MEDICINEINSIGHT

Vaccine Surveillance Report

Herpes Zoster – Phase 2

August 2017

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Suggested citation

NPS MedicineWise. MedicineInsight Vaccine Surveillance Report: Herpes zoster – phase 2. Sydney: NPS MedicineWise, August 2017.

Contents

1. EXECUTIVE SUMMARY

1.1. Purpose

This is the second MedicineInsight report in a series on herpes zoster (HZ) for the Department of Health, Office of Health Protection (OHP). The focus of the first report [MedicineInsight Herpes Zoster Report (Phase 1) June 2017] was disease surveillance. The purpose of this second report is to inform vaccine surveillance activities by describing coverage, effectiveness and safety of the herpes zoster vaccine Zostavax, using MedicineInsight data.

1.2. Data and focus

This report addresses specific questions on the following topics for Zostavax: vaccine uptake, compliance with safety protocols, vaccine effectiveness and adverse events.

1.3. Methods

The information presented in this report is based on general practice clinical information system (CIS) data collected from participating practices recruited to the MedicineInsight program. Data were extracted for 1,336,593 patients aged 50 years and over with at least three clinical encounters during the 5-year study time period (1 May 2012 to 30 April 2017 inclusive) – the 'study population'.

1.4. Results

1.4.1. Uptake of Zostavax

Vaccine coverage for patients aged ≥ 50 years over the 5-year study period was 5.3%. This included the 4.5-year period (1 May 2012 to 31 October 2016) before Zostavax was listed on the National Immunisation Program (NIP), during which 1% of the study population had a vaccine recorded, and the 6-month period since listing (1 November 2016 to 31 April 2017) when a further 4.3% had vaccination recorded.

Since the listing of Zostavax, vaccine coverage in the subset of patients who visited the practice at least once was 24.8% for patients aged 70–74 years and 34.3% for the 75–79 age group.

Overall coverage (for the study population) was higher in South Australia (9.9%) than the national average (5.3%).

1.4.2. Compliance with Zostavax Product Information and NCIRS guidelines

The proportion of patients who were potentially immunocompromised at the time of vaccination was 1.8%. A further 9% may have been immunosuppressed, depending on the dosage schedule of their prescribed medicine, which we were unable to analyse for this study. Interestingly the proportion of patients who were potentially immunocompromised at the time of vaccination in the US Medicare database study was 15%. Further investigation of MedicineInsight data is required to improve the definition of patients who maybe immunocompromised at the time of Zostavax vaccination.

1.4.3. Vaccine effectiveness

This is the first Australian report to our knowledge to assess Zostavax vaccine effectiveness in the Australian primary care population. Based on a recorded diagnosis in MedicineInsight, the incidence of HZ ≥ 31 days after Zostavax vaccination in patients aged ≥ 50 years was 12.3 per 1000 person-years, similar to the finding of a cohort study of US Medicare data in which the incidence of HZ, based

on a general definition of HZ (with or without antiviral medicine), was 11.7 (95% CI: 10.5 to 13.0) per 1000 person-years.

When sufficient follow-up has accrued, repeat analyses will be required to accurately estimate vaccine effectiveness for the patients who received Zostavax since the 1 November 2016 listing on the NIP, as the effectiveness of the vaccine is known to wane over time.

Trends in the incidence of HZ post-vaccination are difficult to interpret due to the small numbers; however, incidence seems to increase with age and be more common in women. This aligns with literature suggesting older patients and women are at higher risk of HZ post-vaccination. The incidence of HZ after vaccination in Queensland was double the national incidence, requiring further investigation.

1.4.4. Adverse events

The most frequent adverse event for Zostavax reported to the TGA was the development of HZ, followed by injection-site reactions. The most frequently reported adverse event in MedicineInsight was rash, whereas development of HZ was not recorded by general practice staff specifically in the 'adverse event' fields of the CIS.

MedicineInsight captured more adverse events than reported in the TGA-DAEN (473 vs 331, respectively) when HZ after Zostavax vaccination was included. Only 78 cases of HZ after vaccination were reported to the TGA, compared to 400 patients in MedicineInsight. This suggests that reporting of HZ to the TGA is low.

1.5. Discussion

This report builds on the first in the series on HZ surveillance by providing an introduction to the use of MedicineInsight data for vaccine surveillance. The MedicineInsight resource provides the opportunity to better understand the use and effectiveness of Zostavax vaccination within the Australian primary care setting.

Overall, vaccine uptake has increased substantially since the listing of Zostavax on the NIP, particularly in the 70–79-year age group, as expected. Based on these initial findings, some recommendations for further analyses, in conjunction with other experts, include the following:

- Refining definitions, eg,
  - the definition of incident HZ could be made more specific by including the prescription of antiviral medicine and exploration of incident HZ before the 30-day cut-off (as is current practice in Zostavax research)
  - whether the restriction of including patients with at least one encounter since the Zostavax listing should be applied
  - conducting a validation study with contributing practices on HZ case identification
  - the definition for patients who are immunocompromised at the time of Zostavax vaccination to assess compliance with contraindications for vaccination.
- Enhancing the analyses, eg,
  - with age standardisation and adjusting for other potential confounders
  - further follow-up surveillance as the effectiveness of the vaccine is known to wane over time.
- Exploring the findings in more detail, eg,
  - patients who develop HZ within 30-days of the vaccine
  - the differences between States and Territories in uptake and development of HZ after vaccination is required.

The MedicineInsight resource is a valuable source of routinely collected data to support Australia's vaccine surveillance activities.

2. INTRODUCTION

2.1. About the report

This is the second MedicineInsight report in a series on herpes zoster (HZ) for the Department of Health, Office of Health Protection (OHP). The focus of the first report [MedicineInsight. Herpes Zoster Report (Phase 1) June 2017] was disease surveillance, describing patients with HZ, including their complications and management.

The purpose of this second report is to inform vaccine surveillance activities by describing coverage, effectiveness and safety of the herpes zoster vaccine, Zostavax, using MedicineInsight data.

The investigation focuses on:

- uptake of Zostavax and patient factors
- compliance with the Zostavax Product Information and NCIRS guidelines
- vaccine effectiveness
- adverse events and allergies.

Section 3 presents a summary of the methods, and Section 4 the results of the investigations.

2.2. MedicineInsight data used in this report

The information presented in this report is based on general practice clinical information system (CIS) data collected from participating practices recruited to the MedicineInsight program. Data were used from 1,336,593 patients aged 50 years and over, with at least three clinical encounters during the study time period (1 May 2012 to 30 April 2017, inclusive) – the 'study population'.

This report uses the following information from the CIS data:

- patient demographics (including age [derived from year of birth], gender, State/Territory of residence, Aboriginal and Torres Strait Islander status)
- vaccinations
- medicines prescribed (including ATC classification,[1] generic names, trade names, reason for prescription)
- encounters (including reason for encounters)
- diagnoses or conditions
- allergy or adverse events.

For more information about MedicineInsight see:

- Appendix B of MedicineInsight Herpes Zoster Report (Phase 1) June 2017
- The NPS MedicineWise Using MedicineInsight data web page, where you can access the MedicineInsight Databook (https://www.nps.org.au/medicine-insight/using-medicineinsight-data)

2.3. Report background

2.3.1. Vaccinations for HZ

Zostavax (Zoster Virus Vaccine Live [Oka/Merck]) contains live attenuated herpes varicella–zoster virus (approximately14 times more virus than childhood varicella vaccines for preventing chickenpox) and is the only zoster vaccine currently registered in Australia. Zostavax was approved by the Therapeutic Goods Administration (TGA) in 2006 for the prevention of HZ in patients aged 50 years and older, and for the prevention of post-herpetic neuralgia (PHN) and other zoster-associated complications in patients aged 60 years and older.

Relevant information from the TGA-approved Product Information for Zostavax on indications, contraindications and precautions is included in Appendix 2.

Funding under the National Immunisation Program

Zostavax became freely available in Australia from November 2016 under the National Immunisation Program (NIP) for people aged 70 years, with catch-up vaccinations for those aged 71–79 years funded until 2021. Zostavax has been available in Australia since 2007 on private prescription (unfunded – non-PBS listed) with limited supply until early 2014.

Contraindications

Zostavax is contraindicated for patients who are pregnant and for those who are immunocompromised because of immunosuppressive therapies, or conditions, such as leukaemia, lymphoma or HIV/AIDS.

Studies of vaccine uptake

As yet there are no published studies on Zostavax uptake in the Australian setting.

A cohort study in the US[2] used a 5% sample of data from Medicare (an administrative claims program covering 15% of the US population) to assess vaccine uptake and effectiveness. All patients were aged ≥ 65 years and had part D Medicare (drug benefit) coverage, meaning they were all eligible for free vaccination with Zostavax. The overall vaccine uptake between 2007 and 2009 was 3.9% of patients and 2.1% of person–time in the cohort. Among those who received the vaccine, 15% (4469 out of 29,785 patients) were classified as immunocompromised at the time of herpes zoster vaccination.

A Canadian study[3] using population-based administrative health data from a community pharmacy dispensing database found that overall vaccine uptake was 8.4% of patients aged ≥ 60 years between 2009 and 2013, even though Zostavax was not publicly funded. Coverage was higher among women compared with men (9.5% and 7.2%, respectively), and among urban versus rural residents.

Studies of vaccine efficacy

The TGA approved the registration of Zostavax based on the efficacy demonstrated in two randomised, placebo-controlled, double-blind clinical trials.[4]

- The Zostavax Efficacy and Safety Trial (ZEST) included immunocompetent patients aged 50–59 years who were followed for a median of 1.3 years; the incidence of HZ was two cases per 1000 person–years in the Zostavax arm compared with 6.6 cases per 1000 person–years in the placebo arm.[5]
- The Shingles Prevention Study (SPS) included immunocompetent patients aged ≥ 60 years who were followed for a median of 3.1 years; the incidence of HZ was 5.4 per 1000 person–years in the Zostavax arm compared with 11.1 per 1000 person–years in the placebo arm ($p < 0.0001$).[6] Zostavax was more efficacious in reducing incidence of HZ among persons aged 60–69 years than those aged 70–79 years (64% compared with 41% efficacy)[6,7]

In the SPS study, efficacy analyses were performed with use of a follow-up period that excluded the first 30 days after vaccination and excluded patients in whom a confirmed case of herpes zoster developed within the first 30 days after vaccination. The results were essentially unchanged when subjects in whom herpes zoster developed during the first 30 days were included.[6] The ZEST study also applied this 30-day exclusion in modified intention-to-treat analyses.[5]

While the ZEST and SPS studies show that Zostavax works under ideal conditions (vaccine efficacy) it is important to confirm these results in real world conditions (ie, vaccine effectiveness) to ensure a vaccine's benefits translate to the general population in clinical practice.

Studies of vaccine effectiveness

As yet there are no published effectiveness studies in the Australian setting. Several international studies have assessed vaccine effectiveness in unselected general populations, outside of the clinical trial setting, as described below.

- The cohort study mentioned previously, using data from Medicare from 2007 and 2009, found that for patients aged ≥ 65 years the incidence of HZ (confirmed by an ICD-10 code plus an antiviral medicine) was 5.4 per 1000 person–years among the vaccinated group and 10.0 per 1000 person–years in the unvaccinated group.
  Using a more general definition of incident HZ (with or without antiviral medicine) the incidence of HZ was 11.7 per 1000 person–years.[2] Incidence of PHN after 30 days of HZ was 0.41 (95% CI 0.29 to 0.59) per 1000 person–years.
- A population-based cohort study in California, USA,[2] using electronic health records from 2007 to 2014 found for patients aged ≥ 60 years the incidence of HZ was 8.0 cases per 1000 person–years among vaccinated patients (95% CI 7.8 to 8.2 cases/1000 person–years) and 14.4 cases per 1000 person–years among unvaccinated patients (95% CI 14.2 to 14.6 cases/1000 person–years).
  Zostavax effectiveness decreased from 68.7% (95% CI 66.3 to 90.9) in the first year to 6.2% (95% CI –24.0 to 25.9) in the eighth year after vaccination. Immunocompromised individuals (those with HIV, leukaemia, or lymphoma diagnoses within 1 year before the index date, or having immunosuppressing medicines dispensed within 1 year before the index date) were excluded from the study. Patients diagnosed with HZ during the 1 year before and 30 days after the index date were excluded from analysis.

Safety

Though the vaccine has had a good safety profile in clinical trials, with fever and rash occurring rarely, infrequent adverse events have been reported, particularly in immunocompromised and immunosuppressed people, therefore disease surveillance and vaccine surveillance are important.[7]

3. METHODS

In this section, we present a summary of the methods used for this HZ report. This section contains the following subsections:

3.1. Report questions

These report questions were agreed with the Office of Health Protection and present a preliminary analysis of the MedicineInsight data for Zostavax surveillance.

Objectives	Questions
Uptake of HZ vaccine (Section 4.1 and Appendix E)	- Overall vaccination coverage: proportion of people vaccinated between 1 May 2012 and 30 April 2017 by age, gender, State and Indigenous status - Vaccination coverage before (1 May 2012 – 31 October 2016) and since (1 November 2016 – 30 April 2017) listing of Zostavax on the NIP - Annual vaccination rate: number of HZ vaccinations between 1 November 2012 and 31 October 2016 per year by age, gender, State and Indigenous status (see Appendix E)
2.Compliance with the Zostavax TGA-approved Product Information and NCIRS guidelines (Section 4.2)	Proportion of patients given HZ vaccines who were potentially immunocompromised due to: - comorbidities (HIV/AIDS, leukaemia, lymphoma) - immunosuppressive therapies (chemotherapy, radiotherapy, disease-modifying antirheumatic drugs [DMARDs], antirejection/transplant medicine)
3. Vaccine effectiveness (Section 4.3)	Incidence of HZ after Zostavax vaccination (1 May 2012 – 30 April 2017) Incidence of HZ complications after Zostavax vaccination (1 May 2012 – 30 April 2017):
4. Adverse events (Section 4.4)	What were the 10 most common adverse events for Zostavax in MedicineInsight? How do the 10 most common adverse events compare with the numbers reported in the TGA database of adverse event notifications (TGA-DAEN)?

3.2. Methods

3.2.1. Study type/design

This was a descriptive analysis of data collected from Australian national general practice clinical information systems (CIS). Analyses were cross-sectional and longitudinal.

3.2.2. Study time period

Five years from 1 May 2012 to 30 April 2017, inclusive, unless otherwise specified.

While there were records of Zostavax in the MedicineInsight database before May 2012, this 5-year study period was chosen to align with the study period of the first report in this series on HZ surveillance.

3.2.3. Study population

Patients were included if they met the following criteria:

- ≥ 50 years of age at data extract (including patients currently marked as deceased or inactive in the CIS)
- had three or more clinical encounters at a clinically representative practice (see Appendix B, 6.2.3) during the 5-year study period.

The study population was restricted to patients aged ≥50 years of age as per the approved indication for Zostavax.

Patients with at least three clinical encounters during the study period were selected for this report, to exclude temporary patients and to ensure that patients included in the study had sufficient opportunities for diagnoses, tests and prescriptions to be recorded.

A clinical encounter, or any professional exchange between a patient and a healthcare professional, was defined as all encounters at the general practice that were:

- not identified as administrator entries or encounters that had been transferred/imported from another practice; and
- not identified by predefined 'administration-type' terms found in the 'reason for encounter' field, such as 'administrative reasons', 'forms', 'recall', etc.

Patients currently marked as deceased or inactive in the CIS, with three or more clinical encounters during the study period, were included because they were alive and active for at least some of the study period. Excluding them would introduce selection bias and could lead to an under- or overestimate of the incidence of HZ, and complications.

Where additional restrictions were applied for specific objectives, these are described under the relevant sections in Chapter 4.

3.2.4. Vaccination records

This report uses data on Zostavax vaccinations from the following areas of the CIS:

- immunisations table (vaccine name)
- prescription (medicine name)
- prescription history (medicine name)

We included the medicine and brand names varicella–zoster and ZOSTAVAX. The final list of included vaccine and medicine names, which includes free text entries, can be found in Appendix C.

For the purposes of this report we did not include:

- records of varicella vaccine where it was not clear whether the chicken pox or shingles vaccine was provided
- a small number of encounters in which the 'reason for encounter' indicated that Zostavax may have been administered but this was not confirmed with records in the immunisations and prescriptions tables.

3.2.5. Diseases and conditions

Depending on the CIS at their practice, clinicians use code systems such as 'Docle', 'Pyefinch' or 'ICPC' to enter medical terms into their system. However, it is not mandatory to use a code and clinicians can enter terms as free text.

For diseases and conditions this report uses data from both coded and free text fields entered into the following areas of the CIS:

- medical history (diagnosis)
- encounter (reason for encounter)
- prescription (reason for prescription).

3.2.5.1. Definition of incident HZ after Zostavax vaccination

A patient was defined as having incident HZ after their vaccination if they had a recorded diagnosis (coded or free text) of herpes zoster, varicella–zoster, shingles, post-herpetic neuralgia, or Ramsay Hunt syndrome in a relevant field after 30 days following vaccination and never before the vaccination. The first 30 days after vaccination were excluded when defining incident HZ to align with methods used in the Zostavax clinical trials ZEST5 and SPS6 as well as population-based cohort studies[5,6]. If the first HZ record was within 12 months of the patient's start date at the practice (defined as the first encounter) this may have been a condition that was first diagnosed at another practice; these patients did not meet the criteria for incident HZ (aligning with studies using administrative health data to identify incident HZ).[2]

Table 11: of Appendix D details codes and free text used to identify patients with HZ. Varicella–zoster was included because, although most often used to describe chickenpox, this study was restricted to patients aged ≥ 50 years, when a diagnosis of zoster is most likely to be herpes zoster. We recognise there is potential for misclassification of chickenpox as HZ with this method but expect this would be minimal, considering up to 95% of the population have already been infected with the varicella–zoster virus by the time they are 30 years of age.[8].

For the purposes of defining incident cases of HZ after Zostavax vaccination there was no requirement for the diagnosis to be confirmed with polymerase chain reaction (PCR) testing (as in the Zostavax clinical trials[5,6]) or by the prescribing of antiviral medicines (as in some of the cohort studies[2] on effectiveness). While PCR testing is not routinely conducted in general practice (see Phase 1 report), including incident cases on the prescribing of antiviral medicines data may be more feasible for future reports.

3.2.5.2. Definition of potentially HZ-related complications

A MedicineInsight patient was considered to have a potentially HZ-related complication if they had a recorded diagnosis (coded or free text) of post-herpetic neuralgia, Ramsay Hunt syndrome (facial paralysis), herpes zoster ophthalmicus, herpes meningitis, pneumonia, pneumonitis, secondary skin bacterial infection, hearing problems, blindness, encephalitis, or stroke in a relevant diagnosis field (diagnosis, reason for encounter or reason for prescription) at any point after the date of diagnosis of HZ after administration of Zostavax.

Some conditions included in this definition, such as pneumonia or stroke, occur fairly frequently in the population aged over 50 and may not be related to HZ. It is difficult to ascertain definitely HZ-related complications using routinely collected general practice clinical data. To reduce misclassification of conditions as being HZ-related a temporal association was used, namely the secondary condition had to occur within 12 months of the HZ diagnosis; however, we recognise there will be some remaining misclassification.

3.2.5.3. Definition of potentially immunocompromised

The methodology used in this report provides an estimate of the proportion of MedicineInsight patients who were 'potentially immunocompromised', rather than 'definitely immunocompromised', the latter being more difficult to ascertain using routinely collected general practice clinical data. The definition was modified from the Phase 1 report to exclude patients prescribed therapies that are only immunosuppressive at certain dosage schedules.

Not all dosage schedules for oral corticosteroid medicines (prednisone and prednisolone), azathioprine, 6-mercaptopurine and methotrexate definitely lead to immunosuppression (particularly short courses and low doses). It was not possible in the timeframe for delivery of this report to analyse the daily dose and duration information recorded in MedicineInsight to categorise prescriptions by dose. Therefore patients prescribed these medicines were reported separately.

A patient was considered to be potentially immunocompromised before their date of vaccination if they met one or more of the following criteria:

- **Immunocompromising condition:**
  - had a recorded diagnosis of HIV/AIDS, leukaemia or lymphoma at any time before their date of vaccination. Refer to Appendix D for the definition of immunocompromising conditions. Immunocompromising conditions could occur at any time before the HZ diagnosis and may not have been immunocompromising at the time of the diagnosis of HZ.
- **Immunosuppressive therapy:**
  - had undergone radiation therapy or chemotherapy within the 12 months before their vaccination. Refer to Appendix D for the definitions of radiotherapy and chemotherapy. Radiation therapy and chemotherapy are markers of, but do not always cause, immunosuppression.
- had a prescription for one or more of the immunosuppressing medicines listed in Appendix D, within the 12 months before their vaccination (excluding oral corticosteroid, azathioprine, or 6-mercaptopurine or methotrexate) .

Patients prescribed medicines that are only immunosuppressive at certain dosage schedules were presented as follows:

- **Unsure if immunosuppressed based on therapy:**
  - had a prescription for an oral corticosteroid, azathioprine, 6-mercaptopurine or methotrexate within the 12 months before their vaccination.

3.2.6. Analysis plan

Analysis of the data was conducted using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA). Definitions of the measures (proportions and rates) calculated for this report are detailed in Section 4.

For the analyses of vaccine effectiveness (incidence of HZ or HZ-related complications after Zostavax vaccination) results are presented separately for patients who received the vaccine before 1 November 2016 and from 1 November 2016 when it became publicly funded for patients aged 70 years and over. We expect these populations to differ in important ways, including differences in sociodemographic characteristics and health status.

There is a maximum of 6 months of follow-up data for patients who received the vaccine as part of the national program. Therefore, to account for the difference in available follow-up time, results are presented using person–years. For a patient who developed HZ after vaccination, the follow-up time for HZ surveillance was the number of days from the vaccination (+31 days) to the first HZ record. For a patient who did not develop HZ, the follow-up time for HZ surveillance was the number of days from vaccination (+31 days) to the earliest of:

- the end of the study time period (30 April 2017) or
- the end of follow-up at the practice; either:
  - the date the patient's status changed due to death or
  - being marked as inactive by the practice or
  - 12 months after the patient's last encounter.

To indicate the reliability of the estimated proportions and incidence rates, 95% confidence intervals (95% CIs) were calculated (a range of values that should contain the actual rate 95% of the time). Comparisons within categories were made by comparing the degree of overlap of the corresponding 95% CIs. All analyses were unadjusted for confounding factors (eg, age, gender) therefore comparisons should be interpreted with caution. Cluster-corrected 95% CIs were calculated using the general practice as the unit of clustering. The analyses used the SAS PROC SURVEYFREQ procedure.

4. RESULTS

In this section, we present a summary of results found from our investigations with additional notes on the methods used, where required. This section contains the following subsections.

- Uptake of Zostavax and patient factors
- Compliance with the Zostavax Product Information and NCIRS guidelines
- Vaccine effectiveness
- Adverse events / allergies

4.1. Uptake of Zostavax

4.1.1. Overall vaccination coverage between 1 May 2012 and 30 April 2017

Out of 1.34 million patients aged ≥ 50 years with at least three encounters during the 5-year study time period – the study population – 70,139 vaccinations were recorded. This represents 5.3% coverage among MedicineInsight patients aged ≥ 50 years.

Overall vaccination coverage by patient characteristics/demographics are presented in Table 1. Coverage was highest in the 75–79-year age group, at 24.3%, followed by the 70–74 age group, at 18.0%. Although coverage was higher in women than men (5.5% vs 4.9%) this was not statistically significant. Non-indigenous patients had a significantly higher vaccination coverage than their Indigenous counterparts (5.9% vs 2.5%); however, this analysis was not adjusted for confounding by age, which might explain most of this difference.

Coverage was similar across States and Territories, with the exception of the NT at 2.9% and NSW at 4.5%, both under the national average of 5.3% (95% CI: 4.9% to 5.6%). Around 1% of patients (n = 721) had a diagnosis of HZ in the 12 months before their Zostavax vaccination record.

Table 1: **VACCINATION COVERAGE FOR PATIENTS AGED ≥ 50 YEARS BY DEMOGRAPHIC CHARACTERISTICS, MEDICINEINSIGHT, MAY 2012 – APRIL 2017.**

	Total study period (1 May 2012 – 31 April 2017)				
	Patients with Zostavax vaccination recorded	Patients in the study population*	Vaccination coverage		
	n	n	%	95% CL	
All patients	70,139	1,336,593	5.25	4.94	5.56
Age					
50–54	491	231,169	0.21	0.18	0.24
55–59	1,063	226,792	0.47	0.41	0.53
60–64	2,289	206,264	1.11	0.98	1.24
65–69	4,641	195,452	2.37	2.15	2.60
70–74	28,119	156,074	18.02	17.07	18.96
75–79	28,238	116,125	24.32	23.10	25.54
80–84	3,584	86,621	4.14	3.80	4.47
85–89	1,238	65,620	1.89	1.63	2.14
90–94	399	37,389	1.07	0.83	1.30
95–100	77	15,087	0.51	0.32	0.70
Gender					

	Total study period (1 May 2012 – 31 April 2017)				
	Patients with Zostavax vaccination recorded	Patients in the study population*	Vaccination coverage		
	n	n	%	95% CL	
Male	29,394	598,996	4.91	4.60	5.21
Female	40,737	736,887	5.53	5.20	5.86
Unspecified	8	710	1.13	0.34	1.92
Indigenous status					
Non-indigenous	56,996	972,249	5.86	5.48	6.24
Indigenous	388	15,778	2.46	2.12	2.80
Unspecified	348,566	3.66	3.29	4.02	348,566
State					
ACT	1,806	26,398	6.84	4.89	8.79
NSW	19,703	435,954	4.52	4.11	4.93
NT	496	17,044	2.91	2.17	3.66
Qld	14,362	251,370	5.71	5.11	6.31
SA	2,798	40,282	6.95	5.74	8.15
Tas	5,576	114,980	4.85	4.26	5.44
Vic	16,518	295,780	5.58	4.56	6.61
WA	8,880	154,785	5.74	4.76	6.71

* Patients were required to have at least 3 clinical visits between 01 May 2012 and 30 Apr 2017.

4.1.2. Vaccination coverage before and since listing of Zostavax on the National Immunisation Program

Before Zostavax was listed on the NIP, 1.0% of the study population were vaccinated (n = 12,918) and since 1 November 2016 until 30 April 2017 a further 4.3% were vaccinated (n = 57,221).

The left side of Table 2 presents vaccination coverage by demographic factors for the study population before Zostavax was available on the NIP. The right side of Table 2 presents vaccination coverage by demographic factors for the subset of the study population – 739,426 patients – who had at least one encounter at the practice between 1 November 2016, when Zostavax was listed on the NIP, and 30 April 2017. The vaccination coverage for this subset of patients was 7.5%.

Before Zostavax was listed, coverage in the total study population was highest in the 75–79-year age group at 1.9%, followed by the 70–74 age group at 1.8%. After listing, coverage in the subset who visited the practice was much higher, at 34.3% for the 75–79 age group followed by 24.8% for the 70–74 age group. After the listing of Zostavax, coverage was similar between men and women, whereas before listing coverage was higher for women than men (1.1% vs 0.8%).

Since the listing of Zostavax, coverage was statistically significantly higher in SA (9.9%) compared with the national average (5.3%).

Table 2: **VACCINATION COVERAGE BEFORE AND AFTER ZOSTAVAX LISTING ON THE NIP BY DEMOGRAPHIC CHARACTERISTICS, MEDICINEINSIGHT MAY 2012 –OCT 2016 AND NOV 2016 – APRIL 2017**

	Before Zostavax listing (1 May 2012 – 31 October 2016)					After Zostavax listing (1 November 2016 – 30 April 2017)				
	Patients with Zostavax vaccination recorded	Study population[a]	Vaccination coverage			Patients with Zostavax vaccination recorded	Study population + 1 visit post Nov 2016[b]	Vaccination coverage		
	n	n	%	95% CL		n	n	%	95% CL	
All patients	12,918	1,336,593	0.97	0.84	1.10	55,333[c]	739,426	7.48	7.15	7.81
Age										
50–54	356	231,169	0.15	0.13	0.18	131	116,169	0.11	0.09	0.13
55–59	794	226,792	0.35	0.30	0.40	245	119,452	0.21	0.17	0.24
60–64	1,678	206,264	0.81	0.70	0.93	579	114,820	0.50	0.45	0.56
65–69	2,711	195,452	1.39	1.20	1.57	1,861	115,928	1.61	1.48	1.73
70–74	2,854	156,074	1.83	1.58	2.07	24,337	97,991	24.84	23.55	26.12
75–79	2,233	116,125	1.92	1.65	2.20	25,273	73,775	34.26	32.77	35.75
80–84	1,245	86,621	1.44	1.19	1.68	2,251	50,637	4.45	4.15	4.74
85–89	698	65,620	1.06	0.84	1.29	531	32,767	1.62	1.44	1.80
90–94	288	37,389	0.77	0.55	0.99	109	14,381	0.76	0.61	0.91
95–100	61	15,087	0.40	0.22	0.59	16	3,506	0.46	0.23	0.69
Gender										
Missing	<5	710	–	–	–	7	299	2.34	0.58	4.11
Male	4,694	598,996	0.78	0.67	0.90	23,829	327,806	7.27	6.92	7.62
Female	8,223	736,887	1.12	0.97	1.26	31,497	411,321	7.66	7.32	7.99

	Before Zostavax listing (1 May 2012 – 31 October 2016)					After Zostavax listing (1 November 2016 – 30 April 2017)				
	Patients with Zostavax vaccination recorded	Study population[a]	Vaccination coverage			Patients with Zostavax vaccination recorded	Study population + 1 visit post Nov 2016[b]	Vaccination coverage		
	n	n	%	95% CL		n	n	%	95% CL	
Indigenous										
Unspecified	2,642	348,566	0.76	0.64	0.88	9,675	153,993	6.28	5.79	6.78
Non-indigenous	10,225	972,249	1.05	0.89	1.21	45,330	576,507	7.86	7.49	8.24
Indigenous	51	15,778	0.32	0.21	0.43	328	8,926	3.68	3.20	4.15
State										
ACT	379	26,398	1.44	0.94	1.93	1,415	15,250	9.28	7.52	11.04
NSW	4,277	435,954	0.98	0.74	1.22	15,110	243,057	6.22	5.82	6.61
NT	28	17,044	0.16	0.11	0.22	452	6,572	6.88	4.60	9.15
Qld	2,938	251,370	1.17	0.87	1.47	11,150	133,896	8.33	7.68	8.98
SA	431	40,282	1.07	0.85	1.29	2,311	23,322	9.91	8.30	11.52
Tas	1,133	114,980	0.99	0.74	1.23	4,382	69,141	6.34	5.54	7.14
Vic	2,586	295,780	0.87	0.53	1.21	13,368	163,547	8.17	7.17	9.18
WA	1,146	154,785	0.74	0.55	0.93	7,145	84,641	8.44	7.34	9.55

a Patients were required to have at least three clinical visits between 1 May 2012 and 30 Apr 2017

b Patients were required to have at least three clinical visits between 1 May 2012 and 30 Apr 2017 AND one clinical visit between 1 Nov 2016 and 30 Apr 2017

c From the total study population 57,221 had a record of Zostavax vaccination after Zostavax was listed on the NIP, but when we applied the inclusion criteria of one encounter at the practice since the listing of Zostavax this number reduced to 55,333 patients, ie, 1888 patients had a record of Zostavax vaccination but no clinical encounter recorded between 1 November 2016 and 30 April 2017

4.1.3. Monthly vaccination rate since listing of Zostavax on the NIP

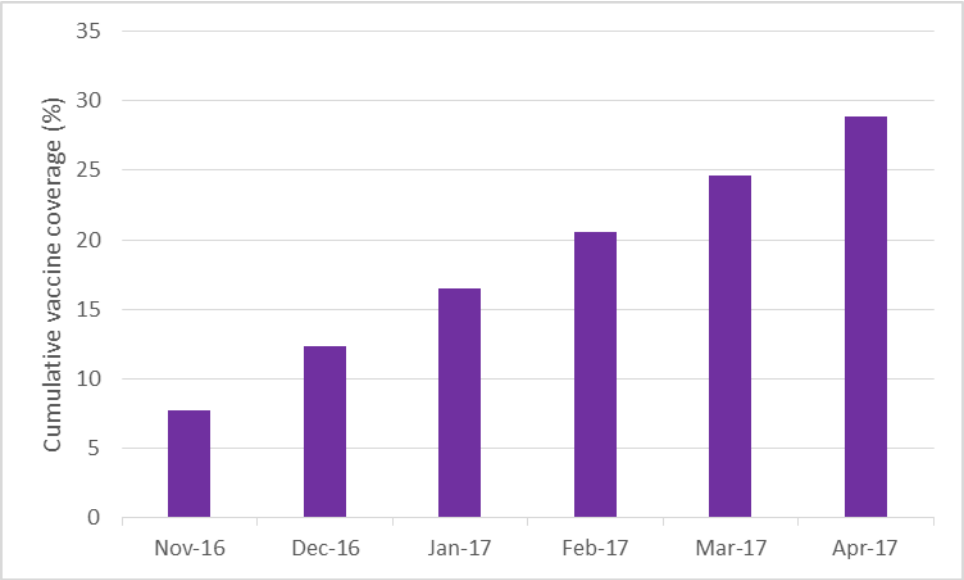
The overall vaccination coverage for patients eligible for Zostavax (aged 70–79 years) by month since Zostavax was listed on the NIP is presented in Table 3 and Figure 1. The vaccination uptake was highest in Nov 2016 and remained steady over the following months. By the end of April 2017 the cumulative coverage of Zostavax was 28.9% of patients aged 70–79 years.

Table 3: **OVERALL MONTHLY VACCINATION RATE FOR PATIENTS AGED 70–79 YEARS,[a] MEDICINEINSIGHT, NOV 2016 – APRIL 2017 (N = 171,766)**

Month	Patients with Zostavax vaccination recorded (n)	Cumulative vaccination coverage	
		(n)	(%)
Nov 2016	13,297	13,297	7.74
Dec 2016	7,948	21,245	12.37
Jan 2017	7,099	28,344	16.50
Feb 2017	7,020	35,364	20.59
Mar 2017	6,966	42,330	24.64
Apr 2017	7,280	49,610	28.88

a Patients aged 70–79years were required to have at least three clinical visits between 1 May 2012 and 30 Apr 2017 AND one clinical visit between 1 Nov 2016 and 30 Apr 2017

FIGURE 1: CUMULATIVE VACCINATION COVERAGE FOR PEOPLE AGED 70–79 YEARS WHO VISITED PRACTICES BETWEEN 1 NOV 2016 AND 30 APR 2017. MEDICINEINSIGHT, NOV 2016 – APRIL 2017 (N = 171,766)



4.2. Compliance with contraindications in the Zostavax Product Information and NCIRS guidelines

Out of 70,139 patients in the study population with a Zostavax vaccination recorded between 1 May 2012 and 30 April 2017 (Table 4):

- 1233 patients (1.8%) were potentially immunocompromised due to having an immunocompromising condition 'ever' recorded (n = 993; 1.4%) or being prescribed an immunosuppressive therapy in the 12 months before receiving the vaccination (n = 240; 0.3%).
- The proportion who were immunocompromised and immunosuppressed did not vary significantly before November 2016 or after 1 November 2016 (Table 4).

Table 4: **NUMBER (N) AND PROPORTION (%) OF PATIENTS WITH ZOSTAVAX RECORDED WHO WERE POTENTIALLY IMMUNOCOMPROMISED, MEDICINEINSIGHT 01 MAY 2012 TO 30 APRIL 2017**

	1 May 2012 – 30 April 2017				1 May 2012 – 31 October 2016				1 November 2016 – 30 April 2017			
	Cases				**Cases**				**Cases**			
	(n)	**%**	**95% CL**		**(n)**	**%**	**95% CL**		**(n)**	**%**	**95% CL**	
Immuno-compromised	993	1.42	1.14	2.14	192	1.51	1.24	1.78	799	1.40	1.28	1.51
Immuno-suppressed	240	0.34	0.29	0.39	46	0.36	0.24	0.48	194	0.34	0.29	0.39
Unsure if immuno-suppressed[a]	6615	9.43	9.02	9.84	1050	8.25	7.59	8.90	5543	9.69	9.24	1.01

a See definition p 5.

4.3. Vaccine effectiveness

Among the 70,139 patients in the study population with Zostavax vaccination recorded between 1 May 2012 and 30 April 2017, a total of 400 patients developed incident HZ 31 days or more after their recorded Zostavax vaccination. This represents an HZ incidence of 5.4 per 1000 MedicineInsight patients and 12.3 per 1000 person–years (Table 5). A further 803 suspected vaccination failures were recorded between day 0 (day of vaccination) and day 30, inclusive, after vaccination.

The results presented in Table 5 demonstrate that the incidence of HZ after Zostavax vaccination was almost three times higher among the patients who received Zostavax before it was listed on the NIP than those who received it afterwards (16 versus 6 per 1000 person years, respectively). However, it is important to note that most patients in the MedicineInsight sample received their vaccine in the last 6 months of the study and only had a short amount of follow-up time available for assessment (mean of 0.2 years).

Table 5: **INCIDENCE OF HZ POST-VACCINATION PER 1000 PERSON YEARS, COMPARISON PRE- AND POST-ZOSTAVAX LISTING ON THE NIP**

	Median average follow-up (years)	Mean average follow-up (years)	Incident HZ cases (n)	Person years	Incidence of HZ per 1000 person years	95% CL	
1 May 2012 – 30 Apr 2017	0.3	0.5	400	32618.06	12.26		
1 May 2012 – 31 Oct 2016	1.5	1.7	338	21499.30	15.72	14.13	17.49
1 Nov 2016 – 30 Apr 2017	0.2	0.2	62	11118.76	5.58	4.35	7.15

The incidence of HZ after vaccination according to demographic factors over the entire study period is presented in Table 6. Trends in the incidence of HZ after vaccination are difficult to interpret due to the small numbers; however, incidence seems to increase with age and be more common in women. The incidence of HZ was highest in Queensland, compared with the national average.

Of the 70,139 patients in the study population with Zostavax vaccination recorded between 1 May 2012 and 30 April 2017, a total of 64 HZ-related complications were reported within 12 months after the vaccination, of which 34 were cases of post-herpetic neuralgia (PHN) (Table 7). The incidence of all HZ-related complications was 0.9 per 1000 vaccinations and the incidence of PHN was 0.5 per 1000 vaccinations.

Table 6: **INCIDENCE OF HZ POST-VACCINATION BY PATIENT DEMOGRAPHICS, MEDICINEINSIGHT 1 MAY 2012 TO 31 APRIL 2017.**

Characteristic	Patients with incident HZ > 30 days post Zostavax vaccination (n)	Number of patients with Zostavax vaccination recorded	Incidence of HZ per 1000 patients	95% CL		Incidence of HZ per 1000 person-years	95% CL	
All patients	400	70,139	5.37	2.2	8.72	12.26	11.12	13.53
Age group								
50–54	6	491	12.22	2.58	21.86	10.43	4.68	23.21
55–59	14	1063	13.17	6.48	19.87	10.83	6.42	18.29
60–64	20	2289	8.74	4.9	12.57	7.35	4.74	11.39
65–69	48	4641	10.34	5.93	14.76	10.08	7.60	13.38
70–74	132	28,119	4.69	0.5	8.89	14.23	12.00	16.88
75–79	106	28,238	3.75	1.21	6.3	11.54	9.54	13.96
80–84	39	3,584	10.88	2.45	19.32	14.39	10.52	19.70
85–89	23	1,238	18.58	7.84	29.32	16.10	10.70	24.23
90–94	11	399	27.57	11.49	43.65	19.95	11.05	36.02
95–100	<5	77	–	–	–	–	–	–
Gender								
Male	131	29,394	4.46	1.24	7.68	10.38	8.75	12.32
Female	269	40,737	6.6	2.75	10.46	13.45	11.94	15.16
Unspecified	0	8	0	0	0	0	0	0
Indigenous ancestry								
Non-Indigenous	348	56,996	6.11	1.88	10.33	13.34	12.01	14.82
Indigenous	0	388	0	0	0	0	0	0
Unspecified	52	12,755	4.08	2.71	5.44	8.15	6.21	10.69

Characteristic	Patients with incident HZ > 30 days post Zostavax vaccination (n)	Number of patients with Zostavax vaccination recorded	Incidence of HZ per 1000 patients	95% CL		Incidence of HZ per 1000 person-years	95% CL	
State								
ACT	5	1,806	2.77	0	5.95	5.70	2.37	13.69
NSW	101	19,703	5.13	3.99	6.26	9.69	7.98	11.78
NT	0	496	0	0	0	0	0	0
Qld	188	14,362	13.09	0	29.83	26.57	23.03	30.66
SA	8	2,798	2.86	0.47	5.25	6.74	3.37	13.47
Tas	28	5,576	5.02	2.66	7.38	11.78	8.13	17.06
Vic	45	16,518	2.72	1.69	3.76	6.39	4.77	8.55
WA	25	8,880	2.82	1.72	3.91	7.17	4.85	10.61

Table 7: **INCIDENCE OF HZ-RELATED COMPLICATIONS POST-VACCINATION, MEDICINEINSIGHT 1 MAY 2012 TO 31 APRIL 2017**

	Patients with complication (n)	Incidence of HZ complication per 1000 patients vaccinated[a]	95% CL		Incidence of HZ complication per 1000 patients with HZ post-vaccination	95% CL	
All complications[b]	64	0.91	0.67	1.16	38.05	28.35	47.75
PHN	34	0.49	0.31	0.66	20.21	13.12	27.31
Ramsay-Hunt Syndrome	<5						

a Using Zostavax recipient study population

b All complications include: post-herpetic neuralgia, pneumonia, pneumonitis, herpes meningitis, secondary skin bacterial infection, hearing problems, blindness, encephalitis, Ramsay Hunt syndrome (facial paralysis), herpes zoster ophthalmicus and stroke.

4.4. Adverse events after Zostavax vaccination

According to the information recorded by GPs in the adverse event/allergy structured area of the CIS, a total of 73 adverse events were recorded that related to Zostavax at any time point leading up to 30 April 2017. This includes 51 records with an adverse event recorded but without details of what the reaction was. The most prevalent reaction was rash (n = 13) followed by pruritus (n = 3). Bronchospasm, hot flushes, musculoskeletal pain, nausea, urticaria and other each had a single recorded reaction (n = 1) (Table 8).

According to the TGA Database of Adverse Events Notifications (TGA-DAEN), there were 331 adverse events reported at any time point leading up to the 20 April 2017 (date of last record available). The most reported adverse event was the development of HZ (n = 78), followed by injection-site reaction (n = 63) and headaches (n = 30) (Table 9).

Although not specifically recorded by practice staff in the CIS field for adverse events, there were 400 cases of HZ occurring more than 30 days after a Zostavax vaccination was reported. This compares with a total of 78 cases reported nationally to the TGA.

Table 8: **MOST PREVALENT ADVERSE EVENTS FROM MEDICINEINSIGHT IN COMPARISON TO TGA-DAEN.**

MedDRA system organ class	MedDRA reaction term	MedicineInsight count	TGA-DAEN count
Missing		51	
Infections and infestations	Herpes zoster		78
Skin and subcutaneous tissue disorders	Rash	13	21
Skin and subcutaneous tissue disorders	Pruritus	3	14
Respiratory, thoracic and mediastinal disorders	Bronchospasm	1	0
General disorders and administration site conditions	Hot flush	1	2
Musculoskeletal and connective tissue disorders	Musculoskeletal pain	1	1
Gastrointestinal disorders	Nausea	1	9
Skin and subcutaneous tissue disorders	Urticaria	1	6
Other		1	278
Total		**73**	**331**
HZ diagnoses post-vaccination (although not recorded specifically in the adverse event table)			
Infections and infestations	Herpes zoster	400	
Total including HZ count sourced from other tables		**473**	**331**

5. DISCUSSION

This is the second report in a series from MedicineInsight on herpes zoster, and the first time Zostavax surveillance activities have been reported using MedicineInsight primary care data.

Study findings are consistent with data from the 2013 herpes zoster vaccine effectiveness study by Langan et al[2] and the Shingles Prevention Study Randomised Control Trial (SPS RCT[5]). This work complements and expands on our previous report on the incidence of HZ in Australian general practice.

5.1. Uptake of Zostavax

Vaccine coverage for patients aged ≥ 50 years over the 5-year study period was 5.3%. This included the 4.5-year period before the listing of Zostavax on the NIP (1 May 2012 to 31 October 2016), during which 1% of the study population had a vaccination recorded, and the 6-month period since listing (1 November 2016 to 31 April 2017) when a further 4.3% of patients had vaccinations recorded.

Interestingly, coverage in the MedicineInsight patient sample was higher than a US Medicare database study[2] in which 3.9% of patients aged ≥ 65 years who were eligible for free vaccination received Zostavax over a 2-year period (2007 to 2009), and lower than a Canadian pharmacy database study[3] in which 8.4% of patients aged 60+ years received Zostavax over a 5-year period (2009–2013) despite there being no public funding.

As in the Canadian study, vaccine coverage was higher for women than men before the listing of Zostavax on Australia's NIP; however, since funding there has been no significant difference in coverage between genders.

Since the listing of Zostavax, coverage in the subset of patients who visited the practice at least once between 1 May 2016 and 30 Apr 2017 was 24.8% among patients aged 70–74 years and 34.3% for the 75–79 age group. Overall coverage was statistically significantly higher in South Australia (9.9%) than the national average.

The methodology and its implications for defining the study population, particularly restricting patients included to those with at least one encounter since Zostavax listing, should be refined in future analyses.

5.2. Compliance with Zostavax Product Information and NCIRS guidelines

The proportion of patients who were potentially immunocompromised at the time of vaccination was 1.8%. A further 9% had a prescription for an oral corticosteroid, azathioprine, 6-mercaptopurine or methotrexate within the 12 months before their vaccination and may have been immunosuppressed, depending on their dosage schedule. Incorporating dosage schedules into the analysis was not possible for this study in the timeframes available. Interestingly, the proportion of patients who were classified as immunocompromised at the time of vaccination in the US Medicare database study[2] was quite high at 15%.

Further investigation of MedicineInsight data is required to improve the definition of patients as immunocompromised at the time of Zostavax.

5.3. Vaccine effectiveness

This is the first Australian report to our knowledge to assess Zostavax effectiveness in the Australian primary care population. In total, 400 cases of HZ following vaccination were observed, representing 12.3 per 1000 person–years. The incidence of HZ after Zostavax vaccination in MedicineInsight is similar to that found in the cohort study of US Medicare data by Langan et al, in which the incidence of

HZ was 11.7 (95% CI: 10.5 to 13.0) per 1000 person–years when the general definition of HZ (with or without antiviral medicine) was used.[2]

The vaccine failure rate was lower in the Langan study when a more stringent definition of HZ was applied (ICD-10 code for herpes zoster as well as an antiviral medicine recorded) at 5.4 cases per 1000 person–years. Langan's results align with efficacy seen in the SPS clinical trial,[6] which also had a more stringent definition of HZ involving confirmation by polymerase chain reaction (PCR) assay, virus culture or clinical assessment by a review panel.

The Californian cohort study from 2007 to 2014 by Tseng et al[8] found the vaccine failure rate was 8.0 cases of HZ per 1000 person–years among vaccinated patients aged ≥ 60 years. This is lower than MedicineInsight figures, but this study excluded patients who were immunocompromised.

The incidence of HZ after Zostavax vaccination was almost three times higher in patients who received Zostavax before it was listed on the NIP than in those who received it afterwards (16 vs 6 per 1000 person years, respectively). The length of follow-up for patients who received Zostavax before it was listed is far greater than the length of follow-up for patients who received Zostavax since 1 November 2016. Repeat analyses are required in the future to accurately estimate vaccine effectiveness for the post-November 2016 cohort, when sufficient follow-up has accrued, as the effectiveness of the vaccine is known to wane over time[9]. Further, the two cohorts of patients who received Zostavax before and after November 2016 will likely differ in important ways (eg, age, comorbidities, socioeconomic status), which might influence the incidence of HZ observed. The difference in available follow-up is likely to be an important factor.

Trends in the incidence of HZ after vaccination are difficult to interpret due to the small numbers; however, incidence seems to increase with age and to be more common in women. This aligns with literature suggesting older patients and women are at higher risk of incident HZ. The incidence of HZ after vaccination in Queensland was double the national incidence (26.6 vs 12.3 per 1000 person–years). This requires further investigation, including adjusting for confounders (particularly age) and considering issues with cold-chain storage of Zostavax.

The definition of incident HZ in this report was based on a recorded diagnosis and could be further refined to improve specificity for future reports to include the prescription of antiviral medicine (as in some of the cohort studies[2] on effectiveness). Further exploration of incident HZ before the 30-day cut-off is recommended.

5.4. Adverse events after Zostavax vaccination

When incident HZ (≥ 31 days) after Zostavax vaccination was included as an adverse event in addition to the information recorded in the adverse event / allergy fields of the CIS, MedicineInsight captured 1.4 times more adverse events than reported in the TGA-DAEN (473 vs 331 respectively). MedicineInsight maybe a more reliable source of data on HZ post-vaccination.

Additional adverse events may have been recorded in other areas of the CIS and not specifically in the adverse event / allergy table. Such events are difficult to link to a particular medicine or vaccine in routinely collected clinical data.

5.5. Conclusion

This report provides an introduction to the use of MedicineInsight data for vaccine surveillance. The MedicineInsight resource provides the opportunity to better understand Zostavax within the Australian primary care setting. Based on these initial findings, some recommendations for further analyses, in conjunction with other experts, include the following:

- Refining definitions, eg,
  - the definition of incident HZ could be made more specific by including the prescription of antiviral medicine and exploration of incident HZ before the 30-day cut-off (as is current practice in Zostavax research)
  - whether the restriction of including only patients with at least one encounter since the Zostavax listing should be applied
  - conducting a validation study with contributing practices on HZ case ascertainment
  - the definition of patients who are immunocompromised at the time of Zostavax vaccination to assess compliance with contraindications for vaccination.
- Enhancing the analyses, eg,
  - with age standardisation and adjusting for other potential confounders
  - further follow-up surveillance as the effectiveness of the vaccine is known to wane over time.
- Exploring the findings in more detail, eg,
  - patients who develop HZ within 30 days of the vaccine
  - the differences between States and Territories in uptake and development of HZ after vaccination is required.

The MedicineInsight resource is a valuable source of routinely collected data to support Australia's vaccine surveillance activities.

6. GUIDE TO INTERPRETING DATA

When interpreting the information presented in this report, readers should note some of the limitations or caveats related to the MedicineInsight data:

- MedicineInsight data are dependent on the accuracy and completeness of data recorded in, and available for extraction from, the general practice clinical systems.
- Identification of conditions is dependent on the GPs recording these items in their clinical software systems. Conditions may be underreported in MedicineInsight data depending on GPs' recording practices.
- Our classification of HZ, HZ complications and immunocompromised conditions is based on commonly accepted definitions and has been reviewed by two GPs. However, there is likely to be variability in GPs' actual diagnostic labelling practices.
- Calculation of the relative proportion of different indications assumes that non-recording of conditions occurs at random.
- Medicine-use information from MedicineInsight relates to records of GP prescribing, and therefore differs in several important ways from national PBS dispensing data. Not all prescriptions and repeats will be dispensed, ie, prescription counts are an overestimate of dispensed prescription counts, specialist and hospital prescriptions are not included and there may be a delay of up to 12 months between prescribing and dispensing.
- Practices were recruited to MedicineInsight using non-random sampling, and systematic sampling differences between regions cannot be ruled out. Comparisons between regions should be interpreted with caution.
- A proportion of adverse reactions known to the GP may go unrecorded, eg, when the reaction is unremarkable or symptoms are managed elsewhere, eg, hospital.
- Coding of adverse reactions may differ between MedicineInsight and TGA for some reactions.
- Due to confidentiality issues we do not have access to progress notes, which may contain further information on reasons for prescriptions, reasons for encounters and diagnoses.
- Patients are free to visit multiple other practices. We do not have data on patients from non-MedicineInsight clinics. Currently we cannot identify patients who have attended multiple MedicineInsight practices.

7. APPENDICES

7.1. Appendix A: Glossary and abbreviations

Term	Definition	Description
95% CI	95% confidence interval	A 95% confidence interval provides information about a range of values that should contain the actual rate 95% of the time (95 times out of 100), as well as information on the direction and strength of the demonstrated effect. Wider confidence intervals reflect less certainty in the estimate of the rate. Confidence intervals enable conclusions to be drawn about the statistical plausibility and clinical relevance of findings.
95% CL	95% confidence limits	An alternative way of citing a 95% CI (see above), providing the lower and upper limits of the range of values.
ABS	Australian Bureau of Statistics	
ASGC	Australian Standard Geographical Classification	Used from 1984 to 2011 by the Australian Bureau of Statistics (ABS) to calculate geographical statistics. We use ASGC in this report to calculate rurality based on postcode (categorised as in major cities, inner regional, outer regional, remote and very remote areas).
ATC	Anatomical Therapeutic Chemical	System used to classify medicines into groups according to certain characteristics.
Average		Measurement of the 'central' value of a set of values.
BEACH	Bettering the Evaluation and Care of Health program	Cross-sectional program collecting information on GP activities in Australia.
Best Practice		Clinical management software for the GP.
CIS	Clinical information system	A generic term to describe one of several Australian national general practice software programs used by GPs to store patient/consultation/ prescription data (of which Best Practice and Medical Director are two examples).
Clinical encounter	Any professional interchange between a patient and a healthcare professional	In this series of reports a clinical encounter is defined as all encounters at the general practice that were: a) not identified as administrator entries or encounters that had been transferred/imported from another practice (ie, the "Provider ID" was valid and ≠ 0) and b) were not identified by pre-defined 'administration-type' terms found in the 'reason for encounter' field such as 'administrative reasons'; 'forms' 'recall', etc.
Clinically representative practice	A general practice that meets MedicineInsight data quality criteria and caters to 'typical' general practice patients rather than specialises, eg, in youth mental health	A clinically representative practice meets the following inclusion criteria applied by the MedicineInsight team: - established for at least 2 years before the end of the analysis period - has no interruptions to practice data of longer than 2 months in the 2 years to the end of the analysis period - records a history item, reason for encounter or reason for prescription in at least 10% of encounters - issues an average of at least 30 prescriptions per week - caters to usual general practice patients rather than specialises, eg, in youth mental health.
Condition		An illness or abnormality that interferes with a person's usual activities or wellbeing.
CRM	Customer Relationship Management	A database used for storing details of customers, etc. (eg, participating practices).
DoH	Commonwealth Department of Health	Federal department overseeing Australia's health system.
DUSC	Drug Utilisation Sub-Committee (PBAC)	Collects and analyses data on actual drug use and provides advice to PBAC.

DVA	Department of Veterans' Affairs (Australia)	Federal department responsible for delivering government programs for war veterans, defence force and federal police members and their dependents.
GP	General practitioner	
HZ	Herpes zoster	
ZOSTAVAX	Zostavax®	Herpes zoster vaccine
Incidence		The number of new cases of a disease or condition in a population over a defined period of time. Can also be used to describe the number of new prescriptions or tests ordered over a period of time.
Incident		A new or 'first ever record' of a diagnosis of disease or condition in a patient previously unaffected
Longitudinal database		A set of statistical data that observes the same analysis units over a substantial period of time.
Median		The number separating the upper and lower half of a sample of values.
Medical Director 3		Clinical management software for the GP.
MedDRA		Standardised medical terminology for regulatory information about medical products used by humans. Allows the consistent coding of adverse drugs reactions to medicines.
NCIRS	National Centre for Immunisation Research & Surveillance	A research organisation that provides independent expert advice on all aspects of vaccine-preventable diseases and social and other issues related to immunisation to inform policy and planning for immunisation services in Australia.
PBAC	Pharmaceutical Benefits Advisory Committee	Committee making recommendations to the federal Minister of Health on which medicines should be available as pharmaceutical benefits.
PBS	Pharmaceutical Benefits Schedule	Program providing subsidised prescription medicines to Australians.
Practice		An organisation operating at one or more locations where GPs and other staff provide general practice consultations to the community, and which contributes data to MedicineInsight from a single clinical information system database.
Prevalence		Proportion of the population with a particular condition at a given time.
Rate		Measure or ratio of how two factors are associated with one another, eg, a proportion of patients with a condition or the incidence of prescriptions per consultation.
RPBS	Repatriation Pharmaceutical Benefits Scheme	
SAS	Statistical Analysis System (SAS Institute)	Statistical software program.
SEIFA	Socioeconomic indices for areas	Calculated by ABS index of relative socioeconomic advantage and disadvantage.
Site		The unit of data collection corresponding to either one practice or to several practices that share the same clinical system database. Practices combined into one site are typically under common administration or operating in the same geographical area.
TGA	Therapeutic Goods Administration	Australia's regulatory agency for medicines and medical devices.
TGA DAEN	TGA Database of Adverse Event Notification	

7.2. Appendix B: Excerpts from the TGA product information for Zostavax[9]

TGA indications

ZOSTAVAX is indicated for the prevention of herpes zoster (shingles) in individuals 50 years of age and older. ZOSTAVAX is indicated for the prevention of post-herpetic neuralgia (PHN) and for other zoster-associated complications in individuals 60 years of age and older, who are at a higher risk of such zoster *related* complications.

Contraindications

- ZOSTAVAX is a live, attenuated varicella–zoster vaccine and administration may result in disseminated disease in individuals who are immunosuppressed or immunodeficient.
- History of hypersensitivity to any component of the vaccine, including gelatin.
- History of anaphylactic/anaphylactoid reaction to neomycin (each dose of reconstituted vaccine contains trace quantities of neomycin).
- Primary and acquired immunodeficiency states due to conditions such as: acute and chronic leukaemias; lymphoma; other conditions affecting the bone marrow or lymphatic system; immunosuppression due to HIV/AIDS; cellular immune deficiencies.
- Immunosuppressive therapy (including high-dose oral corticosteroids) See ADVERSE EFFECTS; however, ZOSTAVAX is not contraindicated for use in individuals who are receiving topical/inhaled corticosteroids or low-dose systemic corticosteroids or in patients who are receiving corticosteroids as replacement therapy, eg, for adrenal insufficiency (see CLINICAL TRIALS, Immunogenicity in subjects on chronic/maintenance systemic corticosteroids).
- Active untreated tuberculosis.
- Pregnancy (see PRECAUTIONS, Pregnancy).

Precautions

The health care provider should ask the patient about reactions to a previous dose of any VZV-containing vaccines (see CONTRAINDICATIONS). As with any vaccine, adequate treatment provisions, including adrenalin injection (1:1000), should be available for immediate use should an anaphylactic/anaphylactoid reaction occur. Deferral of vaccination should be considered in the presence of fever >38.5°C (>101.3°F). The safety and efficacy of ZOSTAVAX have not been established in adults who are known to be infected with HIV with or without evidence of immunosuppression. A phase II safety and immunogenicity study in HIV-infected adults with conserved immune function has been completed (see CLINICAL TRIALS and ADVERSE EFFECTS). WPC-V211-R-I-032016 - 9 - As with any vaccine, vaccination with ZOSTAVAX may not result in protection of all vaccine recipients.

Transmission

Post-marketing experience with varicella vaccines suggests that transmission of vaccine virus may occur rarely between vaccine recipients, who develop a varicella-like rash, and susceptible contacts. This is a theoretical risk following vaccination with ZOSTAVAX. The risk of transmitting the attenuated live vaccine virus to a susceptible individual should be weighed against the risk of developing natural zoster that could be transmitted to a susceptible individual.

Use in the elderly

The mean age of subjects enrolled in the largest (N = 38,546) clinical study of ZOSTAVAX was 69 years (range 59–99 years). Of the 19,270 subjects who received ZOSTAVAX, 10,378 were 60–69 years of age, 7629 were 70–79 years of age, and 1263 were 80 years of age or older. The safety and efficacy data presented in the PHARMACOLOGY, CLINICAL TRIALS and ADVERSE

EFFECTS sections below were obtained from these subjects. ZOSTAVAX was demonstrated to be generally safe and effective in this population.

7.3. Appendix C: Vaccination definitions

Table 9: **VACCINATION TERMS RELATING TO ZOSTAVAX**

Medicine/Vaccine name
ZOSTAVAX
VARICELLA ZOSTER
ZOSTER STUDY VACC
ZOSTER VAX
ZOSTA
ZOSTA SHINGLES VA
ZOSTA VAC
ZOSTAVAS
ZOSTAVEX
ZOSTAVIX
ZOSTAVX

7.4. Appendix D: Medicine and condition definitions

Table 10: **MEDICINES AND THERAPIES THAT CAUSE IMMUNOSUPRESSION**

Medicine name	Therapy – relevant search terms	Therapy – exclusions
Sulfasalazine	Chemo$	Chemosis$
Cyclophosphamide	Chemoprophyl$	
Rituximab	Radiotherapy	
Mycophenolate	Radiation therapy	
Abatacept	Chemo-radiation	
Etanercept	Radiation treatment	
Adalimumab	Radioactive iodine	
Ciclosporin	Radioiodine	
Tacrolimus	Brachytherapy	

7.4.1. Condition definitions

A patient was defined as having a history of a condition of interest if they had ever had a recorded relevant term for that diagnosis in any designated text or code field in relevant diagnosis tables (history [currently active or inactive], reason for prescription and reason for visit).

Table 11 provides a summary of the terms included for HZ.

Terms used to identify immunocompromising comorbidities can be found in Table 12.

Table 11: **DEFINITION FOR HZ; INCLUDED TERMS**

Condition	Source	Included search terms	Excluded search terms
HZ	Text	herp$ and zost$	prevent$
HZ	Text	varicel$ and zost$	prophyl$
HZ	Text	shingle$	Imm$
HZ	Text	herpes zoster neuralg$	vac$
HZ	Text	neuralgia post herp$	Test$
HZ	Text	herpetic neuralg$	
HZ	Text	ramsay hunt	

Table 12: **DEFINITION FOR IMMUNOCOMPROMISING CONDITIONS; INCLUDED/EXCLUDED TERMS**

Condition	Source	Included search terms	Excluded search terms
HIV	Text	HIV	HIV serology / test
HIV	Text	AIDS	HIV exposure / contact
HIV	Text	Acquired Immunodeficiency Disease	HIV negative / -ve
HIV	Text	Human Immunodeficiency Virus	HIV counselling
Leukaemia	Text	Leukaemi$	
Leukaemia	Text	Leukemi$	
Leukaemia	Text	CLL	
Leukaemia	Text	CML	
Leukaemia	Text	AML	
Lymphoma	Text	Lymphoma	Lymphomatoid
Lymphoma	Text	Lymphosarc$	Pseudolymphoma
Lymphoma	Text	Hodgkins	

7.5. Appendix E: Annual vaccination rates before Zostavax listing on the NIP

Table 13: **ANNUAL VACCINATION RATES BEFORE 1 NOV 2016 BY DEMOGRAPHIC FACTORS, MEDICINEINSIGHT, NOV 2012 – OCTOBER 2016[A]**

	1 NOV 2012 – 31 OCT 2013				1 NOV 2013 – 31 OCT 2014				1 NOV 2014 – 31 OCT 2015				01 NOV 2015 – 31 OCT 2016			
	Patients with Zostavax vaccination recorded (n)	Vaccination rate (per 1000 MedicineInsight patients)	95% CL		Patients with Zostavax vaccination recorded (n)	Vaccination rate (per 1000 MedicineInsight patients)	95% CL		Patients with Zostavax vaccination recorded (n)	Vaccination rate (per 1000 MedicineInsight patients)	95% CL		Patients with Zostavax vaccination recorded (n)	Vaccination rate (per 1000 MedicineInsight patients)	**95% CI**	
Zostavax	530	0.61	0.43	0.79	2662	2.89	2.30	3.48	3880	4.12	3.44	4.79	5042	5.34	4.77	5.90
5-year age groups																
50–54	11	0.08	0.03	0.13	55	0.37	0.26	0.48	116	0.74	0.57	0.92	162	1.01	0.79	1.24
55–59	29	0.21	0.12	0.29	139	0.93	0.70	1.16	223	1.42	1.17	1.67	372	2.33	1.97	2.68
60–64	56	0.43	0.28	0.58	259	1.85	1.47	2.23	497	3.41	2.79	4.03	785	5.27	4.52	6.03
65–69	105	0.83	0.60	1.05	496	3.64	2.96	4.31	844	5.95	5.01	6.89	1110	7.71	6.71	8.70
70–74	123	1.16	0.80	1.51	607	5.39	4.17	6.61	864	7.49	6.17	8.80	1066	9.15	8.10	10.20
75–79	92	1.12	0.75	1.50	458	5.35	4.13	6.57	654	7.51	6.08	8.95	835	9.61	8.21	11.00
80–84	48	0.77	0.41	1.13	291	4.55	3.35	5.75	394	6.20	4.63	7.77	424	6.91	5.92	7.90
85–89	41	0.86	0.15	1.56	228	4.82	3.19	6.45	205	4.53	3.36	5.70	194	4.64	3.74	5.54
90–94	21	0.78	0.22	1.34	105	4.09	2.73	5.45	70	3.02	1.36	4.69	78	3.93	2.77	5.08
95–100	4	0.36	0.00	0.79	24	2.53	1.19	3.87	13	1.71	0.55	2.87	16	2.85	1.32	4.39
Gender																
Male	196	0.51	0.32	0.70	1000	2.46	1.90	3.02	1403	3.36	2.77	3.95	1796	4.28	3.74	4.81
Female	334	0.68	0.50	0.87	1662	3.24	2.60	3.87	2477	4.72	3.96	5.49	3245	6.19	5.57	6.81

	1 NOV 2012 – 31 OCT 2013				1 NOV 2013 – 31 OCT 2014				1 NOV 2014 – 31 OCT 2015				01 NOV 2015 – 31 OCT 2016			
	Patients with Zostavax vaccination recorded (n)	Vaccination rate (per 1000 MedicineInsight patients)	95% CL		Patients with Zostavax vaccination recorded (n)	Vaccination rate (per 1000 MedicineInsight patients)	95% CL		Patients with Zostavax vaccination recorded (n)	Vaccination rate (per 1000 MedicineInsight patients)	95% CL		Patients with Zostavax vaccination recorded (n)	Vaccination rate (per 1000 MedicineInsight patients)	**95% CI**	
Indigenous status																
Unspecified	145	0.67	0.20	1.14	557	2.52	1.97	3.08	738	3.39	2.76	4.02	1016	4.82	4.13	5.51
Non-indigenous	383	0.59	0.42	0.77	2094	3.04	2.32	3.76	3129	4.38	3.59	5.18	4006	5.54	4.91	6.17
Indigenous	2	0.20	0.00	0.48	11	1.02	0.42	1.63	13	1.18	0.39	1.97	20	1.78	0.92	2.64
State																
ACT	10	0.63	0.01	1.25	58	3.47	1.78	5.16	112	6.00	2.99	9.01	161	8.59	6.50	10.69
NSW	265	0.93	0.43	1.43	956	3.15	1.88	4.42	1313	4.23	3.07	5.39	1529	4.92	4.05	5.78
NT	3	0.32	0.00	0.72	1	0.10	0.00	0.26	11	1.12	0.38	1.86	10	1.00	0.34	1.67
Qld	130	0.84	0.58	1.10	666	4.03	2.37	5.69	817	4.79	3.16	6.41	1117	6.49	5.19	7.79
SA	9	0.31	0.05	0.57	74	2.45	1.34	3.56	111	3.78	2.66	4.90	202	6.69	5.16	8.22
Tas	19	0.23	0.06	0.40	185	2.20	1.43	2.97	458	5.39	3.92	6.87	411	4.88	3.65	6.11
Vic	83	0.42	0.23	0.62	530	2.55	1.47	3.62	791	3.74	1.87	5.60	1048	5.02	3.45	6.59
WA	11	0.11	0.04	0.19	192	1.88	1.32	2.45	267	2.50	1.70	3.30	564	5.13	3.79	6.48

a Annual vaccination rates were calculated as the number of patients receiving Zostavax vaccination recorded that year divided by the number of patients in the study population with at least one clinical encounter that year, multiplied by 1000

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8. REFERENCES

[1] WHO Collaborating Centre for Drug Statistics Methodology (2003). The Anatomical Therapeutic Chemical Classification System with Defined Daily Doses (ATC/DDD). http://www.who.int/classifications/atcddd/en/ (accessed 25 June 2017).

[2] Langan SM, Smeeth L, Margolis DJ, et al. Herpes zoster vaccine effectiveness against incident herpes zoster and post-herpetic neuralgia in an older US population: a cohort study. PLoS Med 2013, 10(4): e1001420.

[3] Liu XC, Simmonds KA, Russell ML, et al. Herpes zoster vaccine (HVZ): utilization and coverage 2009–2013, Alberta, Canada. BMC Public Health 2014;14:1098.

[4] Australian Government Department of Health, Therapeutic Goods Administration. Zostavax TGA Approved Product Information. https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2010-PI-01547-3&d=20170829161146224 83 (accessed 26 April 2016).

[5] Schmander K, Levin M, Gann Jr JW, et al. Efficacy, safety and tolerability of herpes zoster vaccine in persons aged 50–59 years. Clin Infect Dis 2012, 54:922–8.

[6] Oxman MN, Levin MJ, Johnson GR, et al. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. N Engl J Med 2005;352:2271–84.

[7] National Centre for Immunisation Research & Surveillance. Herpes Zoster: HZV for Australian Adults: information for immunisation providers. http://www.ncirs.edu.au/assets/provider_resources/fact-sheets/zoster-vaccine-fact-sheet.pdf (accessed 29 August 2017).

[8] Tseng HF, Harpaz R, Luo Y, et al. Declining effectiveness of herpes zoster vaccine in adults aged ≥ 60 years. J Infect Dis 2016;213:1872–5.

[9] Therapeutic Goods Administration. Zostavax Approved Product Information. TGA, 26 April 2016.

[10] Merck Sharp and Dohme Australia. Product Information. Zostavax, WPC-V211-R-I-032016, March 2016.