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Disseminated varicella zoster virus infection following live attenuated herpes zoster vaccine: descriptive analysis of reports to Australia's spontaneous vaccine pharmacovigilance system, 2016–2020

Jean Li-Kim-Moy ,[1,2] Anastasia Phillips,[1] Adelaide Morgan,[1] Catherine Glover,[1] Sanjay Jayasinghe,[1,3] Brynley P Hull,[1] Aditi Dey ,[1,2] Frank H Beard,[1,4] Megan Hickie,[5] Kristine Macartney [1,2]

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For numbered affiliations see end of article.

Correspondence to
Dr Jean Li-Kim-Moy; jean.likimmoy@health.nsw.gov.au

ABSTRACT

Objectives To examine the reported incidence and features of disseminated varicella zoster virus (VZV) infection following live attenuated herpes zoster vaccine live (ZVL: Zostavax, Merck) in immunocompromised people in Australia.

Design and setting ZVL was funded in 2016 in Australia for people aged 70 years, with a catch-up programme for those 71–79 years. From 2016 to 2020, three deaths due to disseminated vaccine-strain VZV infection occurred following inadvertent ZVL administration in individuals with varying levels of immunocompromise. This descriptive study examined 4 years of national surveillance data reported to the Therapeutic Goods Administration's Adverse Event Monitoring System (AEMS). Denominator data for rates were from doses recorded in the Australian Immunisation Register.

Participants Individuals vaccinated between 1 November 2016 and 31 December 2020 who experienced adverse event(s) following immunisation (AEFI) after ZVL recorded in the AEMS.

Primary and secondary outcome measures Rates and outcomes of confirmed (Oka strain positive) or probable disseminated VZV infection, and inadvertent administration of ZVL in immunocompromised individuals.

Results 854 AEFI were reported from 1 089 966 doses of ZVL administered (78.4 per 100 000 doses). Of those, 14 were classified as confirmed (n=6, 0.55 per 100 000) or probable (n=8) disseminated VZV infection. The confirmed cases were all hospitalised, and most (5/6) were immunocompromised; three cases died. Thirty-seven individuals were reported as vaccinated despite a contraindication due to immunocompromise (3.4 per 100 000), with 12/37 (32%) hospitalised.

Conclusions Disseminated VZV is potentially life-threatening and occurs mostly in those with severe immunocompromise. Inadvertent administration of ZVL to immunocompromised individuals has occurred despite initial provider guidance and education. Multiple additional strategies to assist providers to identify contraindications have been implemented to prevent adverse outcomes.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The rate of Oka vaccine strain disseminated varicella zoster virus (VZV) infection is described in the context of a funded national immunisation programme where vaccine was available free to all individuals 70–79 years of age.
⇒ Inclusion of vaccine administration errors in the vaccine pharmacovigilance system enabled estimation of the extent of inadvertent administration of live zoster vaccine to immunocompromised individuals.
⇒ The inclusion of 4 years of data from programme commencement through a period of enhanced provider communication regarding vaccine contraindications allowed examination of changes in rates over time.
⇒ Data from spontaneous reporting systems can be subject to under-reporting or over-reporting and the number of doses administered may be under-reported to the national immunisation register.
⇒ It was not possible to independently validate all cases of potential disseminated VZV; some data were limited to that collected at the time of the adverse event(s) following immunisation report and through subsequent follow-up by the Therapeutic Goods Administration.

INTRODUCTION

Herpes zoster (HZ) is a painful reactivation of latent varicella zoster virus (VZV), which classically leads to a vesicular rash in a dermatomal distribution. The risk of HZ increases with age, particularly above 50 years of age.[1–3] In Australia, the incidence of HZ in adults 70–79 years was 15.3 per 1000 persons per

year between 2006 and 2013.[1] Around 20% of HZ cases develop postherpetic neuralgia (PHN), a chronic, potentially debilitating neuropathic pain syndrome.[3]

Zostavax (Merck) is a live attenuated herpes zoster vaccine (ZVL) based on the Oka VZV strain. It was registered by the Australian medicines regulator, the Therapeutic Goods Administration (TGA), in 2006. ZVL has been recommended in Australia for people aged ≥60 years since 2009[4] and was added to the funded National Immunisation Programme (NIP) from 1 November 2016 for adults aged 70 years with a catch-up programme for those aged 71–79 years.[4] There was modest uptake (up to 46.9%) in the eligible Australian population in the first 2 years following programme commencement, with the most rapid uptake occurring within the first 6 months.[5 6] The programme has had clear benefit, reducing the incidence of HZ by 2.25 cases per 1000 persons per year in the target age cohort during the first 2 years of the programme, and resulting in ~7000 cases of HZ averted per year.[7] Vaccine effectiveness in the Australian setting has been estimated at 66.4% up to 8 months following vaccination,[8] although there is evidence that immunity wanes over time.[8–14]

Safety of ZVL in immunocompetent adults was demonstrated in clinical trials prior to Australia's programme implementation.[15–19] The vaccine is well tolerated and the rate of non-injection site VZV-like rashes up to 6 weeks postvaccination was lower or similar in vaccine recipients than placebo recipients.[15–18] However, ZVL is contraindicated in individuals who are severely immunocompromised, due to the potential for dissemination of vaccine virus.[20] ZVL was the first live vaccine to be added to the NIP for older adults, who are more likely than children to have comorbid conditions, such as immunocompromise. A comprehensive vaccine safety plan and communication strategy was developed by the Australian Government Office of Health Protection to accompany the rollout of the programme. This included guidance on contraindications to receipt of ZVL, updates to the Australian Immunisation Handbook (AIH), and online and in-person education sessions which were made available to Australian immunisation providers prior to inclusion of ZVL on the NIP.[21]

One case report of a death from disseminated infection following vaccination in an immunocompromised individual was reported from the UK in 2016.[22] The first Australian death, in an immunocompromised individual contraindicated for vaccination, was reported in early 2017.[23 24] In the subsequent 4 years, two more vaccine-related deaths were reported in Australia, in individuals with varying levels of immunocompromise, despite intensive efforts to improve provider awareness of contraindications for ZVL. This included the introduction of a screening checklist to assist in assessing contraindications, along with TGA safety alerts, letters to vaccine providers and updates to national guidance.[24–31] A 2020 survey of 502 general practitioners, those most likely to deliver ZVL in the primary care setting, suggested that 18% of Australian primary care providers either did not know or were unsure that immunocompromise is a contraindication to ZVL, and that 41% were unaware of TGA safety alerts.[32] The frequency of administration of ZVL to immunocompromised individuals in Australia and any resultant serious outcome, and rates of disseminated infection following vaccination, have not been reported.

We aimed to examine all adverse event(s) following immunisation (AEFI) reported following ZVL over the 4 years since programme implementation (November 2016–December 2020), with a focus on rates and outcomes of inadvertent administration to immunocompromised individuals and potential disseminated VZV infection.

METHODS

Patient and public involvement

Patients were not directly involved in the design or conduct of the study, noting its retrospective and descriptive nature. However, the research question and outcomes investigated were developed and informed by their priorities, recognising the importance of assuring their safety after ZVL by preventing potentially fatal vaccine-related disseminated VZV, and balancing this with the important benefits of preventing HZ and PHN, which can have a debilitating impact on patient quality of life.[33]

Data source

In Australia, AEFI are reported to the TGA's spontaneous vaccine pharmacovigilance system, mostly via local systems in eight States and Territories, and stored in the Adverse Events Monitoring System (AEMS) database. The TGA accepts reports from hospitals, immunisation providers and the public; in most states and territories, reporting is a statutory obligation for healthcare providers.[34] Where reporter contact details and consent are provided, additional information can be sought by the TGA, as required. Events are coded by the TGA using standardised Medical Dictionary for Regulatory Activities (MedDRA) codes,[35] including preferred terms. Coding for serious events is applied based on criteria as defined by the WHO.[36] Coding of AEFI as serious is based on available information; although multiple attempts may be made to obtain additional information from the reporter, it may not be possible to review detailed and verified clinical data in every case.[37]

Deidentified AEMS reports were extracted for adverse events following ZVL for doses administered between 1 November 2016 and 31 December 2020. To allow for reporting lag, AEFI reported up to 18 March 2021 were examined. Reports included age, sex, vaccine administered, concomitant medications/vaccinations, vaccination date, symptom onset date, report date, MedDRA preferred terms, severity code and a free-text case narrative. In instances where the vaccination date was not recorded, it was estimated based on median intervals to symptom onset date or report date in other AEFI reports within the dataset. Vaccination date was only used for

determining inclusion in the descriptive analysis; for detailed case review, case narratives were used to support time to onset of symptoms.

Descriptive analysis

All AEFI reports were analysed by sex, age group and calendar year of vaccination. The proportion of reports coded as serious was calculated. Crude and age-specific rates were calculated based on a denominator of doses recorded in the Australian Immunisation Register (AIR) as administered from 1 November 2016 to 31 December 2020. The top 10 preferred terms associated with reports in males and females were identified.

Case review

To identify potential (1) disseminated VZV infection and (2) vaccine administration errors (including administration to immunocompromised individuals), selected reports were extracted for manual review based on specified preferred terms. The relevant preferred terms were selected from all preferred terms within the dataset after review by, and agreement between, two medical officers (JL-K-M, AP) experienced in AEFI analysis, with reference to terms used in a similar analysis of AEFI following ZVL in the USA, using the Vaccine Adverse Events Reporting System (VAERS).[38] For disseminated VZV infection, reports coded with a fatal outcome, or with a date of death documented, were also included. For vaccine administration errors, free text searches of the medication and case narrative fields were also used; terms were based on immunosuppressive medications or immunocompromising conditions, as listed in the AIH[31] (refer to online supplemental table S1a,b).

All identified cases underwent manual review by one of three medical officers (JL-K-M, AP, AM). Given that disseminated infection and vaccine administration error were not mutually exclusive, each report was classified according to the likelihood of both (1) disseminated infection and (2) immunocompromise based on available information, and regardless of which search strategy identified the case. For disseminated infection, reports were classified as confirmed or probable based on predefined criteria including presence of widespread vesicular rash, antiviral treatment, systemic involvement, time to onset and/or laboratory confirmation (table 1). Confirmed

Table 1 Classification criteria for disseminated VZV infection and degree of immunocompromise for cases identified for manual review

Category	Definition
Disseminated infection	
Confirmed vaccine strain disseminated infection	Widespread rash* with laboratory confirmation of vaccine strain VZV
Probable vaccine strain disseminated infection	(a) Widespread rash* described as 'chickenpox' like or vesicular or painful without laboratory confirmation of vaccine strain VZV AND systemic involvement OR (b) Widespread rash* described as 'chickenpox' like or vesicular or painful rash* without laboratory confirmation of vaccine strain VZV AND treated with antiviral medication AND with onset 6 days† or more following vaccination (where specified) or onset date not specified. OR (c) Widespread rash* described as 'chickenpox' like or vesicular or painful AND laboratory confirmation of unspecified strain VZV AND onset 6 days† or more following vaccination (where specified) or onset date not specified
Degree of immunocompromise	
Confirmed immunocompromise (contraindicated to vaccination)	Documented evidence of contraindication, as per AIH, of any of the following: ► Are receiving high-dose systemic immunosuppressive therapy, such as chemotherapy, radiation therapy or oral corticosteroids (≥20 mg per day of prednisolone equivalent dose). ► Are receiving biological or targeted synthetic disease-modifying antirheumatic drugs (bDMARDs or tsDMARDs). ► Have malignant conditions of the reticuloendothelial system (such as lymphoma, leukaemia or Hodgkin disease, even if they are not receiving active treatment). ► Have AIDS or symptomatic HIV infection. OR have similar immunocompromising conditions due to a disease or treatment Note: This category included cases meeting criteria for immunocompromise even if there was documentation that a specialist advised the patient could be safely vaccinated. These cases were marked separately.
Low level immunocompromise without contraindication	Documented evidence of medication within 'safe dose to vaccinate' table, as per AIH: ► Prednisone <20 mg/day. ► Low-dose csDMARDs: azathioprine, mercaptopurine, methotrexate, sulfasalazine, hydroxychloroquine
Possible immunocompromise	Immunocompromise or immunosuppressive medication mentioned (in case description of preferred terms) but with insufficient detail (eg, dose or timing) to confirm or assess degree of immunocompromise

*Based on available information, affects multiple dermatomes.
†Based on study by Miller *et al*[38] with laboratory documented disseminated vaccine strain VZV infection with onset 6 days after vaccination.
AIH, Australian Immunisation Handbook; bDMARDs, biologic disease-modifying anti-rheumatic drugs; tsDMARDs, targeted synthetic disease-modifying anti-rheumatic drugs; VZV, varicella zoster virus.

infections required identification of vaccine strain virus. Cases not identified for manual review were not further analysed.

Reports indicating possible administration in immunocompromised individuals were classified as 'confirmed immunocompromise' (contraindicated to vaccination) or as 'low level immunocompromise without contraindication' based on the guidance in the AIH; reports that indicated an immunocompromising condition or medication, but where there was insufficient documentation in the report to apply the AIH criteria, were classified as 'possible immunocompromise' (table 1).

All reports coded as confirmed or probable disseminated infection, or as administration to an immunocompromised individual, were further reviewed by all three medical officers; any differences in coding were resolved through discussion. Crude rates of disseminated VZV infection and inadvertent administration of ZVL to immunocompromised individuals were estimated based on doses recorded in the AIR during the study period.

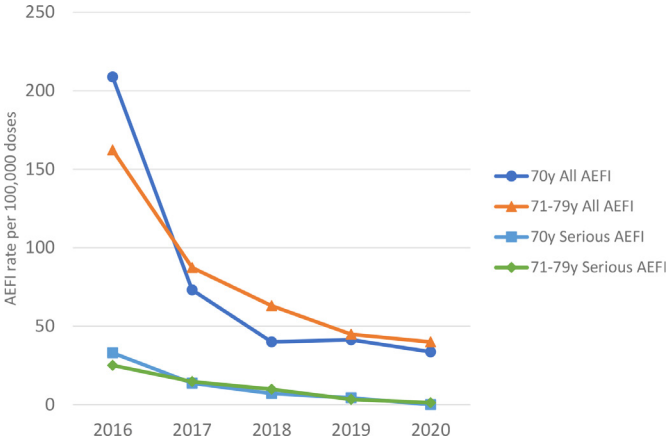

Figure 1 Annual AEFI rates for Zostavax by age groups of 70 years (routine age-based schedule point) and in 70–79 years (catch-up cohort) using data from 1 November 2016 to 31 December 2020 (per 100 000 doses recorded as administered on AIR). AEFI, adverse event(s) following immunisation; AIR, Australian Immunisation Register.

RESULTS

Descriptive AEFI analysis

In total, 854 AEFI were reported to AEMS following vaccination with ZVL between 1 November 2016 and 31 December 2020, of which 143 (17%) were coded as serious by the TGA. During this period, 1 089 966 doses of ZVL were recorded as administered on AIR, giving an overall AEFI reporting rate of 78.4 per 100 000 doses administered. Most reports (84%) were in the 70–79 years age group corresponding to the age cohort eligible for funded vaccination; the reported AEFI rate in this age group was similar to other age groups (table 2). AEFI were reported almost twice as often in females (97.2 per 100 000) than in males (53.4 per 100 000), although the proportion considered serious was similar in both groups (15%–18%). The most common MedDRA preferred terms included HZ (21.2% of all reports), injection site reaction (19.2%) and vaccination error (11.7%) (online supplemental table S2).

Reported AEFI rates were highest at the commencement of the programme in 2016 (167.9 per 100 000 administered doses), decreased progressively from that time, and were lowest in 2020 (41.8 per 100 000) (figure 1 and online supplemental table S3). In the two most recent years of data, 2019 and 2020, rates plateaued to approximately fourfold lower than at programme commencement, at 42–45 per 100 000 for all AEFI and 2–3 per 100 000 for serious AEFI.

Of all 854 AEFI reports, 256 reports were identified for manual review based on selection criteria for disseminated infection (n=147) or vaccine administration error (n=125). Among all these 256 reports, 16 cases were identified as fulfilling manual review criteria in both categories.

Table 2 Number and rate of AEFI reports following Zostavax between 1 November 2016 and 31 December 2020

Characteristic	Overall*	AIR recorded doses	AEFI rate†
Total reports	854	1 089 966	78.4
Serious reports	143 (17%)	1 089 966	13.1
Sex*			
Male	266 (31%)	498 423	53.4
Female	575 (67%)	591 543	97.2
Age group*			
50–59 years	10 (1.2%)	13 501	74.1
60–69 years	42 (4.9%)	55 712	75.4
70–79 years	715 (84%)	976 349	73.2
80+ years	31 (3.6%)	41 019	75.6

*Age was unknown in 37 reports and sex was unknown in 13, which are included in total AEFI.
†Per 100 000 doses recorded as administered on AIR.
AEFI, adverse event(s) following immunisation; AIR, Australian Immunisation Register.

Disseminated VZV infection

Of the 147 reports identified for manual review based on criteria for possible disseminated infection, the majority (n=88; 60%) were determined to be likely cases of localised HZ (shingles), and thus, were considered more likely to represent reactivation of latent wild-type VZV infection (figure 2). Six reports were classified as confirmed disseminated infection (Oka vaccine strain identified), giving a rate of 0.55 per 100 000 doses administered since programme commencement (ie, 1 in 182 000 doses). A further eight reports were classified as probable disseminated infection; considering the 14 reports classified as either confirmed or probable disseminated infection, the rate was 1.28 per 100 000 (1 in 78 000 doses administered).

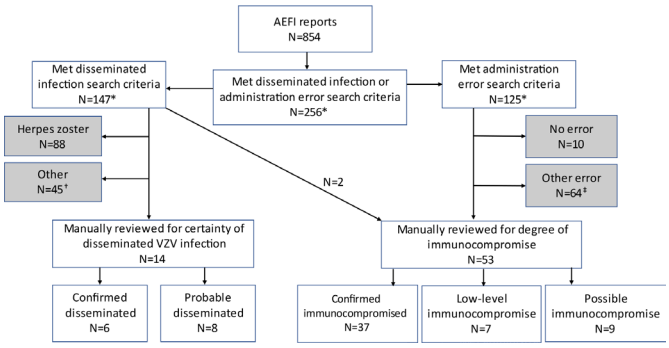

Figure 2 Flow chart of assessment of AEFI following ZVL reports identified for manual review. AEFI, adverse event(s) following immunisation; ZVL, zoster vaccine live.

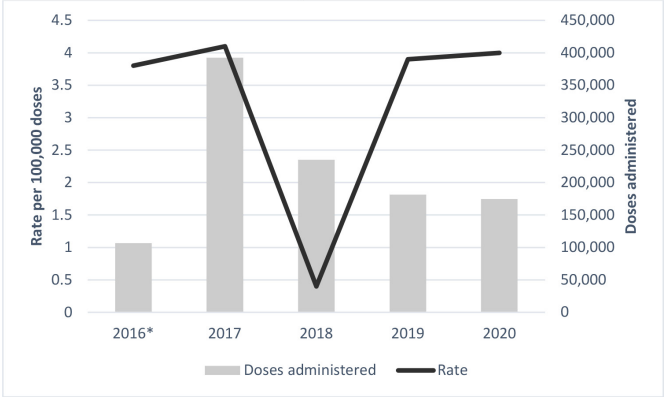

Figure 3 Rate of AEFI reports for inadvertent administration in confirmed immunocompromised individuals contraindicated for ZVL per 100 000 doses administered, 2016–2020. AEFI, adverse event(s) following immunisation; ZVL, zoster vaccine live.

Of the six reports classified as confirmed disseminated infection, four occurred in individuals with significant immunocompromise (two patients with chronic lymphocytic leukaemia (CLL), one on methotrexate and one on corticosteroids/checkpoint inhibitor), one in an individual with low-level immunocompromise (hydroxychloroquine/low dose corticosteroids, who was not contraindicated according to immunisation guidelines at the time)[31] and one in an immunocompetent person (table 3). Time to onset ranged from 15 to 31 days following vaccination in five of six patients where this was documented. All six cases of confirmed disseminated infection required hospitalisation, and three died (two significantly immunocompromised and one with low-level immunocompromise not contraindicated for vaccination at the time).

The eight reports classified as probable disseminated infection were predominantly reports of widespread vesicular rash (n=6) and one each of VZV encephalitis and VZV vasculitis/encephalopathy. Four reports detailed VZV testing, two positive (unknown strain), one equivocal and one negative (although clinically suspected VZV vasculitis/encephalitis). Three of the eight individuals had confirmed immunocompromise (two with CLL, one on immunosuppressants) and required hospitalisation, while five had no mention of immunocompromise and appeared to only have widespread cutaneous infection.

Immunisation errors to immunocompromised people

Fifty-one reports identified through search criteria for vaccine administration errors, and a further two reports identified through manual review of those meeting only the criteria for possible disseminated infection (total 53, figure 2), were assessed as potential reports of administration to an immunocompromised individual. Of these, 37 were classified as individuals with confirmed immunocompromise with contraindication. This corresponded to a rate of 3.4 per 100 000 doses (table 3); analysis by year shows that reporting rates were similar across all years except 2018 (figure 3). Hospitalisation was recorded in 12/37 cases (32%); for those hospitalised that did not develop disseminated infection (5/12), reasons for hospitalisation included assessment and monitoring for the administration error (n=3), other AEFI (n=1) or unrelated conditions (n=1). The most common cause of immunocompromise was a malignant condition of the reticuloendothelial system (n=20, 54%), most commonly CLL. Other causes included a history of radiotherapy or chemotherapy or other immunosuppressive medications.

Seven individuals had low-level immunocompromise which did not contraindicate vaccination; however, one of these patients died from disseminated infection (as described above). This case was one of the three reviewed and reported by the TGA.[25] There were nine cases with possible immunocompromise with insufficient detail of dose or timing to confirm or assess degree of immunocompromise, none of which were classified as disseminated VZV or required hospitalisation.

Table 3 Patients with confirmed and probable disseminated Oka VZV infection following ZVL by level of immunocompromise including number hospitalised

	Level of immunocompromise				Total number (number hospitalised)
	Confirmed	Low level	Possible	None	
Confirmed disseminated VZV infection	4	1	0	1	6 (6)
Probable disseminated VZV infection	3	0	0	5	8 (3)
Total number(number hospitalised)	37 (12)	7 (1)	9 (0)	203 (6)	

Individuals with confirmed immunocompromise were contraindicated to vaccination.
VZV, varicella zoster virus; ZVL, zoster vaccine live.

DISCUSSION

This analysis of 4 years of vaccine safety surveillance data for ZVL in Australia provides valuable insights into the use of this vaccine in immunocompromised individuals and the estimated frequency of vaccine-related disseminated VZV infection in Australia. Overall AEFI rates were similar to those reports from other surveillance systems internationally[38] and declined substantially and stabilised, after programme commencement.

Our finding of an overall AEFI rate of 78.4 per 100 000 doses recorded, of which 13.1 per 100 000 were classified as serious, compares to 106 per 100 000 (total) and 4.4 per 100 000 (serious) reported from a 10-year study of the US VAERS.[38] The target population in the USA is slightly younger (≥60 years), and case ascertainment in Australia may be higher, given AEFI reporting is a statutory requirement in many States and Territories. The overall AEFI rate in our study was highest in the period immediately after introduction of ZVL onto the NIP and plateaued at 42–45 per 100 000 in 2019–2020, as is common with new vaccination programmes as providers and the public become more familiar with the vaccine over time.[39] Similarly, the rate of serious AEFI reported declined to 2.3 per 100 000 by 2019.

We found that the pattern of AEs after ZVL was similar to international postmarketing safety studies[38 40] and clinical trials, noting that trials specifically excluded individuals with underlying immunocompromise.[41 42] The majority of reports to TGA involved diagnoses of HZ, or were coded with other MedDRA preferred terms associated with localised rashes (vesicular or undefined); these AEFI were most likely related to 'breakthrough' HZ occurring due to expected incomplete vaccine protection against reactivation of latent VZV. This is consistent with the knowledge that ZVL is only a moderately effective vaccine, with clinical trials[15 16] estimating efficacy at 51.3% (95% CI 44.2% to 57.6%) against HZ in those aged ≥60 years and 37.6% in those aged ≥70 years over a 3-year follow-up period. Injection site reactions were the second most frequently reported AEFI in our study (19.2% of reports), similar to other vaccine safety studies,[38 43 44] followed by vaccination error (11.7%).

ZVL has had tangible benefits in reducing the incidence of HZ in older adults in Australia.[7] However, vaccine-related disseminated infection has significant and sometimes fatal outcomes, and the three reported cases of death following disseminated vaccine-strain infection are concerning. Formal causality assessment using WHO criteria following expert review of cases found that these deaths occurred due to vaccination in two individuals who were significantly immunocompromised and contraindicated for vaccination,[23 24 26] and one person who was mildly immunocompromised.[25] For the latter patient, the TGA also concluded that the vaccine had been used in line with existing recommendations but that it was important that both providers and vaccine recipients were aware of this very rare adverse event, that patients seek medical attention if they became unwell in the postvaccination period, and mention their vaccination history to the doctor they saw.[25]

Our analysis identified 6 cases of laboratory-confirmed Oka strain disseminated VZV infection from 854 AEFI reports, giving an estimated crude rate of 0.55 per 100 000 doses administered. Although this rate is higher than the US analysis,[38] which found 6 reports among 21 846 030 doses of Zostavax distributed in the USA from licensure in 2006 through to 2014 (0.027 per 100 000), data should be interpreted with caution due to the low numbers and potential for differential case ascertainment. Our denominator was derived from doses recorded as administered in the AIR. This 'whole of life' immunisation register was expanded from a child-based register 1 month prior to introduction of ZVL onto the NIP; with evidence of substantial under-reporting of adult vaccines to the AIR early in the first year after it was established.[5] Assuming, based on early estimates, that only 48% of distributed doses of ZVL were captured in the AIR[5] and the unlikely scenario that all distributed doses were administered, the adjusted rate of disseminated infection would be lower at 0.31 per 100 000. A worldwide review of all postmarketing adverse event reports (n=23 356) found only 14 reports of confirmed Oka strain infection (two disseminated infections), 221 reports of varicella and varicella-like rash and 18 reports suggestive of disseminated HZ (7/18 had history of immunosuppression and one patient died).[40]

Despite the contraindication for use of ZVL in individuals with immunocompromise, our analysis identified ongoing reports of inadvertent administration in immunocompromised individuals at a rate of 3.4 per 100 000 doses, with hospitalisation a frequent outcome in reported events. Reasons for immunocompromise most commonly involved CLL, the underlying condition for the first reported Australian vaccine-related death in 2017[23] and a similar death in the UK.[22] This rate of inadvertent administration was fairly consistent during the study period (November 2016–December 2020) despite the reports of vaccine-related deaths and increased communication strategies including safety alerts by the regulatory authorities.[24–26 30] Multiple strategies were employed, from the time of the first vaccine-related death, that have included increased education of providers,[28] fact sheets,[29] updates to the AIH[31] and development of a ZVL-specific screening tool that can be integrated into providers' practice management software to help providers identify significant immunocompromise in people being considered for vaccination.[27] However, significant regulatory actions have been implemented since December 2020, including further provider letters, boxed warnings on the Product Information and Consumer Medicine Information documents, vaccine-refrigerator stickers and patient alert cards, which were not fully instituted until after the study period.[45] Further analysis is required to determine whether there has been a decline in errors subsequently.

It is likely that death due to disseminated Oka strain VZV infection remains relatively rare even in immunocompromised individuals. In patients contraindicated for

vaccination identified in our study, 2 of 37 died. Two US studies involving analysis of linked data on almost 33 000 vaccinated immunocompromised individuals did not find evidence of serious adverse events after ZVL vaccination within 42 days after vaccination.[46 47] In a UK primary care study, while administration of ZVL to immunocompromised individuals was reasonably frequent (33.2 per 100 adjusted person years at risk; 95% CI 31.9 to 34.5),[48] only 2 of 1742 individuals developed VZV-related disease within 8 weeks of ZVL vaccination (0.1%; 95% CI 0.01% to 0.4%), both diagnosed as HZ (viral strain not determined) not requiring hospitalisation. A case series of 62 higher-risk haematological malignancy and posthaematological stem cell transplant patients who received ZVL, reported no serious adverse events, and only 1 patient developed HZ 3 weeks postvaccination (viral strain not determined), and recovered with antiviral treatment.[49] However, studies lack large numbers of patients who are more significantly immunocompromised and case series may select patients with more intact immunity and a relatively lower risk from vaccination.

Deaths of individuals on only mildly immunosuppressive treatments or low-dose combinations of immunosuppressants have occurred, both in Australia[25] and in Canada.[50] This illustrates the difficulty for providers in determining the safety of ZVL for any given individual. A review by the TGA's Advisory Committee on Vaccines noted that difficulty surrounding the assessment and definition of immunocompromise is a more significant issue for providers than lack of awareness of contraindications.[51] In 2021, the Australian Technical Advisory Group on Immunisation noted that Zostavax is generally contraindicated in immunocompromised adults and that the non-live recombinant glycoprotein E subunit zoster vaccine (Shingrix, GSK) should be used (although it is not funded under the NIP).[52]

Our analysis is limited by the use of spontaneous reporting surveillance data, which inherently contains incomplete data, leading to the potential for misclassification of the presence, degree or timing of immunocompromise and of outcomes. We were unable to perform validation through medical record review above and beyond that already undertaken through TGA case investigation. Imprecision may arise due to under-reporting of adverse events, which may underestimate the true rate of disseminated VZV, although we would expect this to be minimal for the most serious outcomes of death and hospitalisation due to laboratory-confirmed Oka strain infection, particularly given statutory requirements for reporting in Australia. Additionally, the lack of complete reporting of administered doses to the national immunisation register may have underestimated delivered doses and overestimated rates of adverse events. The selection criteria for manual review were chosen to be highly sensitive for disseminated infection or immunocompromised recipients to ensure relevant reports were captured but was dependent on accurate initial coding by the TGA. Lastly, while the study raises concerns about possible ongoing inadvertent administration of ZVL to immunocompromised people, it is unable to reliably assess the effectiveness of regulatory risk minimisation measures introduced after the study period.

Strengths of our study include the detailed review of spontaneous reports over the critical period of programme implementation, during which time three deaths due to disseminated VZV infection occurred. Reported rates are derived from a national AEFI database in a setting of more than 1 million administered doses through the funded national immunisation programme. Future analysis of disseminated VZV infection following administration of ZVL in a large population cohort would further quantify the identified risk.

CONCLUSION

Our study is the first comprehensive national analysis of spontaneous AEFI reports associated with ZVL in Australia and provides detailed data on vaccine-related disseminated VZV infection rates and outcomes, as well as reported errors in vaccine administration between November 2016 and December 2020. The challenge in managing the very rare but potentially serious risks of administration of ZVL to immunocompromised individuals has been identified as a broad and ongoing issue that has resulted in a review of the benefit compared with risk of ZVL in the Australian context. As a consequence, strategies continue to be used in Australia to minimise harm, particularly to avoid administration to immunocompromised patients, while still providing access to the benefits ZVL provides in protection from HZ and PHN when administered appropriately. The availability of an alternative non-live vaccine for use in immunocompromised individuals offers another option to address the burden of HZ in this high-risk group.

Author affiliations
[1]National Centre for Immunisation Research and Surveillance, Westmead, New South Wales, Australia
[2]Discipline of Child and Adolescent Health, The University of Sydney, Sydney, New South Wales, Australia
[3]Children's Hospital Westmead, Faculty of Medicine and Health, The University of Sydney, Sydney, New South Wales, Australia
[4]School of Public Health, The University of Sydney, Sydney, New South Wales, Australia
[5]Medicines Regulation Division, Pharmacovigilance Branch, Therapeutic Goods Administration, Woden, Australian Capital Territory, Australia

Twitter Aditi Dey @dey_aditi

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Contributors JL-K-M, AP and AM conceived and designed the study, reviewed case reports, analysed outcomes, interpreted findings and drafted all sections of the manuscript. SJ made substantial contributions to the literature review, and reviewed the final manuscript. CG and was involved in data cleaning and analysis. BPH was involved in analysis of Australian Immunisation Register data for the study. MH was involved with data acquisition and review of the final manuscript. AD, FHB and KM conceived and designed the study, assisted with drafts of all sections, and reviewed the final manuscript. All authors approved the final manuscript as

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ORCID iDs
Jean Li-Kim-Moy http://orcid.org/0000-0003-1632-0431
Aditi Dey http://orcid.org/0000-0001-7178-8606
Kristine Macartney http://orcid.org/0000-0002-4675-0232

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