (4.2%).[10] Of 23,092 reports submitted to the US Vaccine Adverse Events Monitoring System (VAERS) from May 2006 to January 2015, 96% were classified as non-serious, with ISR, HZ and rash the most frequently reported non-serious AE.[11]

Post-marketing surveillance methods are limited by the potential for biased reporting and, for ZVL, is confounded by the higher prevalence of chronic disease in the older target population.[11] The self-controlled case series (SCCS) method was developed for vaccine safety assessment and avoids confounding by allowing individuals to act as their own control.[12] SCCS methodology has been used to examine ZVL[13] using data from managed care cohorts in the US. In Australia, however, managed care organisations do not exist. Older patients are likely to receive ZVL from their private general practitioner (GP). While practices maintain their own patient records, the National Prescribing Service (NPS) collates GP data through the MedicineInsight program. This study examined the risk of pre-specified AE in the target NIP cohort using nationally representative GP data. This is the first time MedicineInsight data has been used to examine vaccine safety in an Australian GP cohort.

**2. Methods**

**2.1 Study setting**

The MedicineInsight data set consists of longitudinal, de-identified, whole-of-practice data extracted from the clinical information systems (CISs) of participating practice sites across Australia. It includes between 15% and 20% of the Australian population. Data is 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 (an entry by administration staff) encounters. Within-site individual identifiers are used to identify records common to an individual.

**2.2 Study population**

The primary vaccine of interest was ZVL, however, individuals who had received 23-valent pneumococcal (23vPPV) and influenza vaccines were included because these vaccines are often co-administered with ZVL. MedicineInsight records were obtained for individuals aged 70–79 years who received ZVL, 23vPPV or influenza vaccine(s) between 1 November 2016 to 31 July 2018. We treated this study population as a random sample of the target population.

Individuals with multiple vaccination encounters for ZVL or 23vPPV were excluded as these vaccines are generally recommended to be given as a single dose for older adults. Those with multiple vaccination encounters for influenza were excluded if these encounters were within 126 days because a single dose is generally recommended each season. Individuals with records for historical events of stroke and myocardial infarction were excluded. Individuals who died were censored at 31 December of the preceding year because only the year of death was available.

* 1. **Study design**

The SCCS design was developed for vaccine safety evaluation [12] and has been used in a variety of settings.[12-16] It identifies the relative incidence of an outcome event within a risk window following exposure (i.e. vaccination) compared to the incidence at all other times under observation. Only individuals who have experienced an outcome event are included and the design automatically controls for fixed confounders.[12]

This study compared the incidence of seven pre-specified outcome events (ISR [positive control], burn [negative control], myocardial infarction, stroke, any rash, rash with a prescription for an antiviral within 2 days of the rash-related encounter, and clinical attendance) in a post-vaccination, at-risk window with the incidence of these outcome events at a time distant to vaccination. 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 that was considered unrelated to vaccination.

Data were only available as free text and were not coded. With the exception of clinical attendance, outcome events were identified using free-text regular expression searches of MedicineInsight vaccination, practice encounter, diagnosis and prescription fields (see supplementary information for search terms). Records of clinical attendance were identified by excluding non-clinical (administrative) encounter records. Outcome dates were obtained from practice encounter dates, diagnosis dates and prescription dates.

Exposure (vaccination) was defined as an immunisation record for one of the three vaccines under study. Vaccination events were identified via targeted, free-text search criteria (see supplementary information for search terms). The date of vaccination was set as the administration date specified in the vaccination record.

Risk windows were identified based on biologically plausible windows supported by evidence. These were defined as 1–7 days post vaccination for ISR and 1–42 days post vaccination for all other outcome events. To account for the potential for an event to affect the likelihood of vaccination (healthy vaccinee effect),[12, 17] a washout period of 42 days pre-vaccination was defined. A 42 day post-risk washout period was included to minimise the potential for risk to carry over into the control period that may be attributable to the vaccine (Figure 1).[17] Pre-exposure and post-risk washout periods were excluded from the control period. All other time an individual was under observation was allocated to the control period (table 1).

**Figure 1: Study design**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Control** | **Washout** | **Vaccination** | **Risk window** | **Washout** | **Control** |
|  | 42 days |  | 42 days (7 days ISR) | 42 days |  |
|  | | | TIME |  | |

The basis for the length of the risk window for systemic adverse events was the 42 day window used in pre-licensure clinical trials [6, 8, 9, 18] and post-licensure studies [13, 19]. This time period is also biologically plausible for cardiovascular events, which have been observed following wild-type varicella-zoster virus, particularly 1 to 4 weeks following infection,[20, 21] with viral replication in arterial walls the proposed mechanism for cerebrovascular disease.[22] This risk window is also biologically plausible for rash, with varicella-like rash after 6 weeks more likely to represent wild-type infection.[10] The risk windows for burn (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 SPS and post-licensure surveillance [10, 18] and the identification of a signal for cellulitis within 7 days in another post-licensure SCCS.[13]

* 1. **Statistical methods**

Relative incidence estimates were obtained from the SCCS model. Given that the study period spanned 1 November 2016 to 31 July 2018, the model was adjusted for seasonal effects. The main analysis modelled all exposures (vaccines) together and allowed for recurrent events for each outcome (i.e. every outcome event occurring during the observation period could contribute towards the relative incidence estimate). Sensitivity analyses assessed vaccines independently, excluding co-administered vaccines from the analysis. For events where the risk of an outcome event was not considered independent of the first occurrence (i.e. stroke, myocardial infarction), sensitivity analyses were undertaken which only included the first outcome event. Analyses were conducted using R version 3.5.1 and the gnm package version 1.1.0.

**2.5. Ethical approval**

This 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 also approved by the Sydney Children’s Hospital Human Research Ethics Committee (HREC/17/SCHN/159).

1. **Results**

A total of 337,294 vaccination records for 150,756 individuals from 456 MedicineInsight sites were obtained. These include sites in major cities and in rural and remote areas, similar to the distribution of the Australian population in these areas.[23] After excluding individuals with multiple ZVL or 23vPPV vaccinations or multiple influenza vaccinations within 126 days of each other, a total of 332,988 vaccination encounters were included in analysis for 150,054 individuals.

**3.1 Population, exposure and outcome characteristics**

In general, the number of vaccination records declined with age (Figure 2) with ZVL increasing slightly at 79 years of age. About 82% of zoster and 89% of influenza vaccinations were administered alone, while 47% of pneumococcal vaccinations were administered alone and 43% were administered with influenza vaccine.

The most common outcome event identified was clinical attendance, with over 2 million attendances observed among exposed individuals during the study period. The next most commonly observed outcome event was any rash, with 12,309 events observed. The rarest outcome event identified was injection site reaction, with 177 events observed.

**3.2 Self-controlled case series analysis**

No change in risk of burn, which was considered a negative control, was observed for any vaccine (Table 2).

**Clinical attendance**

There was a reduced risk of clinical attendance following ZVL (RI = 0.94, 95% CI 0.94 to 0.95) and a small increased risk of clinical attendance following 23vPPV (RI = 1.06, 95% CI 1.04 to 1.07)) and influenza (RI = 1.03, 95% CI 1.02 to 1.03)) vaccines (Table 2). These associations held in the sensitivity analysis for individual vaccines ZV and 23vPPV, but there was no increased risk for clinical attendance following influenza vaccination given alone (Table 3).

**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 ([ZVL RI=77.39, 95% CI 48.06 to 124.62], [23vPPV RI=65.02, 95% CI 31.65 to 133.58], [influenza RI=6.62, 95% CI 3.42 to 12.80]. (Table 2). This was consistent in sensitivity analyses excluding co-administered vaccines ([ZV RI=60.54, 95% CI 37.43 to 97.91], [23vPPV RI = 125.61, 95% CI 46.09 to 342.34], [Influenza RI = 4.76, 95% CI 2.37 to 9.56]) (Table 3).

In both the main analysis and when excluding co-administered vaccines, the incidence of injection site reactions was also increased in the 42-day post-risk washout period following ZVL (RI=3.4, 95% CI 1.8 to 6.5 in the main analysis). This was attributed to an increased relative incidence of injection site reactions in the 8 to 14 days post vaccination (RI=16.20, 95% CI 6.77 to 38.73); the incidence returned to baseline levels after 15 days post vaccination.

**Myocardial infarction**

There was no increased risk of myocardial infarction following any vaccine in the main analysis (ZVL RI = 0.74, 95% CI 0.41 to 1.33) (Table 2) or when including first events only as part of a sensitivity analysis (Table 3). An increased relative incidence was observed during the post-risk washout period (days 43–84) for ZVL in the main analysis (RI=1.7, 95% CI 1.1 to 2.5). The increased relative incidence of MI in the post-risk washout period following ZVL was also observed in sensitivity analyses (first events only (RI = 1.80, 95% CI 1.15 to 2.83) and first events excluding co-administered vaccines (RI = 2.08, 95% CI 1.29 to 3.36) (Table 3). A 7-day partition of the post-risk washout period for the main ZVL analysis identified increased relative incidence from days 57–63 post vaccination (RI=3.2, 95% CI 1.5 to 6.5) and from days 71–77 post vaccination (RI=3.0, 95% CI 1.4 to 6.4) only (Table 4).

**Stroke**

In the main analysis, a reduced relative incidence of stroke was observed (RI=0.6, 95% CI 0.4 to 0.8) following ZVL. This effect continued into the post-risk washout window (RI=0.7, 95% CI 0.5 to 0.9). In a sensitivity analysis considering only first stroke events, the incidence was reduced only during the at-risk period (RI = 0.54, 95% CI 0.37 to 0.77) (Table 3).

**Rash**

There was no change in the risk of rash (RI = 0.97, 95% CI 0.8 to 1.08) or rash with antiviral (RI = 0. 83, 95% CI 0.62 to 1.10) following ZVL compared to the control period in the main analysis (Table 2), although a reduced risk was noted in the post-risk washout period (RI = 0.67, 95% CI 0.54 to 0.83) for rash with antiviral. There was a reduced risk for rash with antiviral following ZVL in the sensitivity analysis where co-administered vaccines were excluded (RI = 0.67, 95% CI 0.49, 0.92) (Table 3).

**Pre-exposure risk**

For a number of outcomes and vaccines, reduced risk was identified in the pre-exposure washout window. A reduced risk of clinical attendance was observed for ZVL and influenza vaccines in the pre-exposure washout window ([ZVL RI= 0.95, 95% CI 0.95 to 0.96]; [Influenza RI = 0.93, 95% CI 0.93 to 0.94]) in the main analysis. A lower relative incidence of MI (RI=0.4, 95% CI 0.2 to 0.9) and rash with antiviral was observed during the pre-exposure period (RI=0.7, 95% CI 0.5 to 0.9) for ZVL.

An increased risk of clinical attendance in the pre-exposure period was observed for 23vPPV (RI = 1.02, 95% CI 1.01 to 1.04) and an increased relative incidence of MI was observed prior to influenza vaccination (RI=1.5, 95% CI 1.0 to 2.1).

1. **Discussion**

The results of this SCCS analysis of MedicineInsight GP data provide evidence to support the safety of ZVL in individuals aged 70–79 years. An expected increased risk of injection site reaction up to seven days following vaccination was observed following all three vaccines. In the Shingles Prevention Study (SPS) safety sub study[18], ISR were more common in vaccine (48%) compared to placebo (16%) recipients. The intensity of erythema and swelling were significantly greater in vaccine recipients and persisted for longer, although fewer than 1% of vaccine recipients reported them as severe. A post-marketing study of 193 083 adults over 50 years in eight US managed care organisations demonstrated a small but significant increased risk of cellulitis and infection one to seven days following vaccination using the case-centred method.[13] In our study, the apparent ongoing risk of ISR up to 14 days following ZVL warrants further investigation. While the SPS sub study did demonstrate ISR significantly later in vaccine recipients compared to placebo recipients[18] events still occurred a median of 2.3 days following vaccination. Similarly, in global passive surveillance have been reported at a median of 2 days following vaccination.[10] In this SCCS, the risk of ISR was also elevated in the sensitivity analysis that excluded concomitantly administered vaccines. Similarly, a clinical trial of ZVL administered concomitantly with influenza vaccine, ISR and systemic reactions were comparable in those administered the vaccines concomitantly versus ZVL alone.[24]

It was reassuring that ZVL was associated with a reduced risk of clinical attendance following vaccination. This is consistent with pre-licensure studies which found no increased risk of serious adverse events.[6-8] Similarly, it was reassuring that there was no increased risk of MI or stroke identified following ZVL. Although there is a reported risk of ischemic [20, 21] and haemorrhagic stroke [21] and MI [20] in the 1 to 4 weeks following infection with wild-type herpes zoster virus,[22] the SPS did not identify an increased risk for cardiovascular events.[18] Post-licensure studies have not identified an increased risk for inpatient or ED encounters with cardiovascular or cerebrovascular events; [13, 19] and no temporal clustering and events following vaccination with ZVL has been observed.[19] VAERS post-marketing passive surveillance identified 3 deaths due to stroke and 28 due to heart disease between May 2006 and January 2015.[11] The authors noted that some deaths from heart disease and stroke following ZVL would be expected in this age group due to chance alone. No unusual pattern was observed that would suggest a causal relationship to ZVL.[11] The SCCS methodology used in this study supports the safety of ZVL by reducing the confounding and bias that affects passive surveillance systems.

This SCCS observed a higher relative incidence for MI in the post-risk washout period (between 43 and 84 days following vaccination). Within this washout period, there was no consistent pattern of increased risk, with higher relative incidence on days 57 to 63 and 71 to 77, but not earlier (43 to 56 or 64 to 70 days). Whether this increased risk several months after vaccination relates to age-related confounding requires further investigation.

The apparent reduced risk of stroke following ZVL in this SCCS may be biased by the use of general practice (rather than hospital) data. Further investigation within emergency department and hospital data may provide greater sensitivity in identifying cardiovascular outcome events. However, while presentation of cardiovascular and cerebrovascular events may be limited in the general practice setting, rash is a common presentation to general practice.[25] While rash has been considered a non-specific finding in post-marketing observational studies,[13] the pairing of rash with antiviral prescription is likely to represent a more specific outcome event. A reduced risk of rash with antiviral following ZVL was identified, which may suggest efficacy or be considered reassuring given that a herpes zoster-like rash may be a marker of disseminated infection if a patient is immunocompromised.[26] In a recent survey of immunisation providers in the US, family physicians report recommending ZVL to immunocompromised populations.[27] In Australia in 2016, a death was reported following administration of ZVL to an immunocompromised individual who developed a vesicular facial rash 22 days after receiving ZVL followed by disseminated infection and meningoencephalitis.[26] This event led to widespread dissemination of education to GPs regarding appropriate administration of ZVL.[26, 28]

This SCCS identified a reduced risk of rash requiring antiviral, clinical attendance and MI in the pre-exposure window may supports the healthy vaccinee effect and the strength of the SCCS methodology.[17] Previous analysis of the MedicineInsight data (5.28 million individuals aged 50 to 84 years from November 2016 to October 2017) had shown that recipients of ZVL were less likely to be current smokers (4.3%) than non-recipients (6.5%) and that approximately 20% had practice encounters once per week (J. Marsh, personal communication).

Recently, the US Advisory Committee on Immunization Practices (ACIP) has recommended the new non-live recombinant herpes zoster subunit vaccine be used in preference to ZVL for in immunocompetent adults aged 50 years and older.[29] The new vaccine was registered in Australia in July 2018 and while efficacy has been demonstrated, and it is not contraindicated in immunocompromised individuals,[27] a recent meta-analysis suggests that it may be associated with more ISR than ZVL.[30] The MedicineInsight data will be valuable in evaluating the comparative risk of adverse events following introduction on the new vaccine.

Although our results are reassuring, there are limitations to the use of MedicineInsight data. The quality of data is dependent on GP data entry into the on-site clinical information system. Where an outcome is not recorded, it is not possible to know whether this reflected an absence of the outcome or of documentation, particularly for minor outcomes such as ISR. As data is entered as free text, exposures and outcome events were identified by regular expression searches of text strings which are difficult to validate. It was not possible to determine event onset dates as these could only be inferred from the encounter or diagnosis date recorded. It was not possible to determine whether cases were immunocompromised due to the complexity of classifying the immune status of individual patients based on limited information; immunocompromise may affect the experience of adverse events.[26, 31] Outcomes such as stroke and MI may be more likely to present to an emergency department than to primary care, such that general practice data may be insufficiently sensitive for these events.

The use of general practice data and the SCCS design is a critical step in moving beyond passive surveillance and its inherent limitations. In Australia, many patients, especially older patients, see a regular general practitioner and GPs are immunisation providers for most patient cohorts. There is significant scope to better utilise routinely collected GP data for vaccine safety surveillance once the limitations and applications are more fully understood and validation of methodology has occurred. For more severe adverse events, the application of SCCS to hospitalisation data has been effective internationally.[15, 16] Linkage with hospitalisation data in Australia will make primary care data a rich source of information.

1. **Conclusion**

No new safety concerns were identified for ZVL in this study based on a novel data source using a SCCS design. Expected findings in relation to the positive (ISR) and negative (burn) control conditions confirm the validity of the SCCS in this setting, using general practice data. Findings in relation to cardiovascular disease and stroke were reassuring. Further work should focus on validation of identified exposures and outcomes and linkage with hospitalisation data.

**Statement**

*….This paper contains original unpublished work and is not being submitted for publication elsewhere. Any conference/other presentation….*

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**Conflicts of interest statement**

**Author contributions?**

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