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## **Australian vaccine preventable disease epidemiological review series: varicella-zoster virus infections, 1998–2015**

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# Australian vaccine preventable disease epidemiological review series: varicella-zoster virus infections, 1998–2015

Meru Sheel, Frank Beard<sup>I</sup>, Helen Quinn<sup>II</sup>, Aditi Dey, Martyn Kirk, Ann Koehler, Peter Markey, Peter McIntyre, Kristine Macartney

## Abstract

### Introduction

In 2005, the National Immunisation Program implemented a varicella vaccine for children aged 18 months, and in 2016, a herpes zoster (HZ) vaccine for adults aged 70–79 years. This epidemiological review analyses national trends in varicella and HZ for the years 1998–2015 to examine the impact of a funded varicella vaccine and provide a baseline for monitoring the impact of a funded HZ vaccine.

### Methods

Varicella and HZ notifications (2002–2015), hospitalisations (1999–2013) and deaths (1998–2013) were sourced. We stratified analyses by age, sex and Indigenous status, and estimated rates and incidence rate ratios.

### Results

Funded varicella vaccine led to a rapid decline in varicella notifications, hospitalisations and deaths. During the post-varicella vaccine period, hospitalisations declined in all age groups <40 years, with greatest reduction of 84% in children aged 18–59 months. Annual HZ hospitalisation rate was 10.8 per 100,000. HZ hospitalisation rates increased with age and were highest in persons aged ≥75 years (87.6 per 100,000). Post-herpetic neuralgia (PHN) was diagnosed in 32.5% HZ hospitalisations with highest hospitalisation rate in persons aged ≥75 years (32.1 per 100,000). Varicella and HZ hospitalisation rates were significantly higher among Indigenous Australians. Twenty one deaths were coded as due to varicella and 340 deaths were coded as due to HZ in persons aged <40 years and ≥40 years, respectively.

### Conclusions:

The national varicella immunisation program substantially reduced varicella associated morbidity and mortality. Burden of HZ and PHN in Australia is substantial. Following the introduction of a funded HZ vaccine, timely and high quality surveillance will be crucial to assess the impact of the national HZ immunisation program.

**Keywords:** varicella zoster virus, varicella, herpes zoster, chickenpox, shingles, epidemiology, disease surveillance, immunisation, vaccine preventable disease

## Introduction

Varicella-zoster virus (VZV) is a herpes virus and is the aetiological agent for varicella (chickenpox) and herpes zoster (shingles).<sup>1</sup> Varicella is an acute and self-limiting disease with an average incubation period of 14-16 days (range from 10 to 21 days). The disease is highly contagious with a secondary attack rate of 90% in susceptible contacts of persons with varicella.<sup>1,2</sup> Varicella typically presents as a vesicular rash accompanied by fever and malaise but can occasionally be asymptomatic or have atypical presentations. Complications include secondary skin infections, pneumonia, meningitis and encephalitis. Primary infection with VZV usually provides long lasting immunity.<sup>2,3</sup> Further episodes of clinical disease are not commonly reported but can occur in immunocompetent individuals.<sup>4,5</sup>

VZV remains dormant for years in the dorsal root ganglia adjacent to the spinal cord: reactivation of the latent virus can lead to herpes zoster (HZ). Characteristics of HZ include a vesicular rash with a unilateral dermatomal distribution which is usually accompanied with acute pain. Post-herpetic neuralgia (PHN) is the most common complication of HZ, and is defined as pain persisting for 90 days or more from the onset of the rash. PHN is often debilitating and refractory to treatment.<sup>6-8</sup>

In Australia, varicella vaccine was registered for use in 1999 and included on the National Immunisation Program (NIP) in November 2005 as a single dose at 18 months of age, along with a school-based single cohort catch-up program for 12-13 year olds.<sup>9,10</sup> Uptake of varicella vaccine assessed at 2 years of age was 76.1% in 2007, and increased to 84.4% in 2012.<sup>9,11,12</sup> In July 2013, a combination vaccine (measles-mumps-rubella-varicella or MMRV) replaced the mono-valent varicella vaccine at age 18 months; following which vaccine uptake increased to 89.6% in 2014.<sup>13</sup> A vaccine for HZ was registered in Australia in 2005, but was not widely available on private prescription or added onto the NIP until November 2016.<sup>14</sup> Although the vaccine is registered for use in people aged  $\geq 50$  years, it

is funded on the NIP for people aged 70 years with a 5 year catch-up program for people aged 71-79 years.<sup>14</sup>

Early assessment of the impact of inclusion of varicella vaccine on the NIP demonstrated a decline in hospitalisations due to varicella, especially in children less than 4 years of age, along with a reduction in severe outcomes of varicella, including congenital and neonatal varicella.<sup>11,15,16</sup> Several studies have documented increasing incidence of HZ in Australia, both before and after the introduction of the varicella vaccine.<sup>17,18</sup> Age-related increases in the risk of HZ are associated with a decline in cellular immunity to VZV, however, the underlying cause of the rising incidence (even after age adjustment) remains unclear.<sup>18</sup>

This study aims to review the epidemiology of varicella and HZ in Australia from 1998 to 2015, assess the impact of the national varicella immunisation program and provide a baseline for monitoring the impact of the national HZ immunisation program.

## Methods

### Data sources

### Notification data

The National Notifiable Diseases Surveillance System (NNDSS) receives varicella and HZ notifications from all Australian states and territories (jurisdictions) except New South Wales (Table 1). Varicella and HZ became notifiable as early as 2002 in South Australia and as late as 2009 in Victoria.

National case definitions exist for varicella-zoster infection (chickenpox), varicella-zoster infection (shingles) and varicella-zoster infection (not elsewhere classified).<sup>19</sup> For chickenpox and shingles, confirmed and probable cases are required to be notified. Confirmed cases of shingles (HZ) and chickenpox (varicella) require laboratory definitive evidence and clinical evidence. Laboratory confirmation requires detection of VZV from a skin or lesion swab, or VZV-specific IgM in

**Table 1: Proportions (varicella, herpes zoster or not elsewhere classified) of total varicella zoster virus (VZV) related conditions reported through the National Notifiable Diseases Surveillance System (NNDSS), by state or territory, Australia 2002-2015.**

Jurisdiction (state or territory)	Year notification commenced	Notified by laboratory	Follow up laboratory notification	VZV-related conditions (percentage of total notifications)		
				Varicella	Herpes zoster	Not elsewhere classified
New South Wales	N/A	N/A	N/A	N/A	N/A	N/A
Victoria	2009	Yes	No	13.2	19.8	66.9
Queensland	2006	Yes	No	7.1	3.8	89.1
South Australia	2002	Yes	Yes	24.1	66.3	9.7
Western Australia	2006	Yes	No	17.1	38.9	44
Tasmania	2006	Yes	No	11.4	63.8	24.8
Northern Territory	2006	Yes	Yes	41.9	56.4	1.8
Australian Capital Territory	2006	Yes	No	12.7	26.5	60.7
National	2006	-	-	14.1	26.3	59.6

an unvaccinated person (for varicella). In case of varicella, a case is considered confirmed if clinical and epidemiological evidence of disease is available. For probable cases of chickenpox and shingles, clinical evidence of disease is sufficient. Varicella-zoster infection (not elsewhere classified) requires only laboratory confirmed definitive evidence of VZV.<sup>19</sup>

Notification data for the years 2006 to 2015 were sourced from the NNDSS database. South Australian notification data for the years 2002 to 2005 were sourced from the South Australian Department for Health and Ageing. Analysis of notification data was restricted to South Australia and Northern Territory, as these are the only jurisdictions that routinely follow up laboratory notifications of VZV infection for clinical and/or epidemiological evidence and had a low proportion of 'not elsewhere classified' notifications (Table 1).

### Hospitalisation data

We obtained national data from the Australian Institute of Health and Welfare (AIHW) National Hospital Morbidity Database. All hospital admissions (public and private) in Australia are captured through this administrative database which collects demographic and clinical details. All eligible hospitalisations between 1 January

1999 and 31 December 2013 were identified using the International Statistical Classification of Diseases, 10<sup>th</sup> Revision, Australian Modification (ICD-10-AM) codes B01.0-B01.9 (varicella or its complications), B02.0-B02.9 (HZ or its complications), where listed as the principal or other diagnosis. Cases of PHN were identified using ICD-10-AM codes B02.2 (PHN), G53.0 (PHN under cranial nerve disorders) and G53.1 (multiple cranial nerve palsies in infectious and parasitic diseases classified elsewhere).

### Mortality data

Mortality data were obtained from the AIHW's National Mortality Database (1998-2005) and the Australian Coordinating Registry (2006-2013). We restricted analysis to underlying cause of death (UCOD), which was identified using ICD-10-AM codes B01.0-B01.9 (varicella) and B02.0-B02.9 (herpes zoster). Age-specific analyses were limited due to the small cell size rule applied by the data custodians. In addition, as the positive predictive value for varicella coded deaths is known to be poor and due to issues of misclassification of HZ and varicella,<sup>20</sup> we restricted analyses to persons aged <40 and ≥40 years for varicella and HZ associated deaths, respectively.

## Population estimates

National, jurisdictional and age-specific mid-year resident population estimates were obtained from the Australian Bureau of Statistics (ABS).

## Data analysis

Annual crude and age-specific rates were calculated using ABS mid-year population estimates as the denominator and are expressed as rates per 100,000 total population or population in sex, geographical or Aboriginal and Torres Strait Islander (from here on referred to as Indigenous) subgroups as appropriate. Reported rates refer to hospitalisations where the relevant condition was coded as the principal diagnosis, unless otherwise stated.

We calculated varicella and HZ notification and hospitalisation rates for the period 1999 to 2015. To assess changes in disease epidemiology following introduction of the national varicella immunisation program, we undertook comparative analyses over two time periods: pre-vaccine (1999-2004) and post-vaccine (2007-2015). Analysis of HZ hospitalisation rates for older age groups was restricted to non-Indigenous populations as age-specific counts for Indigenous persons were unavailable for persons aged  $\geq 75$  years for the latter years of the study period.

Summary statistics including median and range were calculated for length of hospital stay. *P*-values were derived using the Wilcoxon-Mann-Whitney test. Incidence rates and 95% confidence intervals (CI) were calculated for the total population, non-Indigenous and Indigenous populations at the national level and relevant jurisdictional groupings, as indicated, assuming a negative binomial distribution. Negative binomial regression was used to analyse yearly trends in rates of hospitalisation and calculate the incidence rate ratios (IRR). All analyses were conducted using Microsoft Excel 2010 and STATA software (version 13.1; StataCorp, College Station, Texas USA).

## Indigenous hospitalisation data

We restricted analyses to the four jurisdictions (Queensland, Western Australia, South Australia and Northern Territory) with adequate Indigenous data quality prior to 2007,<sup>21</sup> with supplementary analyses incorporating data from New South Wales and Victoria for the years 2007 to 2013. Hospitalisations with missing information on state of residence (<1% of total) were excluded.

Ethics approval was not required as de-identified aggregated population-based data were used for routine public health surveillance purposes only.

## Results

### Notifications of varicella and herpes zoster

#### *Varicella*

Varicella notification rates in South Australia declined from 41.8 per 100,000 (95% CI 38.6–45.2) in 2002 to 26.3 per 100,000 (95% CI 23.4–28.9) in 2015 (Figure 1A). Varicella notification rates in the Northern Territory reduced from 92.3 per 100,000 (95% CI 79.8–106.3) in 2006 to 48.2 per 100,000 (95% CI 39.4–57.8) in 2015.

Declines in age-specific varicella notification rates were observed in both South Australia and the Northern Territory (Figures 1B and 1C). In South Australia, varicella notification rates in persons aged 0-4 years reduced by 63% during the post-vaccine (2007-2015) period (IRR 0.37; 95% CI 0.23-0.59). Reduced varicella notification rates were also observed in other age groups <40 years during the post-vaccine period.

#### *Herpes zoster*

In contrast to varicella, HZ notification rates increased over time in both South Australia and in the Northern Territory (Figure 2A). In South Australia, HZ notification rates increased steadily from 23.1 per 100,000 (95% CI 20.7–25.6) in 2002 to 136.9 per 100,000 (95% CI 131.4–142.6) in 2015. In the Northern Territory, HZ notification rates increased from 38.2 per 100,000

(95%CI 30.3–47.6) in 2006 to 148.4 per 100,000 (95% CI 133.5–164.5) in 2015. Similar trends were also observed in age-specific rates with the highest incidence in persons aged  $\geq 70$  years, both in South Australia and the Northern Territory (Figures 2B and 2C). Fluctuations in notification rates in the Northern Territory are likely to be associated with its small population size, especially in older age groups.

## ***Varicella and herpes zoster associated hospitalisations***

### ***Varicella***

There were 18,615 episodes of varicella associated hospitalisation between January 1999 and December 2013, of which 12,824 (68.9%) had a principal diagnosis of varicella. The annual varicella hospitalisation rate reduced from 6.9 per 100,000 (95% CI 6.3–7.1) in 1999 to 2.1 per 100,000 (95% CI 1.9–2.3) in 2013.

The average annual hospitalisation rate for the period 1999–2013 was 4.2 per 100,000 (95% CI 3.4–5.3). Hospitalisation rates were similar in females (3.3 per 100,000; 95% CI 2.6–4.1) and males (4.5 per 100,000; 95% CI 3.5–5.6). There was a rapid decline in hospitalisation rates after the varicella vaccine was added onto the NIP in 2005 (Figure 3A). Hospitalisation rates were 41% lower in 2007 compared to 2005 (IRR 0.59; 95% CI 0.53–0.65).

Age-specific trends in hospitalisation rates are presented in Figure 3B. During 1999–2013, hospitalisation rates were highest in children aged  $\leq 17$  months (30.3 per 100,000; 95% CI 23.0–40.0) and lowest in adults aged  $\geq 40$  years (1.5 per 100,000; 95% CI 1.4–1.6).

There were significant reductions in hospitalisation rates for all age groups  $< 40$  years during the post-vaccine period (2007–2013) compared to the pre-vaccine period (1999–2004) (Table 2). The largest decreases were seen in children aged 18–59 months (IRR 0.16; 95% CI 0.12–0.23), and in those aged  $\leq 17$  months (IRR 0.33; 95% CI 0.26–0.40). Despite the rapid decline during the first five years after varicella vaccine was intro-

duced under the NIP, limited additional decline in hospitalisation rates was observed in more recent years (Figure 3A and 3B). Similar findings were observed on analyses of hospitalisations where varicella was recorded in any diagnosis field (Table 2). Trends in hospitalisation rates by jurisdiction were broadly similar (Figure 4).

Between 1999 and 2013, there were 47,477 bed days recorded for hospitalisations coded as due to varicella. The overall median length of stay was 2 days with length of stay longest in those aged  $\geq 40$  years (5 days).

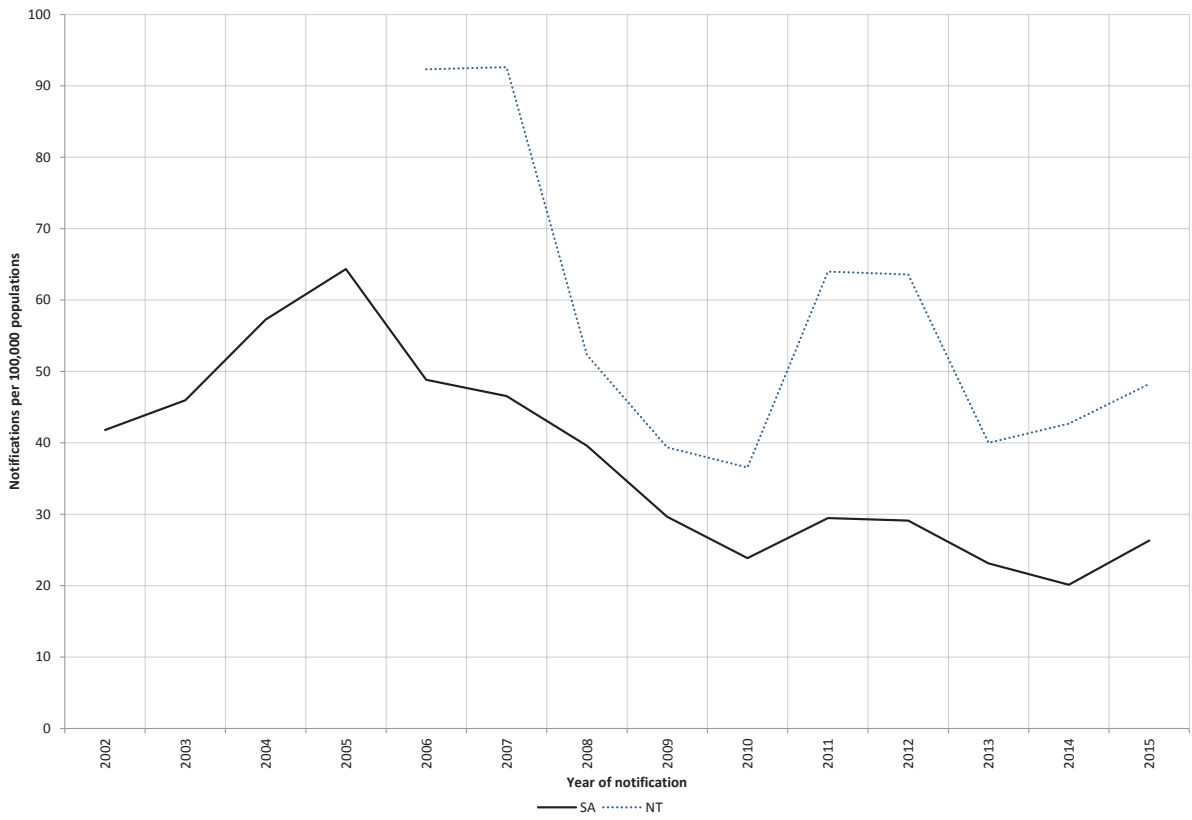
### ***Herpes zoster***

There were 80,960 episodes of HZ associated hospitalisations during 1999–2013. Of these, 33,549 (41.4%) episodes had a principal diagnosis of HZ. Over this period, the average annual HZ associated hospitalisation rate was 10.8 per 100,000 (95% CI 10.5–11.1). The HZ hospitalisation rate increased from 9.7 per 100,000 (95%CI 9.2–10.1) in 1999 to 11.4 per 100,000 (95% CI 11.0–11.9) in 2013 (Figure 5A), an average annual increase of 1.0% (IRR 1.01; 95% CI 1.01–1.02). Over this period, the HZ hospitalisation rate for females (30.0 per 100,000; 95% CI 28.7–31.3) was higher than for males (21.8 per 100,000; 95% CI 20.7–22.9). The difference was most pronounced in females  $\geq 75$  years with a hospitalisation rate of 95.1 per 100,000 (95% CI 92.6–97.6) compared to males aged  $\geq 75$  years (76.4 per 100,000; 95% CI 73.6–79.2).

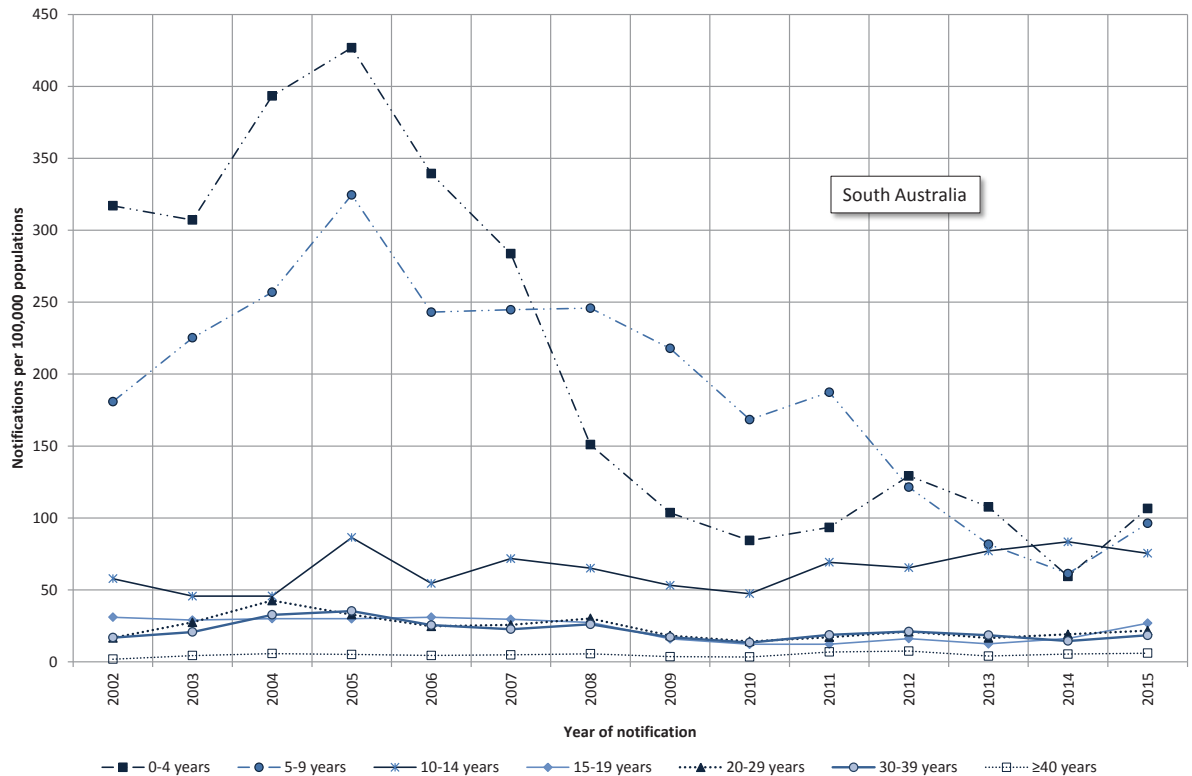
HZ hospitalisation rates increased with age (Figure 5B). Hospitalisation rates were highest in persons aged  $\geq 75$  years (87.6 per 100,000; 95% CI 85.9–89.4), followed by those aged 70–74 years (37.4 per 100,000; 95% CI 35.8–39.0) and lowest in those aged 0–49 years (2.4 per 100,000; 95% CI 2.3–2.4). Amongst non-Indigenous populations, for whom data were available for older age groups (Figure 5C), people aged  $\geq 85$  years old had the highest hospitalisation rate of 129.0 per 100,000 (95% CI 124.3–134.0) (Table 3).

When we compared hospitalisation rates during the post-varicella vaccine period (2007–2013) to the pre-varicella vaccine period (1999–2004) in

**Figure 1: Notification rates for varicella by jurisdiction [South Australia (SA) and Northern Territory (NT)] (A) and age group (B and C), 2002- 2015**

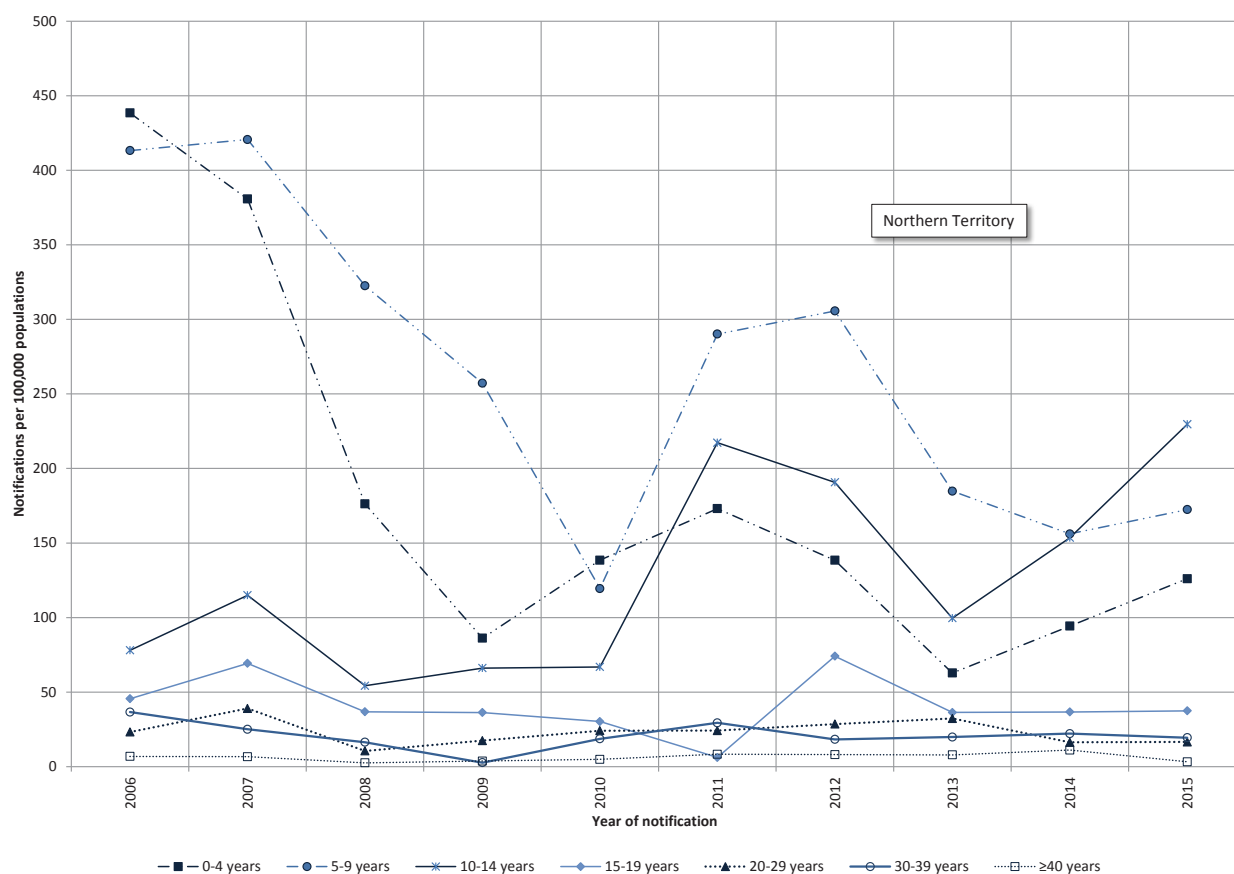


(A)



(B)





(C)

non-Indigenous people, the IRR was 1.08 (95% CI 1.03–1.13) for all ages, 0.94 (95% CI 0.88–1.02) for those aged 70–74 years, and 0.89 (95% CI 0.84–0.95) for those aged 75–79 years (Table 3).

### Post-herpetic neuralgia (PHN)

Almost a third (32.5%) of all hospitalisations (principal) coded as HZ also had a diagnosis of PHN recorded in the diagnostic field (within the first 30 diagnostic fields). The overall rate of PHN hospitalisations remained stable (Figure 6A) for the years 1999–2013 (IRR 1.00; 95% CI 0.99–1.01), with the highest rate in those aged  $\geq 75$  years (32.1 per 100,000) followed by people aged 70–74 years (14.1 per 100,000). PHN-associated hospitalisations increased disproportionately with age, where 36.6% HZ hospitalisations in those aged  $\geq 75$  years had an episode of PHN compared to 26.7% in those aged 50–59 years (Figure 6B).

Between 1999 and 2013, there were 226,276 bed days for hospitalisation coded as due to HZ. The overall median length of stay was 4 days with

length of stay increasing with age. Median length of stay per admission was 4 days and 6 days for people aged 70–74 and  $\geq 75$  years, respectively. HZ hospitalisations in which a diagnosis for PHN was also recorded were associated with a higher median length of stay (5 days) compared to those not also recorded as having PHN (4 days) ( $p < 0.05$ ).

### VZV associated hospitalisations in Indigenous Australians

#### Varicella

We compared varicella hospitalisation rates in Indigenous people over the pre- and post-vaccine periods using data from four jurisdictions (Queensland, Western Australia, Northern Territory and South Australia). We observed significant decreases in hospitalisation rates in all age groups, with the greatest reduction of 89% (IRR 0.11; 95% CI 0.06–0.22) in children aged 18–59 months (Table 4). Similar findings were observed when we compared varicella hospitalisation rates in children aged 18–59 months from

**Table 2 Varicella associated hospitalisations, Australia, 1999-2013\***

Age group	Pre-varicella vaccine 1999-2004		Post-varicella vaccine 2007-2013		
	Hospitalisations (n)	Rate <sup>†</sup> (95% CI)	Hospitalisations (n)	Rate <sup>†</sup> (95% CI)	IRR <sup>‡</sup> (95% CI)
<b>Principal varicella in all Australians</b>					
0-17 months	1,020	45.2 (41.6-49.1)	454	14.8 (12.1-18.1)	0.33 (0.26-0.40)
18-59 months	2,188	40.7 (35.1-47.2)	458	6.7 (5.0-8.9)	0.16 (0.12-0.23)
5-9 years	713	8.9 (7.82-10.2)	338	3.6 (2.5-5.0)	0.40 (0.27-0.58)
10-14 years	269	3.3 (2.9-3.9)	202	2.1 (1.8-2.4)	0.63 (0.52-0.76)
15-19 years	291	3.6 (3.1-4.2)	165	1.6 (1.4-1.9)	0.45 (0.36-0.56)
20-29 years	913	5.6 (5.2-6.1)	432	2.0 (1.6-2.3)	0.35 (0.29-0.41)
30-39 years	850	4.8 (4.4-5.3)	584	2.7 (2.3-3.2)	0.56 (0.46-0.68)
≥40 years	690	1.4 (1.3-1.5)	1,105	1.6 (1.4-1.7)	1.15 (1.01-1.30)
All ages	6,934	6.0 (5.5-6.5)	3,738	2.4 (2.2-2.7)	0.41 (0.35-0.47)
<b>All varicella in all Australians</b>					
0-17 months	1,421	62.9 (56.8-69.7)	592	19.3 (15.4-24.2)	0.31 (0.24-0.39)
18-59 months	2,455	45.6 (40.1-52.0)	529	7.7 (5.5-10.1)	0.17 (0.12-0.25)
5-9 years	1,129	14.1 (12.5-15.9)	525	5.5 (4.0-7.6)	0.39 (0.27-0.56)
10-14 years	420	5.2 (4.6-5.8)	302	3.1 (2.8-3.9)	0.60 (0.52-0.69)
15-19 years	409	5.1 (4.2-6.1)	228	2.2 (1.9-2.6)	0.44 (0.35-0.56)
20-29 years	1,366	8.4 (7.6-9.3)	648	2.9 (2.4-3.5)	0.35 (0.28-0.43)
30-39 years	1,205	6.8 (6.3-7.4)	821	3.8 (3.4-4.3)	0.55 (0.48-0.64)
≥40 years	1,236	2.4 (2.3-2.6)	2,369	3.4 (3.0-3.8)	1.37 (1.18-1.59)
All ages	9,641	8.3 (7.6-9.1)	6,014	3.9 (3.6-4.2)	0.47 (0.42-0.53)

\*Age-specific hospitalisations identified using ICD-10-AM code B01.0-B01.9

†Average annual hospitalisation rate per 100,000 population

‡ Incidence rate ratio between hospitalisation rates during pre and post-varicella vaccine periods

the four jurisdictions for the pre-vaccine period (38.1 per 100,000; 95% CI 29.8-48.7) to hospitalisation rates in Queensland, Western Australia, South Australia, Northern Territory, New South Wales and Victoria for the post-vaccine period (6.3 per 100,000; 95% CI 3.1-12.3).

For Queensland, Western Australia, South Australia and the Northern Territory in the pre-vaccine period, the hospitalisation rate in Indigenous children aged 18-59 months was 36% higher compared to non-Indigenous children (IRR 1.36; 95% CI 1.01-1.83) but similar during the post-vaccine period (IRR 0.91; 95% CI 0.42-1.96). During the pre-vaccine period, Indigenous children aged ≤17 months were hospitalised at significantly higher rates compared to non-Indigenous people (IRR 1.69; 95% CI

1.30-2.19) (Figure 7A). However, during the post-vaccine period, varicella hospitalisation rates in Indigenous people aged ≤17 months were not significantly higher compared to non-Indigenous people (IRR 1.52; 95% CI 0.99-2.33). Indigenous Australians had higher varicella hospitalisation rates compared to non-Indigenous Australians in all other age groups (Tables 2 and 4).

### *Herpes zoster*

When we analysed data from six jurisdictions (New South Wales, Victoria, Queensland, South Australia, Northern Territory and Western Australia) for the years 2007-2011, we found HZ hospitalisation rates in Indigenous people to be almost double those in non-Indigenous people aged 50-59 years (IRR 1.87; 95% CI 1.29-2.71)

Table 3: Herpes zoster associated hospitalisations, Australia, 1999-2013\*\*

Age groups	Study period 1999-2013		Pre-varicella vaccine 1999-2004		Post-varicella vaccine 2007-2013		IRR ** (95% CI)
	Hospitalisations (n)	Rate†† (95% CI)	Hospitalisations (n)	Rate†† (95% CI)	Hospitalisations (n)	Rate†† (95% CI)	
<b>Principal herpes zoster in all Australians</b>							
0-49 years	5,103	2.4 (2.3-2.4)	1,982	2.4 (2.3-2.6)	2,458	2.3 (2.2-2.4)	0.97 (0.91-1.04)
50-59 years	3,115	8.1 (7.7-8.5)	1,084	7.8 (7.3-8.4)	1,619	8.3 (7.7-9.0)	1.07 (0.96-1.20)
60-69 years	5,079	18.6 (18.0-19.3)	1,620	17.7 (16.7-18.9)	2,828	19.3 (18.5-20.0)	1.09 (1.02-1.16)
70-74 years	3,720	37.4 (35.8-39.0)	1,438	38.2 (36.8-39.6)	1,780	35.9 (33.4-38.6)	0.94 (0.86-1.02)
≥75 years	16,532	87.6 (85.9-89.4)	5,846	87.1 (84.9-89.4)	8,492	87.9 (84.8-91.2)	1.01 (0.96-1.06)
All ages	33,549	10.8 (10.5-11.1)	11,970	10.3 (10.0-10.6)	17,177	11.1 (10.7-11.6)	1.08 (1.03-1.14)
<b>All herpes zoster in all Australians</b>							
0-49 years	10,009	4.6 (4.5-4.8)	3,907	4.7 (4.6-4.9)	4,771	4.5 (4.3-4.8)	0.96 (0.89-1.03)
50-59 years	6,898	17.9 (17.2-18.6)	2,463	17.7 (17.0-18.4)	3,490	17.9 (16.7-19.3)	1.01 (0.93-1.10)
60-69 years	11,852	43.2 (41.4-45.0)	3,724	40.8 (38.7-43.0)	6,656	45.3 (42.8-47.8)	1.11 (1.03-1.20)
70-74 years	9,002	90.2 (86.3-94.3)	3,478	92.4 (89.4-95.5)	4,428	88.9 (81.6-96.9)	0.96 (0.87-1.06)
≥75 years	43,199	228.1 (221.9-234.5)	14,796	220.4 (216.9-224.0)	22,788	235.5 (225.4-246.2)	1.07 (1.01-1.12)
All ages	80,960	25.9 (25.0-27.0)	28,368	24.4 (23.0-24.8)	42,133	27.3 (25.8-28.9)	1.12 (1.05-1.19)
<b>Principal herpes zoster in non-Indigenous Australians§§</b>							
70-74 years	3,689	37.4 (35.8-39.0)	1,427	38.2 (36.3-40.2)	1,763	35.8 (33.3-38.6)	0.94 (0.88-1.02)
75-79 years	4,787	59.4 (57.4-61.6)	1,938	62.7 (60.0-65.6)	2,181	56.1 (53.8-58.5)	0.89 (0.84-0.95)
80-84 years	5,349	92.0 (89.0-95.1)	1,886	94.0 (88.8-99.5)	2,746	90.9 (86.6-95.4)	0.97 (0.90-1.04)
≥85 years	6,340	129.0 (124.3-134.0)	2,011	126.5 (118.5-135.1)	3,528	130.8 (123.7-138.3)	1.03 (0.95-1.13)
All ages	33,007	10.9 (10.6-11.2)	11,805	10.4 (10.2-10.7)	16,867	11.3 (10.9-11.7)	1.08 (1.03-1.13)
<b>All herpes zoster in non-Indigenous Australians§§</b>							
70-74 years	8,931	90.2 (86.2-94.4)	3,457	92.5 (89.5-95.7)	4,386	88.9 (81.3-97.0)	0.96 (0.87-1.06)
75-79 years	12,145	150.8 (146.3-155.3)	4,808	155.7 (148.7-163.0)	5,729	147.3 (142.0-152.9)	0.95 (0.89-1.00)
80-84 years	13,759	236.4 (228.0-245.1)	4,636	231.7 (220.0-243.9)	7,204	238.3 (224.7-252.6)	1.03 (0.95-1.11)
≥85 years	17,184	348.2 (338.1-358.6)	5,330	335.8 (325.5-346.4)	9,779	361.5 (347.8-375.7)	1.08 (1.02-1.14)
All ages	79,874	26.4 (25.4-27.4)	28,069	24.8 (24.5-25.2)	41,487	27.7 (26.1-29.4)	1.12 (1.05-1.19)

\*\* Age-specific hospitalisations identified using ICD-10-AM code B02.0-02.9

†† Average annual hospitalisation rate per 100,000 population

‡‡ Incidence rate ratio between hospitalisation rates during pre and post-varicella vaccine periods

§§ Hospitalisations for Indigenous Australians were excluded.

and 60-69 years (IRR 1.77; 95% CI 1.27-2.48) (Figure 7B). However, no significant difference was observed in people aged 70-79 years (IRR 0.83; 95% CI 0.51-1.36).

### Varicella and herpes zoster associated mortality

During the period 1998-2013, there were 21 deaths with varicella coded as the underlying cause of death (UCOD). In people aged <40 years the number of deaths was two-thirds lower in the post-vaccine period (2007-2013; 5 deaths) compared to the pre-vaccine period (1998-2004; 15 deaths). In children aged <10 years, the number of deaths reduced from 6 deaths in 1998-2004 to <4 deaths in 2007-2013.

During the same period, there were 340 deaths where HZ was coded as the UCOD with an overall crude mortality rate of 0.23 per 100,000 (95% CI 0.21-0.26) in those aged  $\geq 40$  years. Of these deaths, 5 (1.5%) were in people 40-59 years of age, 7 (2.1%) in those aged 60-69 years, 40 (11.8%) in those aged 70-79 years and 288 (84.7%) in those aged  $\geq 80$  years. The number of HZ-related deaths recorded for females (230, 67.6%) was twice that of males (110, 32.4%).

## Discussion

Introduction of the national varicella immunisation program in 2005 for children aged 18 months was associated with a rapid and significant decline in varicella hospitalisation rates in Australia, particularly in children aged  $\leq 10$  years. While the varicella vaccine was available through the private market from 2000 and was recommended for use in 2003,<sup>2</sup> the vaccine did not have significant impact on hospitalisation rates until it was introduced under the NIP in 2005 as a single dose at 18 months of age with no formal catch-up program. According to the 2014 coverage estimates, the uptake of MMRV at 18 months of age measured at 2 years of age was 89.6%.<sup>13</sup> Previously published data on varicella hospitalisations until 2010 reported 70% and 60% reductions in the age groups of 1-4 year olds and <1 year olds, respectively.<sup>11</sup> By December 2013, we found 84% reduction in hospitalisation rates in the post-varicella vaccine period in children aged 18-59 months, most of whom would have received the vaccine. Significant herd effect with 67% reduction in varicella hospitalisation rates was evident in children aged <18 months, who are not eligible for varicella immunisation. In the 20-29 years and 30-39 years age groups, varicella hospitalisation rates also reduced by 65% and 44%, respectively, suggesting that the herd

**Table 4: Varicella hospitalisations (principal diagnosis) by age groups and vaccine period in Indigenous populations, Australia, 1999- 2013** <sup>\*\*\*, †††</sup>

Age group	Pre-varicella vaccine 1999-2004		Post-varicella vaccine 2007-2013		IRR <sup>§§§</sup> (95% CI)
	Hospitalisations (n)	Rate <sup>***</sup> (95% CI)	Hospitalisations (n)	Rate <sup>***</sup> (95% CI)	
0-17 months	69	73.0 (57.7-92.5)	25	21.1 (12.6-35.3)	0.29 (0.18-0.46)
18-59 months	64	38.1 (29.8-48.7)	9	4.3 (1.7-11.0)	0.11 (0.06-0.22)
5-9 years	38	15.6 (11.4-21.4)	11	3.5 (1.9-6.2)	0.22 (0.11-0.43)
10-14 years	9	4.2 (1.7-10.8)	19	6.2 (4.0-10.0)	1.49 (0.66-3.33)
15-19 years	4	2.2 (0-5.8)	7	2.5 (0-6.6)	1.17 (0.29-4.71)
20-29 years	13	4.3 (2.5-9.3)	6	1.4 (0-3.0)	0.32 (0.12-0.84)
30-39 years	7	2.6 (1.2-5.4)	10	2.9 (1.4-6.1)	1.12 (0.39-3.24)
$\geq 40$ years	8	2.9 (1.1-4.4)	12	2.0 (1.0-3.8)	0.90 (0.36-2.24)
All ages	212	11.5 (10.0-13.1)	99	3.8 (2.7-5.2)	0.33 (0.25-0.44)

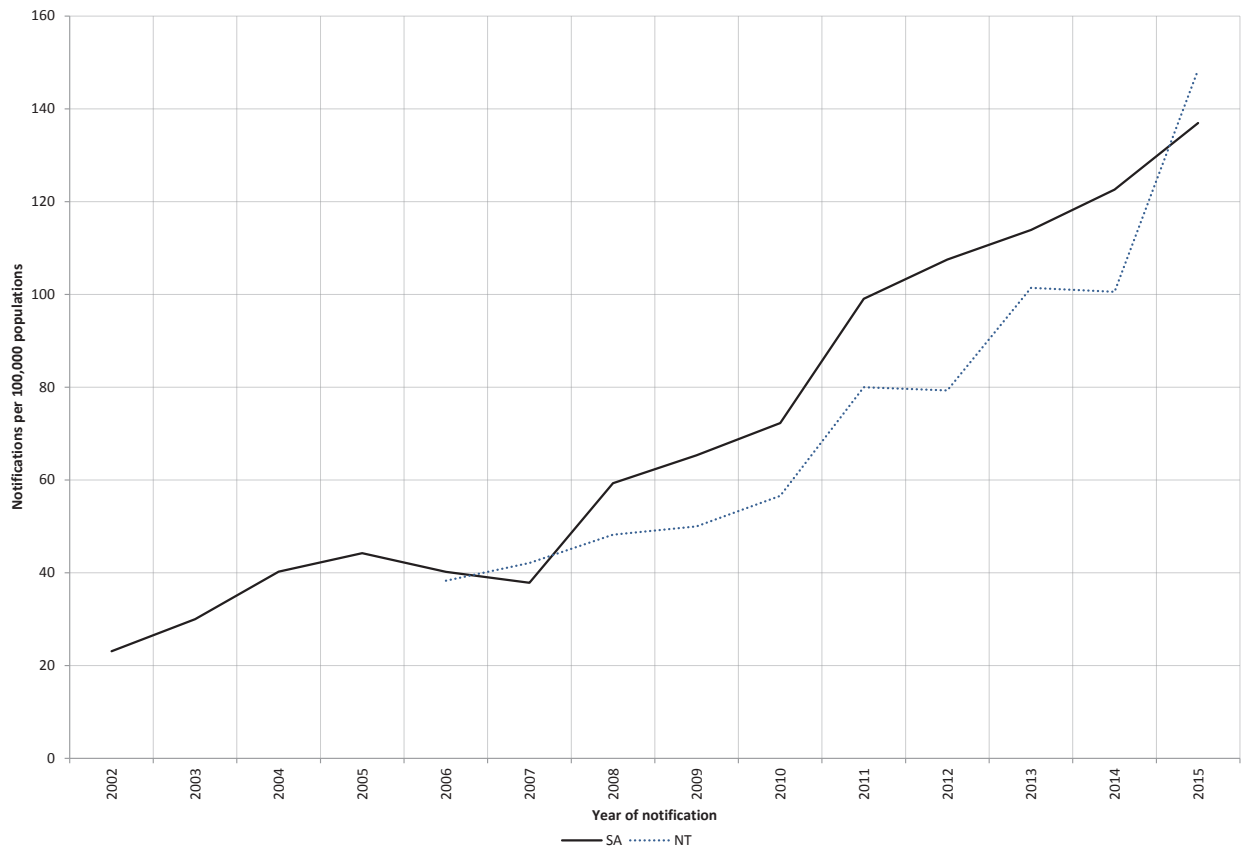
<sup>\*\*\*</sup>Analyses restricted to Queensland, South Australia, Western Australia and the Northern Territory

<sup>†††</sup>Age-specific hospitalisations identified using ICD-10-AM code B02.0-02.9

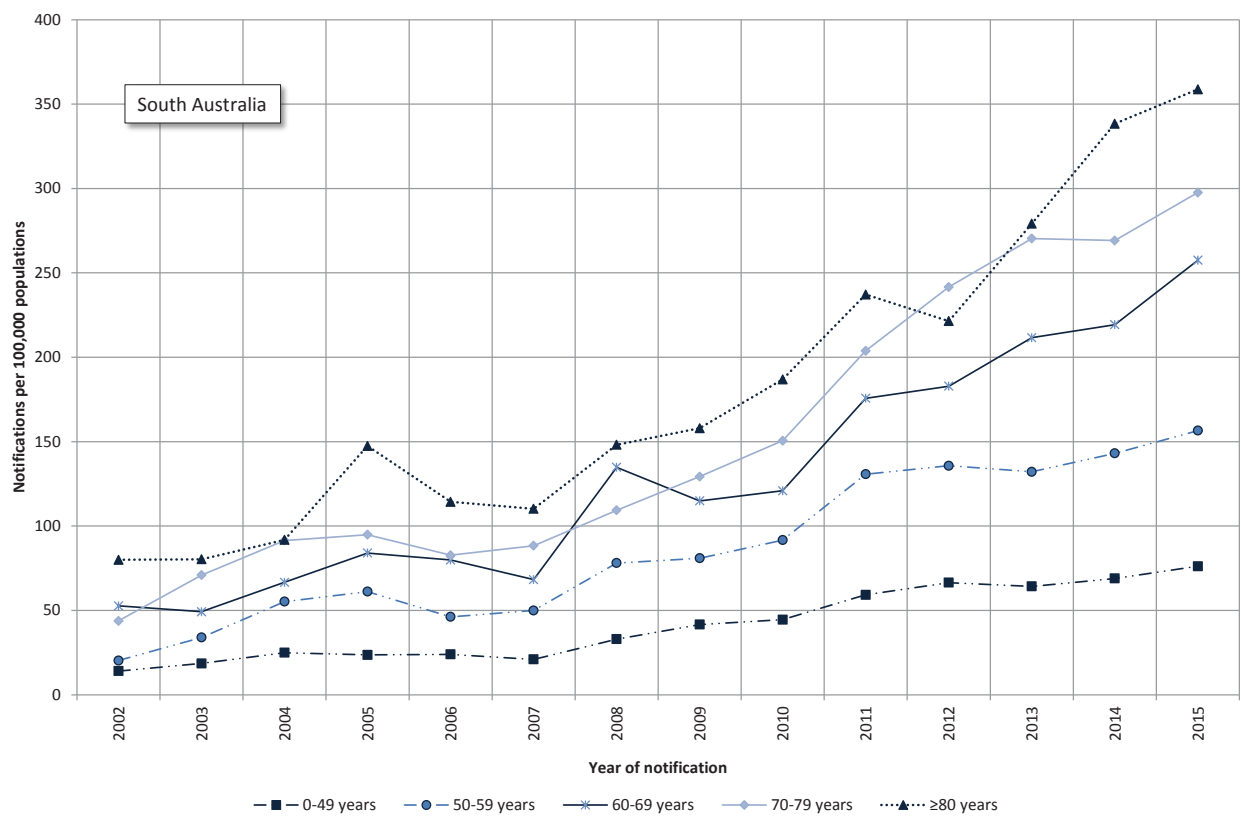
<sup>\*\*\*</sup>Average annual hospitalisation rate per 100,000 population

<sup>§§§</sup>Incidence rate ratio between hospitalisation rates during pre and post-varicella vaccine periods

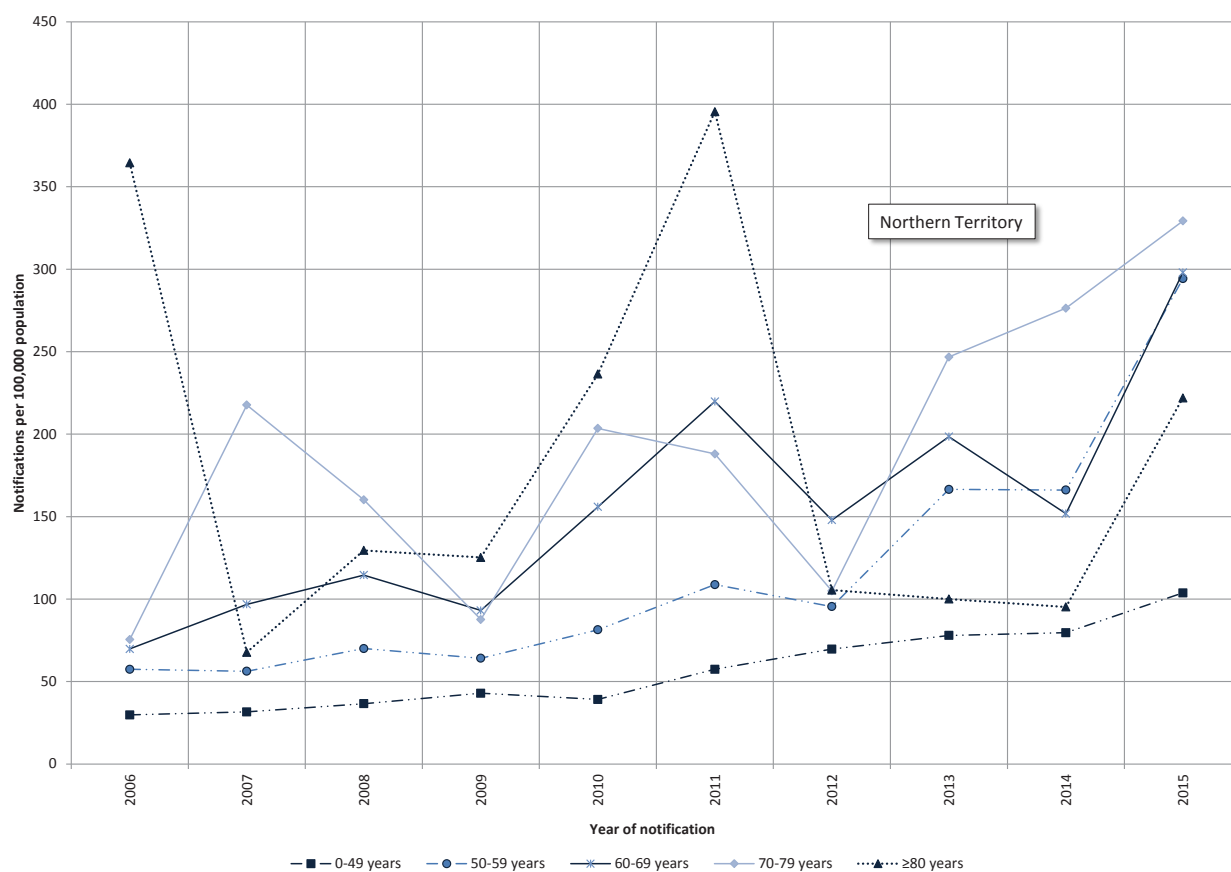
Figure 2: Notification rates for herpes zoster, by jurisdiction [South Australia (SA) and Northern Territory (NT)] (A) and age group (B and C), 2002- 2015



(A)



(B)



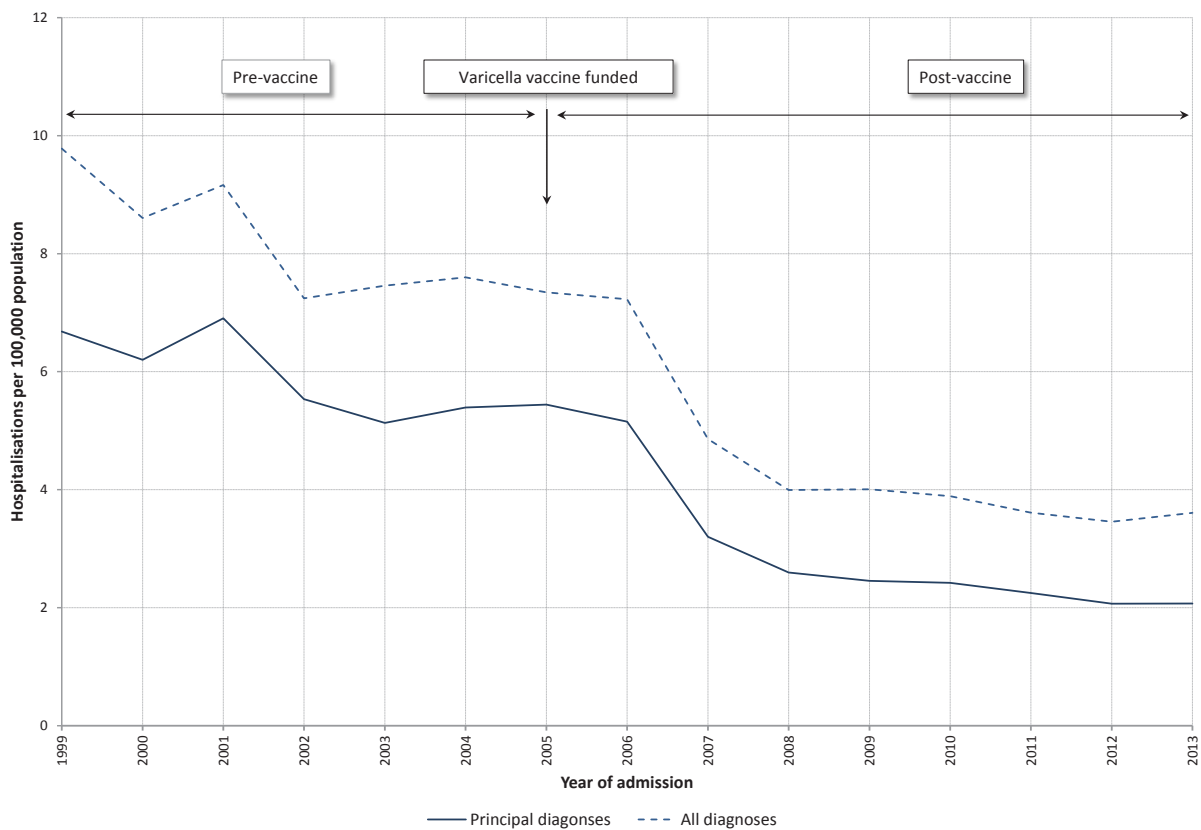
(C)

protection effects of universal childhood immunisation also extend to adults of childrearing age, who are susceptible to more severe disease than children.<sup>22-24</sup> Similar impacts following one-dose varicella immunisation programs have been documented in other countries including the USA, Canada, Italy, Germany, Taiwan and Uruguay.<sup>25</sup> Hospitalisation rates in those aged  $\geq 40$  years did not decline during the post-vaccine period (IRR 1.15; 95% CI 1.01–1.30), most likely due to naturally acquired VZV-specific immunity in this age group and possible misclassification of HZ as varicella.<sup>20,26</sup>

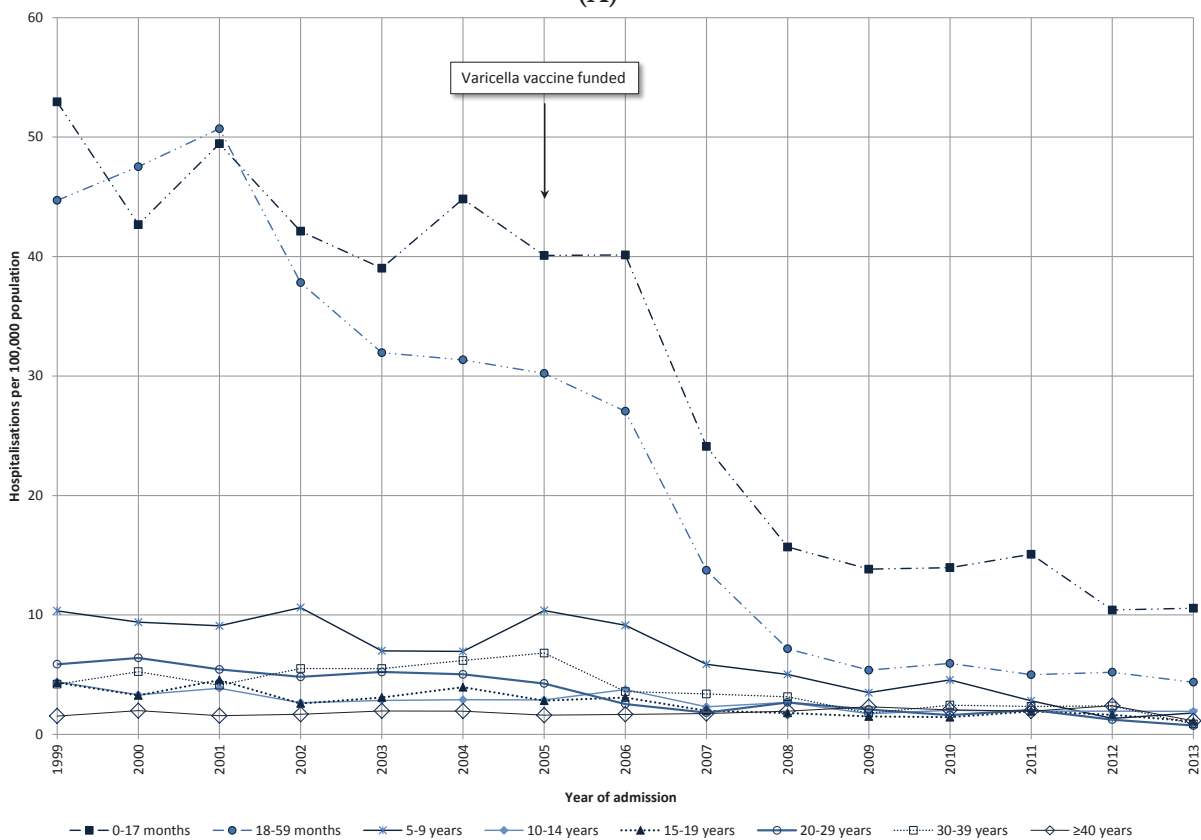
Despite the relatively high vaccine coverage and rapid initial decline in hospitalisation rates, little change in varicella hospitalisation rates was observed from 2010 onwards. Approximately 300 varicella hospitalisations continue to occur each year in those aged  $< 40$  years. Two recent Australian studies, one in Queensland and one nationally across all sentinel sites in the Paediatric Active Enhanced Disease Surveillance (PAEDS) network, have shown a single dose of varicella vaccine to have moderate effectiveness

against varicella-associated hospitalisations of 81.9% and 64.6%, respectively.<sup>27,28</sup> Further decreases in hospitalisation rates and interruption of community-wide transmission will likely require a second dose of vaccine.<sup>29</sup> In the USA, continuing varicella outbreaks and episodes of breakthrough disease were documented, despite high coverage attained under their one-dose varicella immunisation program, and prompted a switch to a two-dose program in 2006.<sup>30-33</sup> Introduction of a second dose led to a greater than 40% decline in hospitalisations during the years 2006–2010 compared to 2002–2005, as reported from two sentinel surveillance sites, and was accompanied by reduction in severe disease and outbreaks.<sup>34-36</sup> Similar to the USA, where overall deaths reduced by 66% in the first 6 years following the introduction of the one-dose program,<sup>37</sup> we found a 67% reduction in varicella-attributable deaths in people aged  $< 40$  years during the post-vaccine period. In 2007, addition of a second dose of varicella vaccine to the NIP was deemed not cost-effective by the Pharmaceutical Benefits Advisory Committee.<sup>38</sup> However, our findings suggest that it may be

Figure 3: Varicella hospitalisation rates (A) and varicella hospitalisation (principal diagnosis) by age group (B), Australia, 1999-2013



(A)



(B)

time to re-examine the potential for NIP funding of a second dose in the childhood schedule, if Australia is to achieve any further significant reductions in varicella-associated morbidity and mortality.<sup>39</sup>

A national HZ immunisation program, using the live attenuated zoster vaccine, was introduced in Australia in November 2016 for people aged 70-79 years. Our report focussed on HZ-related hospitalisations - although only around 3% of HZ cases are hospitalised,<sup>40</sup> hospitalisation rates are a measure of severe disease posing a significant economic burden on the health system.<sup>41,42</sup> Consistent with other studies, our results demonstrate higher hospitalisation rates and mortality associated with HZ in older people (associated with immunosenescence) and in females (in whom a different response to latent VZV infection has been identified).<sup>40,43</sup> We found similar HZ hospitalisation rates between the pre- and post-varicella vaccine periods, including in those aged 70-74 years (IRR 0.94; 95% CI 0.86-1.02) and  $\geq 75$  years (IRR 1.01; 95% CI 0.96-1.06), but an increasing trend in the HZ notification rate in South Australia and the Northern Territory. While this increase in notifications may be partly due to increased testing, similar to that seen with influenza and pertussis,<sup>44</sup> several studies have documented increases in community-based consultations and emergency department presentations for HZ, which may be due to a combination of ageing of the Australian population, greater use of immunosuppressive medications and reduced natural boosting to VZV since the introduction of universal childhood varicella immunisation.<sup>18,45-48</sup> Similarly, the increase in all herpes zoster associated hospitalisations in the recent years (Figure 5A) might also be influenced by a combination of factors mentioned above.

One third of all hospitalised cases in our study had PHN recorded in a diagnostic field, with the highest hospitalisation rate (32.1 per 100,000) in people aged  $\geq 75$  years. In Australia, the economic burden of HZ and PHN are significant, with an estimated total cost of 32.8 million Australian dollars each year to the health care system.<sup>42</sup>

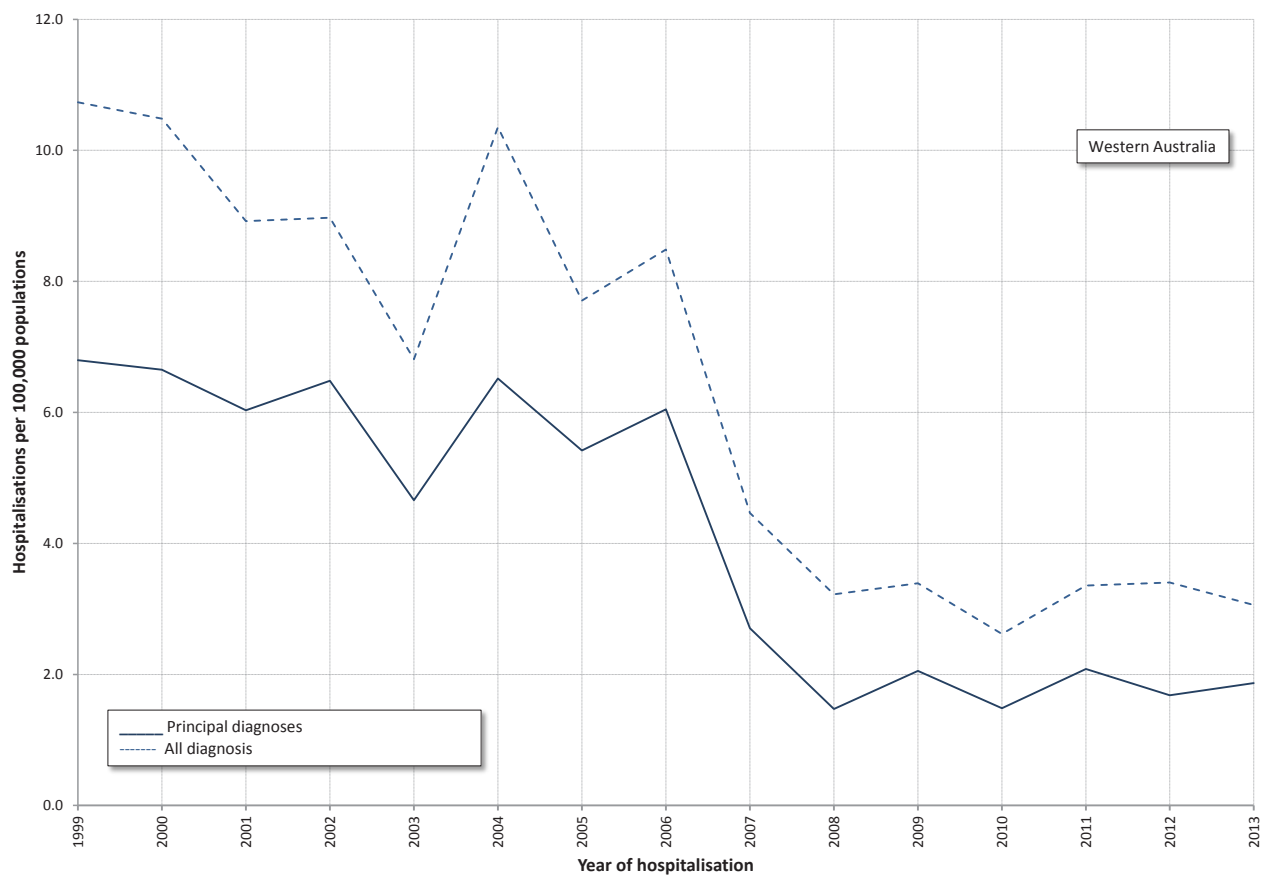
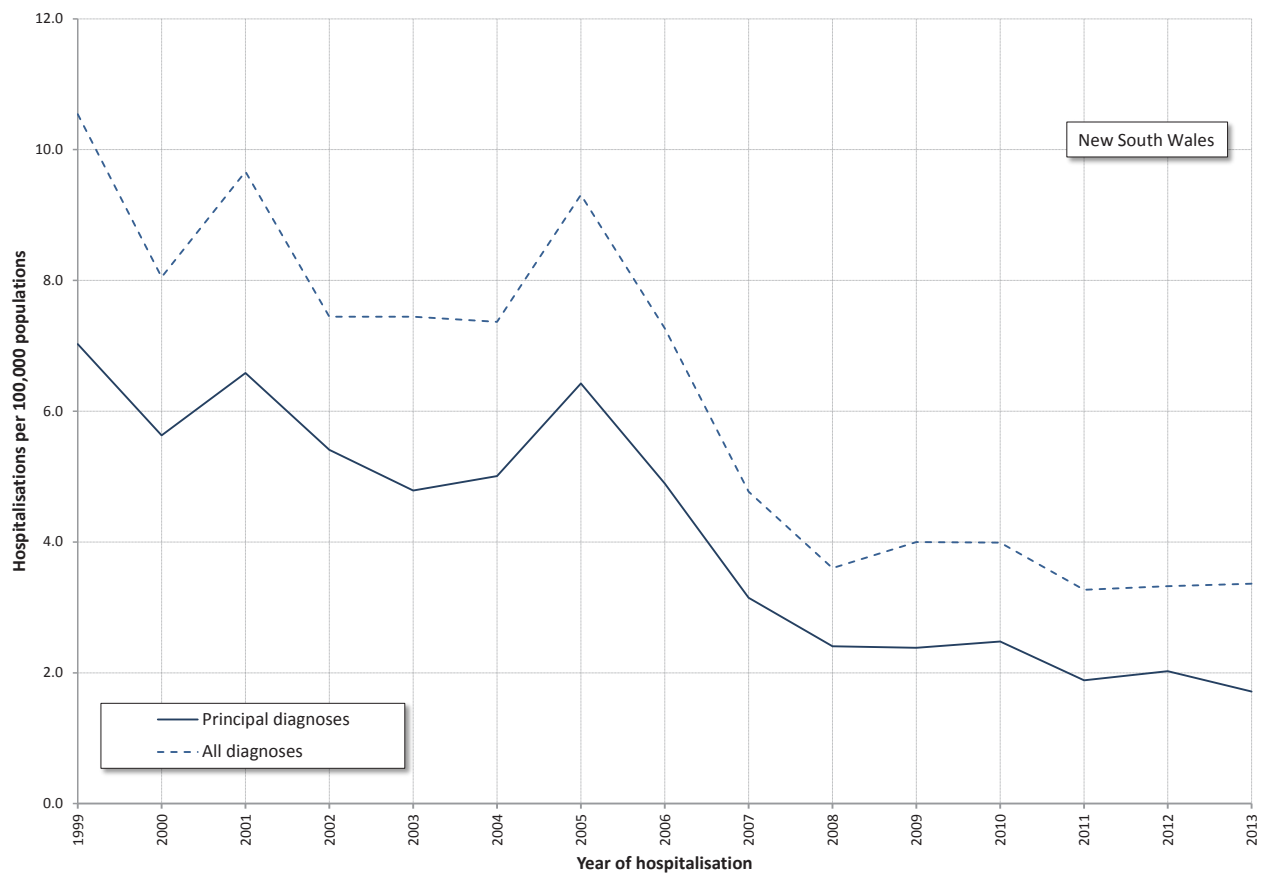
Pain associated with PHN is often refractory to treatment and can have substantial negative impact on the health-related quality of life.<sup>14,49,50</sup>

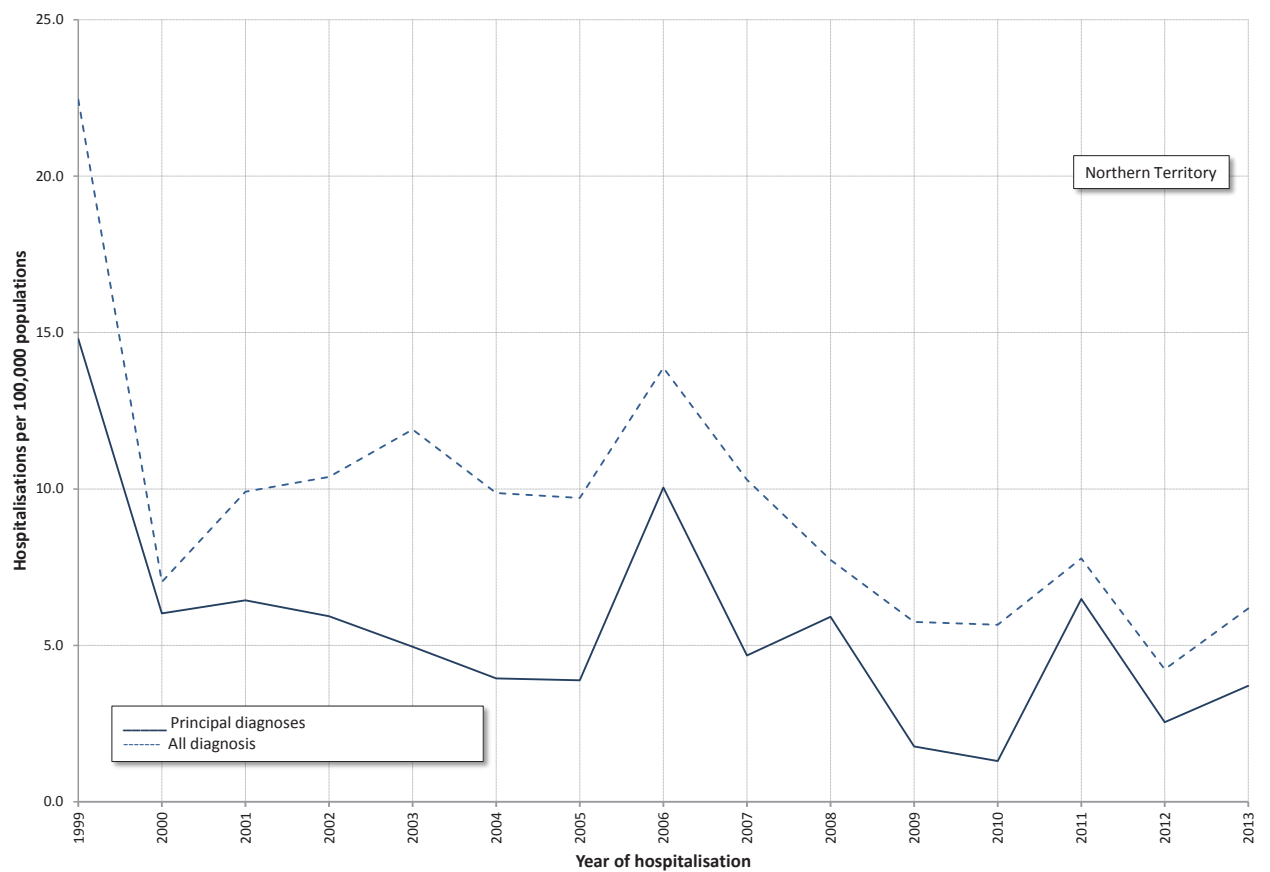
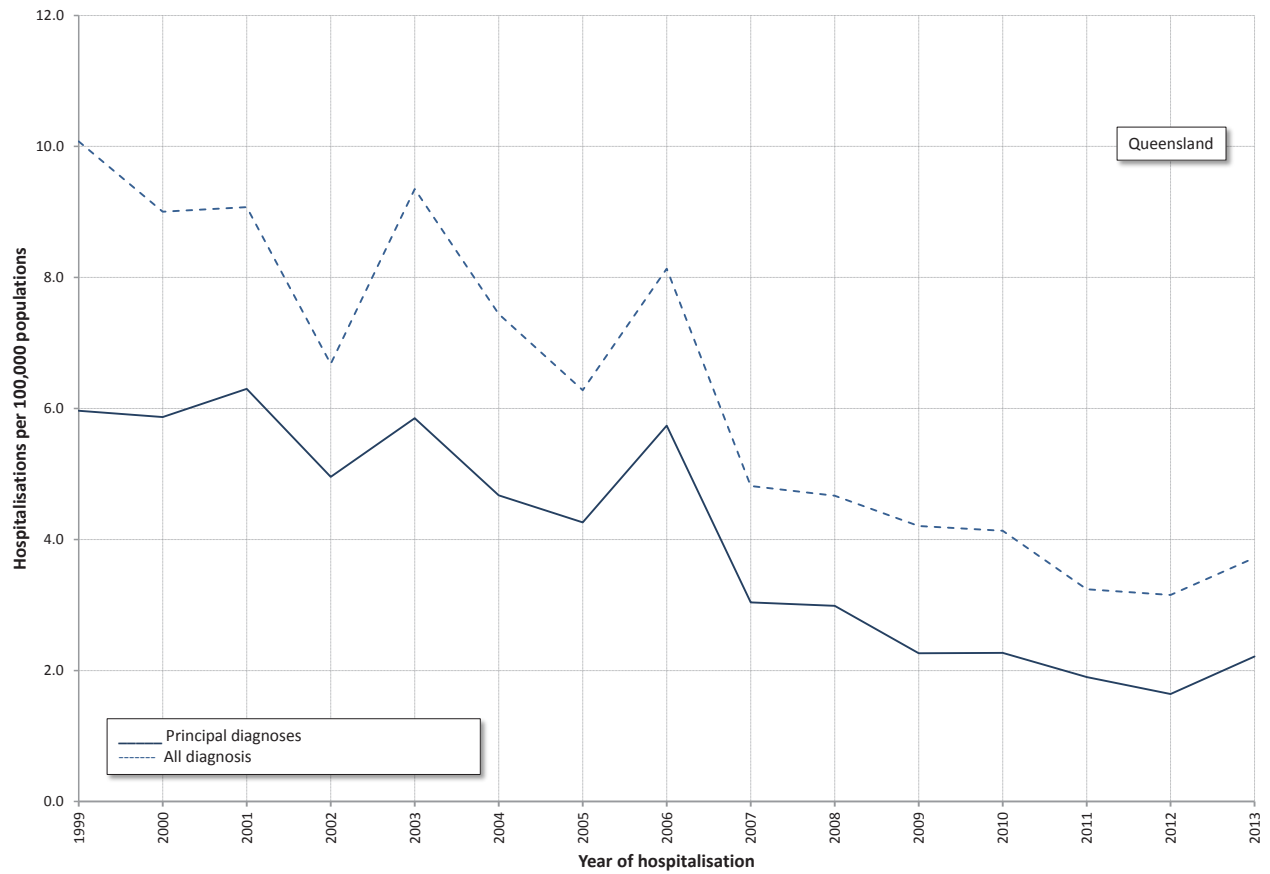
During the pre-vaccine period, Indigenous children aged 18-59 months had higher varicella hospitalisation rates compared to their non-Indigenous counterparts. Funded childhood varicella immunisation has contributed towards 'closing the gap'— during the post-vaccine period, Indigenous children aged 18-59 months had similar varicella hospitalisation rates compared to their non-Indigenous counterparts. However, Indigenous people overall continue to be hospitalised due to varicella and HZ at almost double the rate compared to non-Indigenous people. Our recent work demonstrated that Indigenous Australians aged 60-69 years had higher HZ hospitalisation rates compared to non-Indigenous Australians aged 70-79 years, who are currently eligible for funded HZ immunisation.<sup>51</sup>

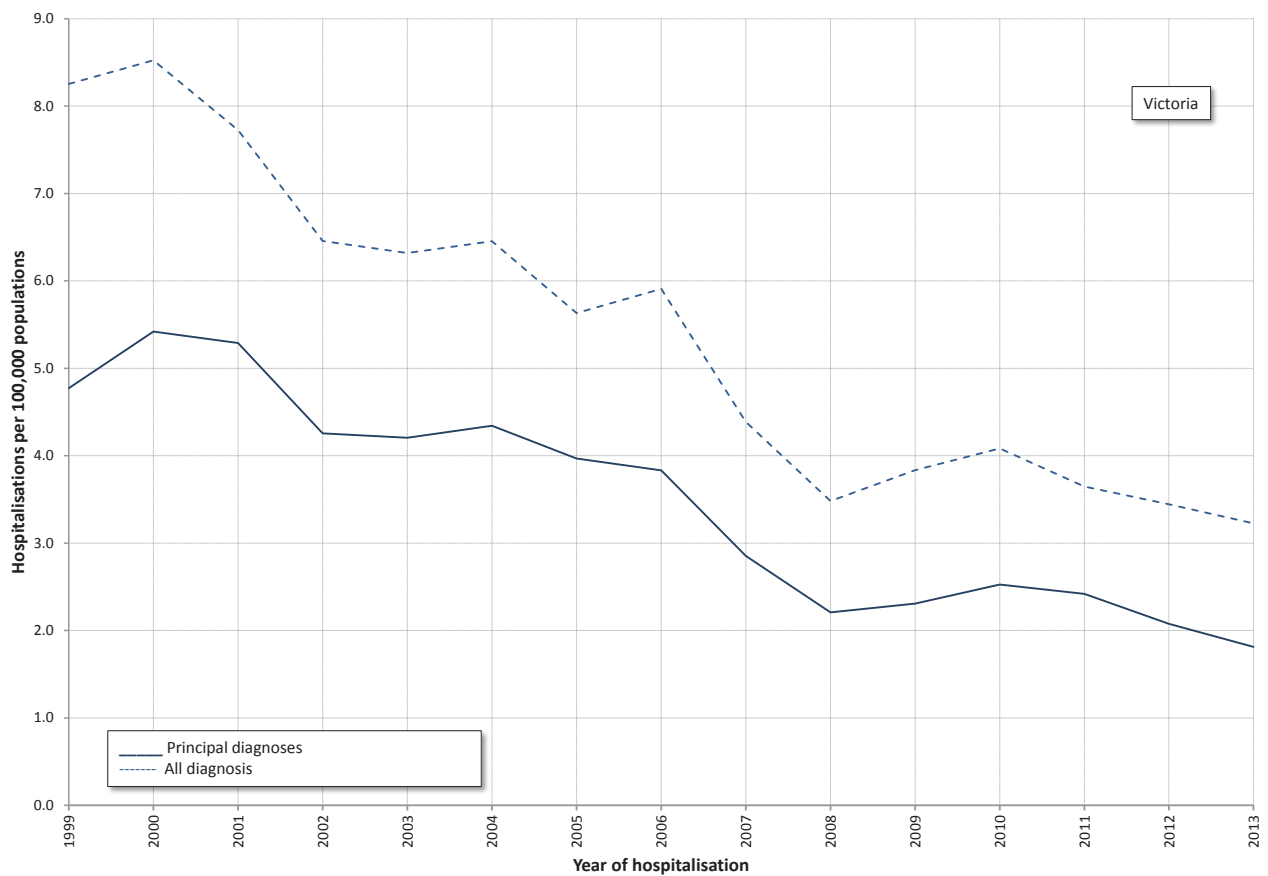
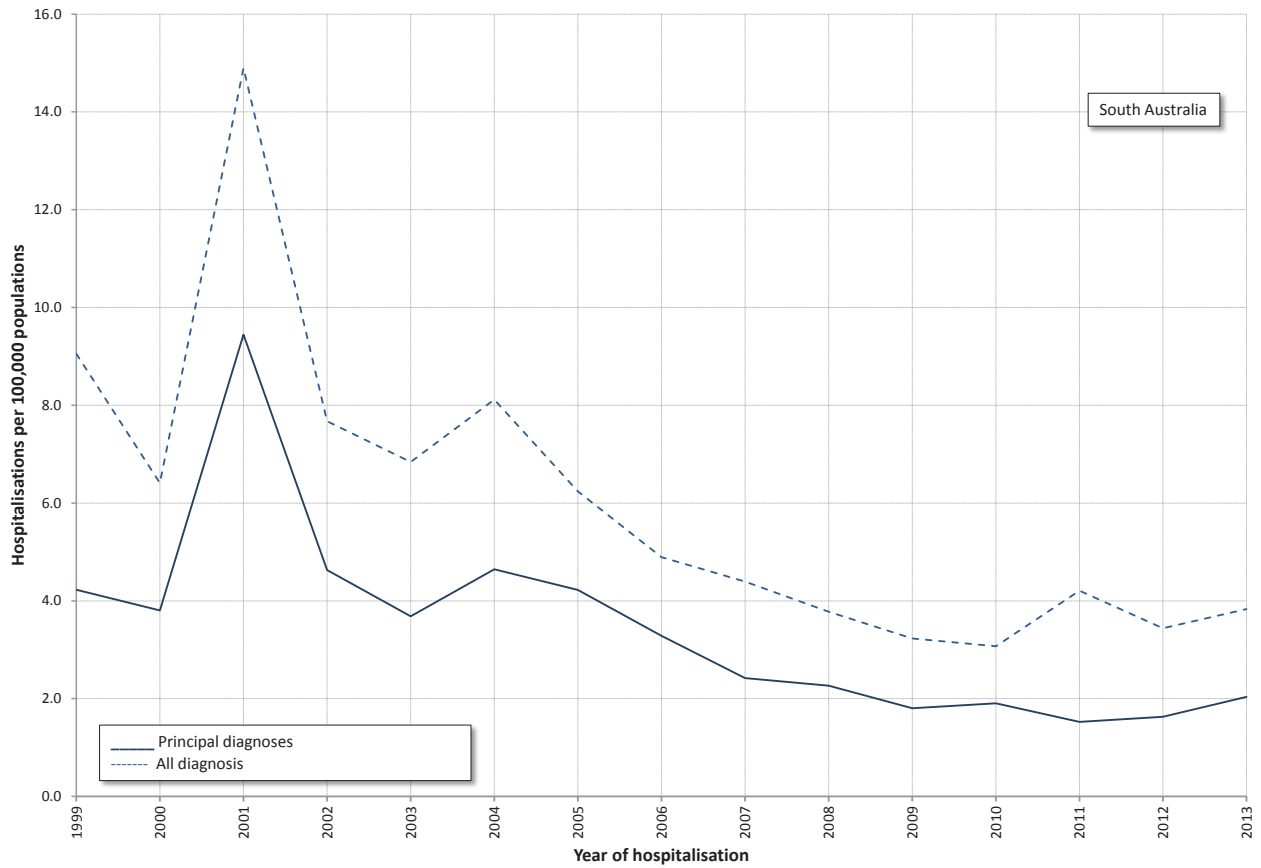
High quality disease surveillance strategies are imperative for monitoring the population-wide impact of immunisation programs and driving evidence-based policies. Our study highlights a number of limitations of using notification and hospitalisation data for surveillance of varicella and HZ. While varicella and HZ are considered to be nationally notifiable diseases, differences in reporting mechanisms, the inherent challenges in reporting of these diseases (related to reliance on clinical/ epidemiological information rather than solely laboratory diagnosis) and absence of routine reporting from New South Wales to the NNDSS significantly limit interpretation of the data. South Australia and the Northern Territory are the only jurisdictions that routinely follow up laboratory notifications of VZV in order to be able to align cases with national case definitions. Both notification and hospitalisation data considerably underestimate the true burden of varicella and HZ, as both diseases are generally self-limiting and only a small proportion are likely to be tested for, notified and/or hospitalised. Notification data may be influenced by changes in testing practices over time. Surveillance using hospitalisation data is



Figure 4: Varicella hospitalisation rates, by state or territory, Australia, 1999-2013







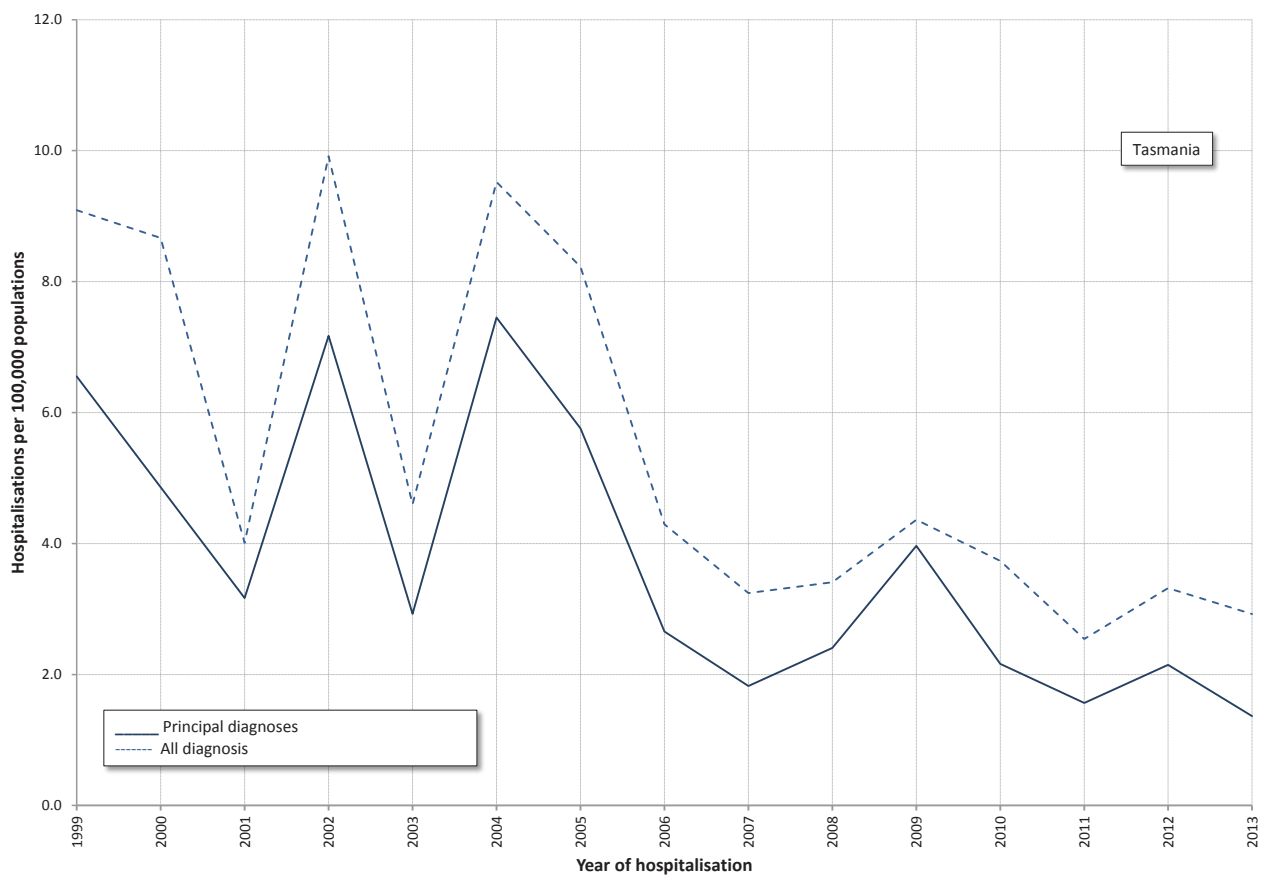
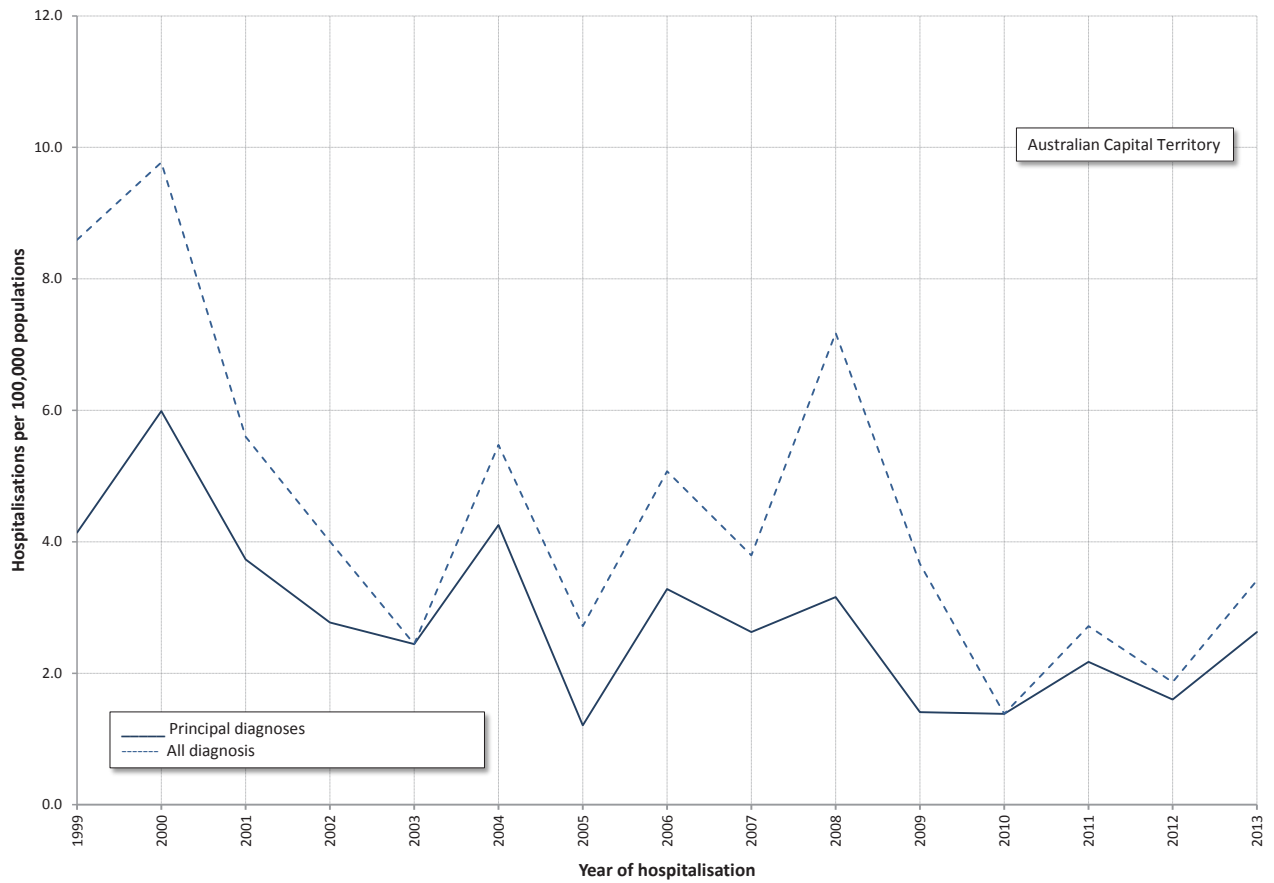
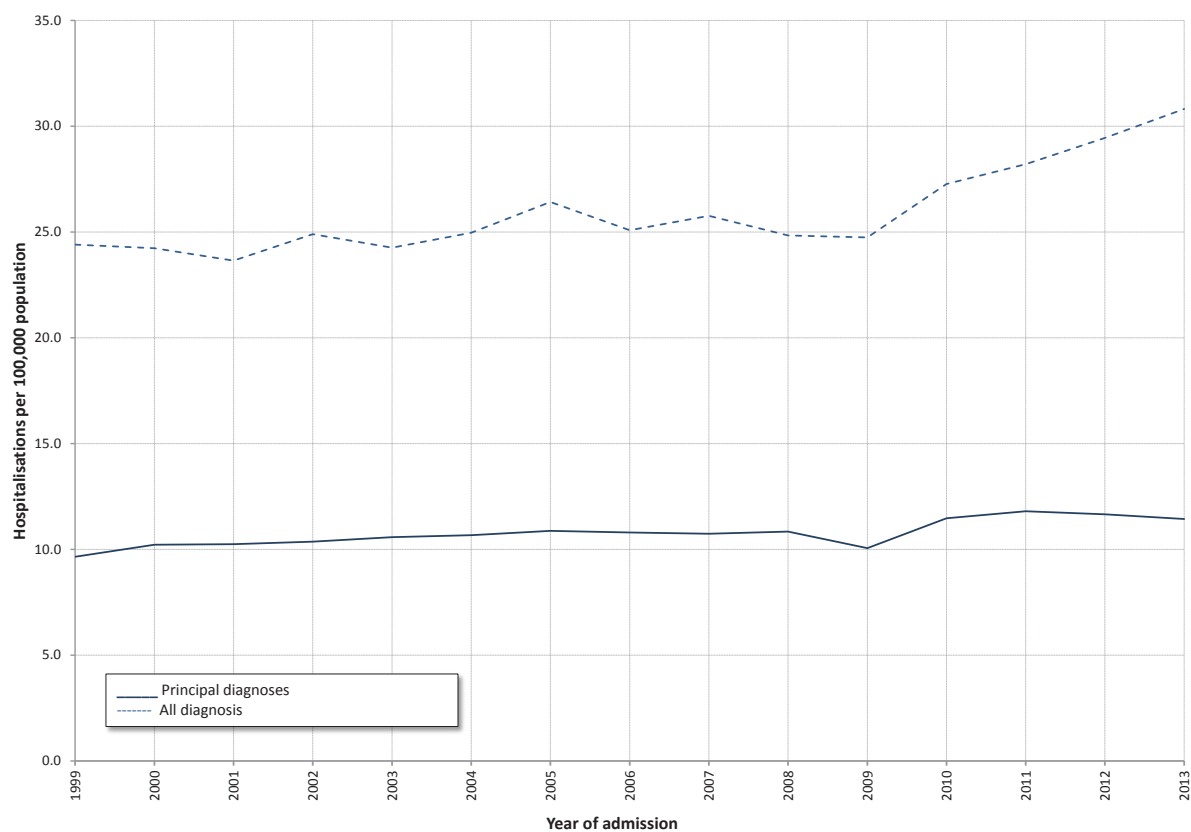
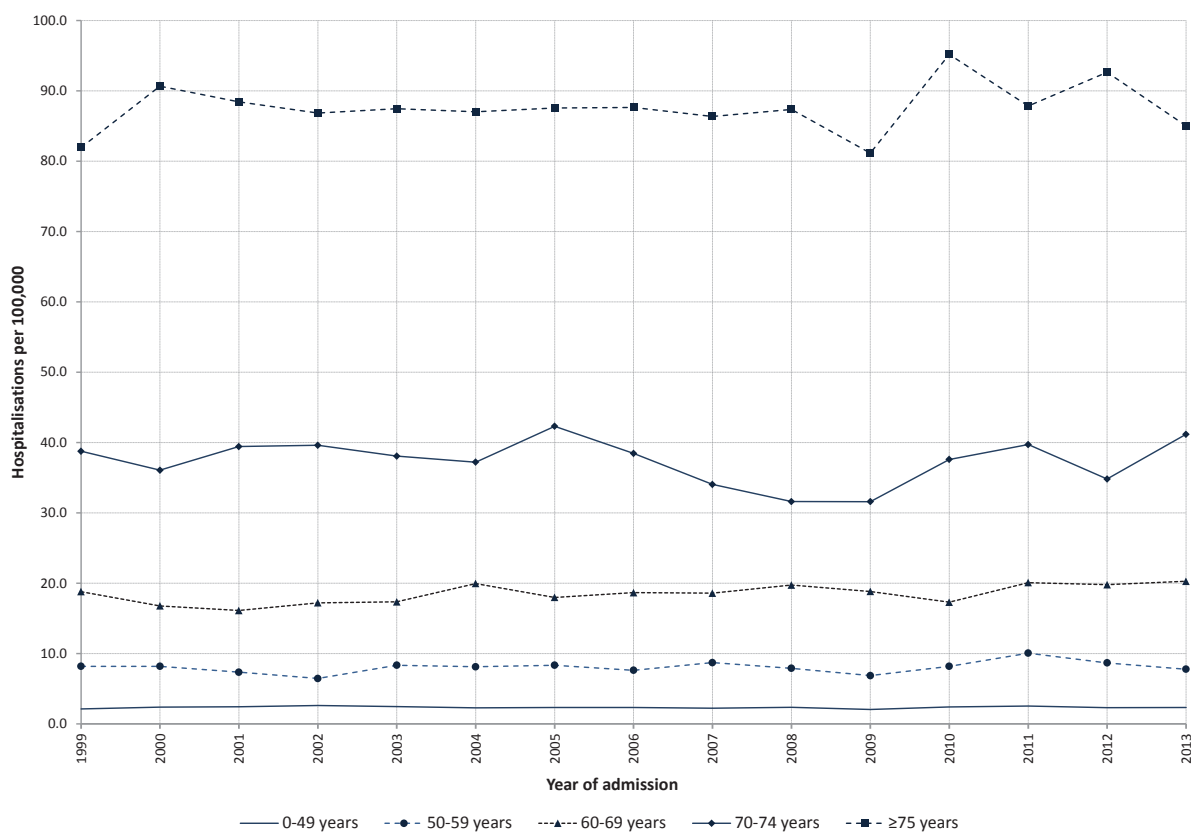


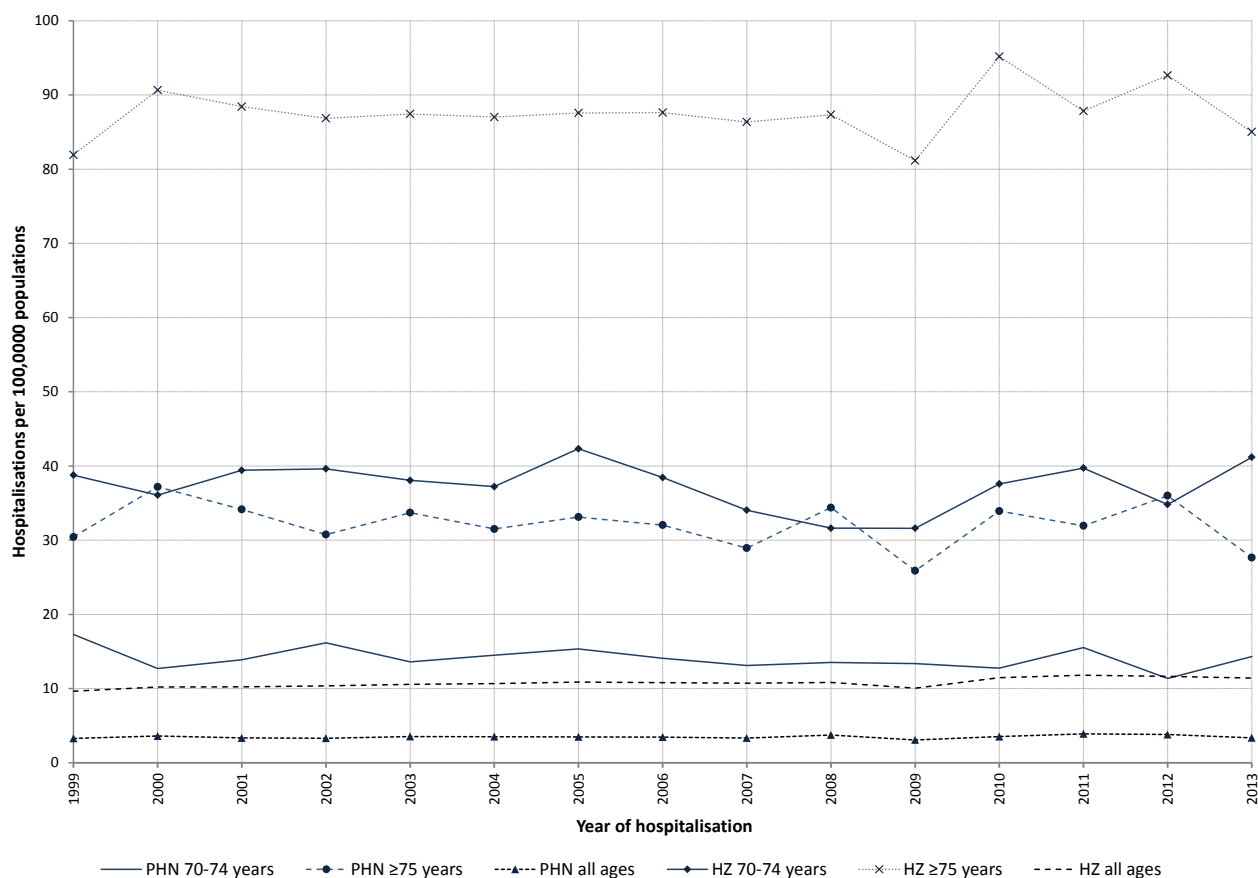
Figure 5: Herpes zoster hospitalisation rates (A), hospitalisation rates (principal diagnosis) by age group in all Australians (B) and in older non-Indigenous people (C), Australia, 1999-2013 (A)



(A)



(B)



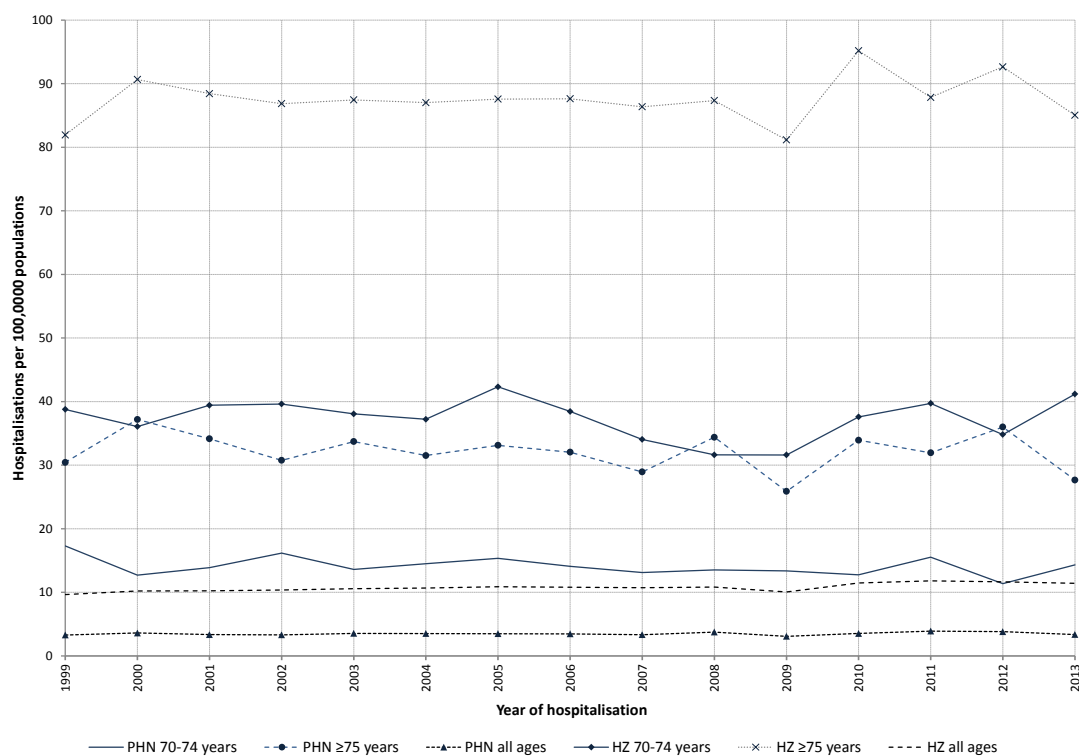
(C)

not timely and data may be influenced by access to hospitals over time, coding practices and misclassification between varicella and HZ.<sup>20,26,52</sup>

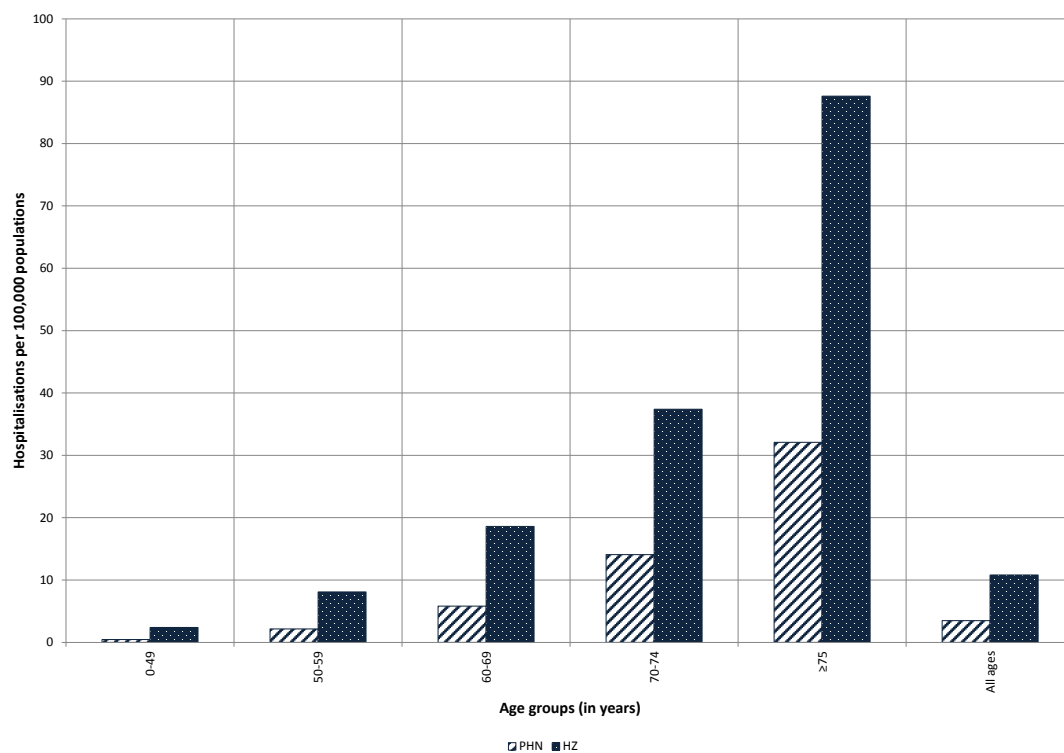
Other industrialised countries with national HZ immunisation programs have implemented a variety of surveillance systems targeted at capturing cases of HZ. In the UK, enhanced surveillance using sentinel GP clinics and pain clinics was established to monitor the effectiveness of their HZ immunisation program.<sup>53,54</sup> Several other European countries conduct active surveillance for HZ including sentinel surveillance.<sup>55</sup> In the USA, active sentinel surveillance sites initially established for varicella surveillance were also successful at monitoring the epidemiology of HZ after the introduction of HZ vaccine in 2006.<sup>56,57</sup> Based on this, Australia will need to adopt a national and unified approach to identify ideal surveillance strategies.

In conclusion, introduction of a national varicella immunisation program in 2005 substantially reduced varicella associated morbidity and mortality in Australia. Minimal decline has been observed during recent years and further reductions in disease incidence will most likely require a second dose of varicella vaccine to be added on the NIP. A vaccine for HZ was introduced under the NIP in 2016. Timely and high quality surveillance, including data on HZ encounters at the primary health care level, along with HZ vaccine coverage data sourced from Australian Immunisation Register, will be crucial to evaluate the population-wide impact of the national HZ immunisation program.

Figure 6: Hospitalisation rates for post-herpetic neuralgia [PHN] and herpes zoster [HZ] (A) and by age groups (B), Australia, 1999-2013\*



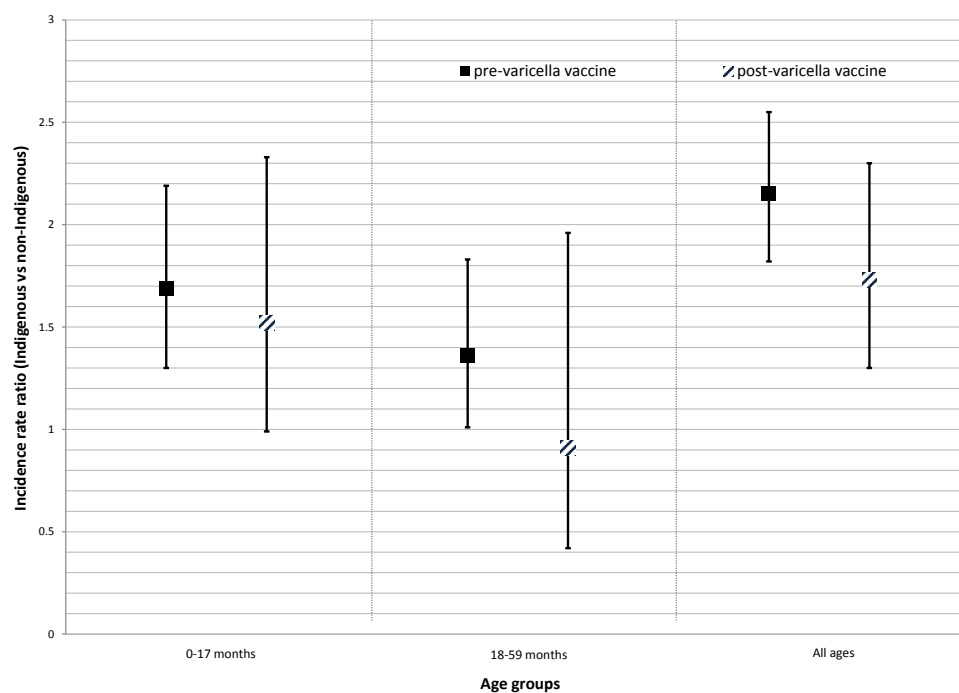
(A)



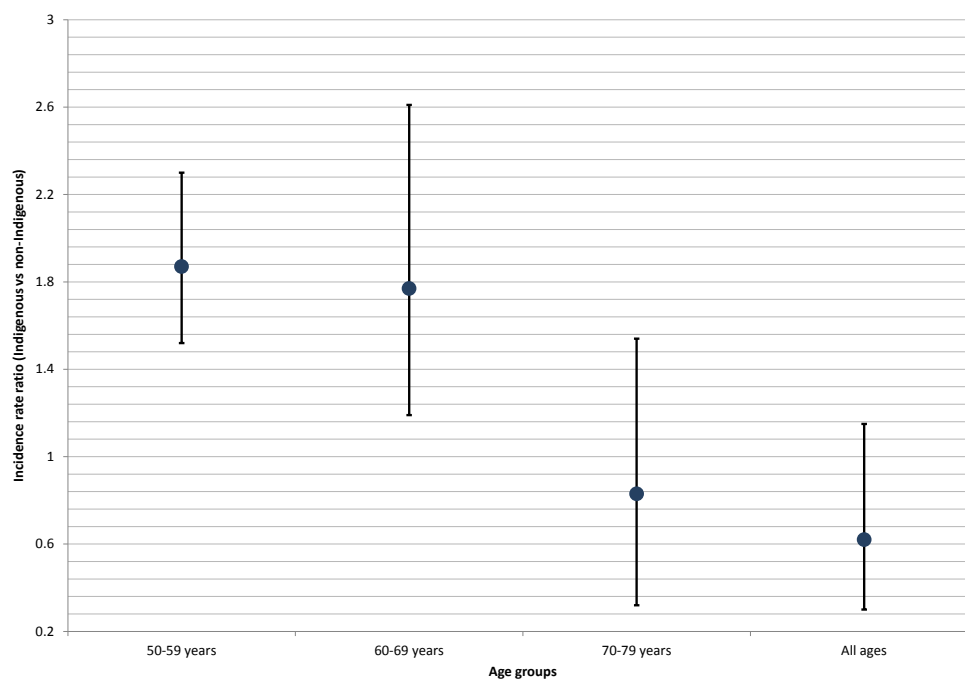
(B)

\* Analyses restricted to episodes where HZ was recorded as a principal diagnosis and PHN was recorded within the first 30 diagnostic fields. Principal HZ includes episodes of PHN.

**Figure 7: Incidence rate ratios for varicella (A)\* and herpes zoster (B)\*\* hospitalisation rates between Indigenous and non-Indigenous Australians by age groups, Australia, 1999- 2013**



(A)



(B)

\* Analyses restricted to Queensland, South Australia, Western Australia and the Northern Territory. Pre-varicella vaccine=1999-2004 and post-varicella vaccine=2007-2013.

\*\* Analyses restricted to New South Wales, Victoria, Queensland, South Australia, Western Australia and the Northern Territory for the years 2007-2011.



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