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Use of hospitalization and pharmaceutical prescribing data to compare the prevaccination burden of varicella and herpes zoster in Australia

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SUMMARY

The aims of the study were to compare the burden of varicella and herpes zoster in Australia. No national surveillance exists for varicella or herpes zoster. We used hospital morbidity data from 1993–9 and pharmaceutical prescribing data from 1995–9.

In the financial year 1998/99, there were 4718 hospitalizations for zoster compared to 1991 for varicella. For varicella the mean age of patients was 15 years compared to 69 years for zoster. The mean length of stay in hospital was 4·2 days for varicella and 12·7 days for zoster. Varicella accounted for 8396 (3726 with principal diagnosis varicella) bed days compared to 26 266 (5382 with principal diagnosis of zoster) for zoster. The in-hospital case-fatality rate was 0·4% for varicella and 1% for zoster. In 1999, 59 200 community-based cases of zoster were treated with antivirals. We estimate that 157 266 cases of zoster occurred in the community in 1999, a rate of 830 per 100 000 population.

Herpes zoster has a higher burden of disease than varicella, and must be a component of disease surveillance in order to determine the full impact of vaccination on the epidemiology of varicella zoster virus (VZV).

INTRODUCTION

In unvaccinated populations, varicella is primarily a childhood illness with more than 90% of the population in temperate countries developing clinical or subclinical infection by adolescence [1, 2]. Varicella is generally a benign, self-limiting illness in children, but morbidity and mortality rates are higher in adults [3], at the extremes of ages, and in the immunocompromised [4].

Herpes zoster is a sporadic disease, caused by the reactivation of latent varicella zoster virus (VZV). Although herpes zoster can affect persons of any age, most are individuals older than 50 years of age, and incidence increases with advancing age [5]. Also at risk are children who were infected *in utero*, or who acquired varicella before the age of 1 year, those on immunosuppressive drugs, and individuals infected with human immunodeficiency virus [6–8]. Herpes zoster is usually self-limiting, but is characterized by severe dermatomal pain, sometimes followed by postherpetic neuralgia, which can be chronic and debilitating [9]. Herpes zoster is responsible for far more hospitalizations and deaths than varicella [5, 10]. In view of the burden of herpes zoster in the elderly, it has been suggested that it may be cost-effective to use varicella vaccine in elderly people to prevent reactivation of herpes zoster [11]. Herpes zoster is also more common in immunocompromised people, and may be prevented by vaccination against varicella zoster [12].

Varicella vaccination for children was introduced in the USA in 1995 [13]. In the short term, the incidence

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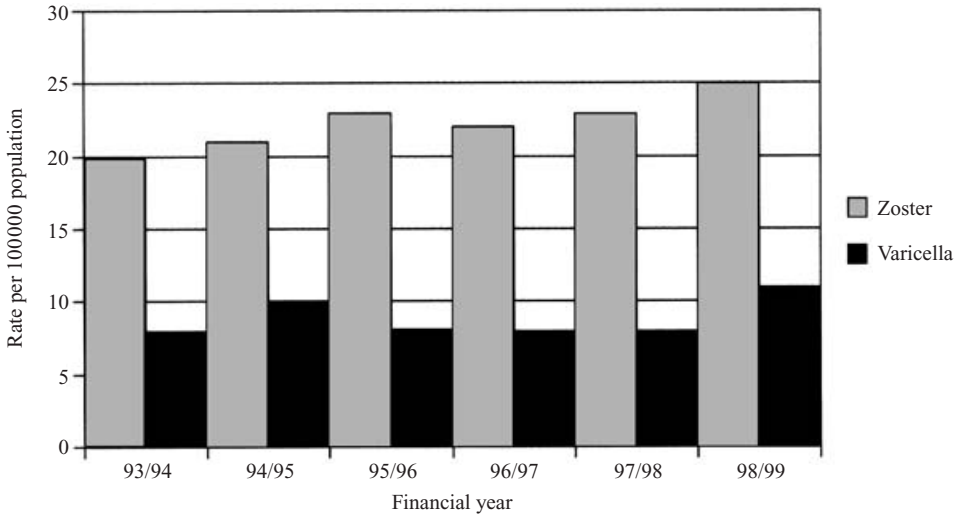

Fig. 1. Rate of hospital admission for zoster and varicella, Australia, 1993/94–1998/99.

of varicella has decreased by over 70% in the selected surveillance sites in the USA [13]. However, the longer term effect on the incidence of herpes zoster is unknown. It is important to have good surveillance data for varicella and herpes zoster before and after introducing the vaccine into the population in order to monitor the impact of the vaccination programme. Varicella vaccine was registered in Australia in the year 2000, and has been recommended for inclusion in the routine childhood schedule, but not yet funded. No routine national surveillance exists in Australia for varicella or herpes zoster, although one state, South Australia, introduced surveillance for varicella in 2002.

The aims of this study was to describe and compare the burden of varicella and herpes zoster in Australia prior to the introduction of universal vaccination.

METHODS

Hospitalization data and pharmaceutical prescribing data were used to describe the epidemiology of varicella and zoster.

Data were extracted from the Australian Hospital Morbidity Database for the financial years 1993/94–1998/99 and analysed using Excel 2000. Data from the entire period were used to examine trends, and more detailed analysis was performed on data from 1998/99. Some states were using ninth and some the tenth revision of the International Classification of Diseases – Clinical Modification (ICD-9-CM or ICD-10-CM). ICD-10 to 9 conversion was used for states using ICD-10-CM and the following ICD-9-CM codes were used to determine hospital separations for varicella or herpes zoster in any diagnostic field:

> 052-0529 (chicken pox, post varicella encephalitis, varicella pneumonitis, chicken pox with other specified complications, chicken pox with unspecified complications and varicella without mention of complication) and 053-0539 (herpes zoster, herpes zoster with meningitis, herpes zoster with other nervous system complications, herpes zoster with ophthalmic complications, herpes zoster with other specified complications, herpes zoster with unspecified complication, herpes zoster without mention of complication). These corresponded to ICD-10-Cm codes B01, B01.0+, B01.1+, B01.2+, B01.8, B01.9, B02, B02.0+, B02.1+, B02.2+, B02.3+, B02.7, B02.8 and B02.9.

The separations were divided into two groups – those who had a principal diagnosis of varicella or zoster, and those who were principally admitted for some other diagnosis, but who had a diagnosis of varicella or zoster coded in any of the other diagnosis fields. Varicella and zoster episodes were analysed by Australian National Diagnosis Related Group (ANDRG) [14].

The total bed days for patients who had a secondary diagnosis of varicella or zoster are not necessarily a reflection of the portion of their stay for VZV, but of their principal reason for hospitalization. The bed days attributable to varicella or zoster for patients who had a secondary diagnosis of varicella or zoster were therefore calculated by using the mean length of stay (LOS) of people with varicella or zoster

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Table 1. *Characteristics of hospitalized patients with varicella as a principal* vs. *a secondary diagnosis in Australia* (*July 1998 to June 1999*)

Variable	All varicella	Principal diagnosis varicella	Secondary diagnosis varicella	*P* value*
Hospital episodes	1991	1137	854	
Mean age (years)	15·3	14·2	17·1	0·0086
Median age (years)	5	5	7	
Age range (years)	0–90	0–88	0–90	
Mean LOS (days)	4·2	3·3	5·5	0·0001
Median LOS (days)	2	2	2	NS
LOS range (days)	1–171	1–71	1–171	
Total bed days (days)	8396	3726	4670	
Total bed days attributable to varicella†	6544	3726	2818†	
% male	53	56	49	0·002
% in public hospitals	91	90	92	NS
% acute care	98	99	97	0·001
% deaths	0·5 (9/1991)	0·4 (4/1137)	0·6 (5/854)	NS

* For difference between varicella as principal and secondary diagnosis.
† Bed days attributable to varicella for patients with a secondary diagnosis of varicella were calculated by using the mean LOS of people with varicella as a principal diagnosis, and multiplying it by the number of hospital episodes with varicella as a secondary diagnosis.

respectively as a principal diagnosis, and multiplying it by the number of hospital episodes. Although possibly an underestimate, this allows comparison between the group with principal diagnosis of varicella or zoster respectively.

Age specific rates of hospitalization for varicella and zoster were calculated in 5-year age groups, using population denominator data for 1998/99 from the Australian Bureau of Statistics.

Herpes zoster incidence in the community was also estimated using data from the Restricted Pharmaceutical Benefits Scheme (RPBS) on community (non-hospital) use of the antiviral drugs acyclovir, valaciclovir and famciclovir for the specific indication of herpes zoster. The RPBS maintains a coded database of pharmaceutical use, with each unit being a single prescription. The codes 1052J, 8002E and 8064K indicate use of the above mentioned drugs specifically for herpes zoster, and all prescriptions coded as such between 1995 and 1999 were analysed. Although we cannot exclude multiple prescriptions for a single patient, and we cannot estimate use of these drugs outside of the RPBS scheme, the RPBS remains a useful source of data.

Data extrapolated from one study, which looked at physician visits and hospitalizations, suggested that about 3% of zoster cases are hospitalized [15]. These data are supported by Brisson et al., who quoted rates of 0·6–14·4% in the UK, with the highest figures for the oldest age groups [10]. These data were used to estimate a community incidence of zoster from hospitalization data.

Australian population data was obtained from the Australian Bureau of Statistics [16, 17].

RESULTS

Trends in hospitalizations for varicella and zoster

Over the study period, varicella rates range from 7–11 per 100 000, and zoster rates from 20–25 per 100 000 (Fig. 1). Including principal and secondary diagnoses, this represented 4718 hospitalizations for zoster compared to 1991 for varicella. From July 1998 to June 1999 the rate of herpes zoster was 25/100 000, compared to 11/100 000 for varicella.

Varicella

From July 1998 to June 1999, 1991 out of a total of 5 735 049 hospital episodes (0·03%) were coded as varicella. Of these, 57% (1137/1991) had varicella

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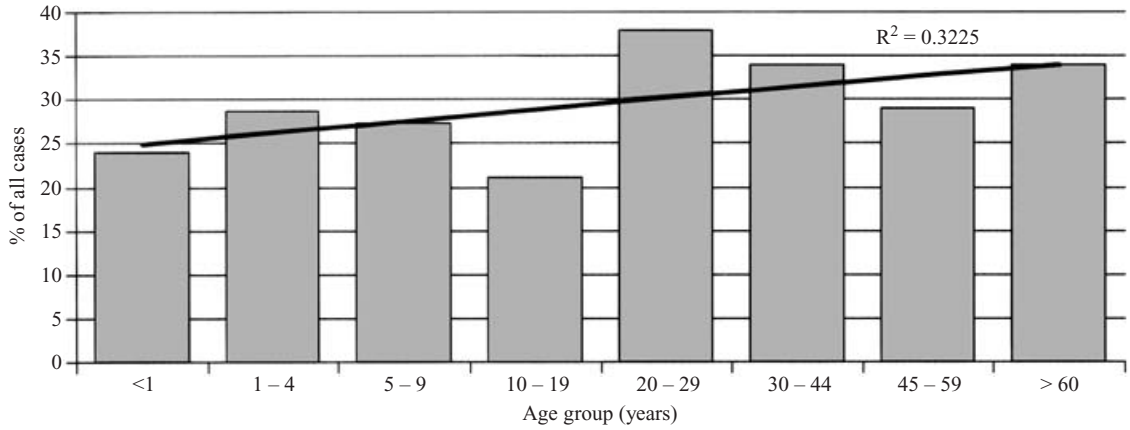

Fig. 2. Complication rate of hospitalized varicella cases (with principal diagnosis varicella) by age group.

Table 2. *Complications in hospitalized patients with a principal diagnosis of varicella in Australia from July 1998 to June 1999*

Diagnosis	Number	%
Postvaricella encephalitis	49	4·3
Varicella pneumonitis	116	10·2
Varicella, specified or unspecified complications	294	25·9
Uncomplicated varicella	678	59·6

coded as a principal diagnosis and 43% (854/1991) as a secondary diagnosis.

Table 1 shows that the two groups of patients with principal or secondary diagnoses of varicella are similar. The mean age of hospitalized patients was 15·3 years (median 5·0 years, range 0–90 years) and 3% (60/1991) were aged >50 years (Table 1). The mean LOS was 4·2 days (median 2 days, range 1–171 days), with a total of 8396 bed days. The majority of episodes (91%) were in public hospitals, and 98% were acute care admissions. The overall mortality during the episode of hospitalization was 0·5% (9/1991).

Table 2 shows that in 40% of episodes, patients with a principal diagnosis of varicella had complications. Complication rates tended to rise with age (Fig. 2).

Herpes zoster

From July 1998 to June 1999, 4718 out of a total of 5 735 049 hospital episodes (0·08% of all hospital episodes) were coded as herpes zoster (Table 3). Of these, 40% (1903/4718) had zoster as a principal diagnosis and 60% (2815/4718) as a secondary diagnosis.

The mean age of patients was 68·6 years (median 75·0 years, range 0–101 years) and 53% (2490/4718) were aged >50 years. The mean LOS was 12·7 days (median 6 days, range 1–8342 days), with a total of 60 055 bed days. The high outlier bed-days represented a very small number of patients with long term hospitalization. Most episodes (74%) were in public hospitals, and 91% were acute care admissions. The overall mortality during the episode of hospitalization was 4% (186/4718). There were significant differences between the two groups of patients with principal or secondary diagnoses of zoster, mainly in the length of stay in hospital, which was more than twice as long in patients with a secondary diagnosis (Table 3). Deaths were also significantly more common in the group with a secondary diagnosis of zoster.

Fifty-nine percent of principal episodes had complicated zoster, with neurological complications being the most common (Table 4).

The most common ANDRGs, reflecting principal diagnosis, for patients with a secondary diagnosis of zoster were rehabilitation, respiratory infection/inflammation and chronic obstructive airway disease (Table 5).

The age specific rates of hospitalization per 100 000 population for zoster increases with increasing age, particularly over the age of 65 years, with the highest rate in the age group >85 years (Fig. 3). The rate for varicella decreases with increasing age, particularly over the age of 4 years.

There was a trend to increasing prescription of antivirals between 1995–9 (Fig. 4). In 1999, there were 59 200 cases of zoster treated with antivirals in Australia, at a rate of 329/100 000.

If 3% of all cases of zoster are hospitalized [15], 157 266 cases would have occurred in the general

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Table 3. *Characteristics of hospitalized patients with zoster as a principal* vs. *secondary diagnosis in Australia from July 1998 to June 1999*

Variable	All zoster	Principal diagnosis zoster	Secondary diagnosis zoster	*P* value*
Episodes	4718	1903	2815	
Mean age (years)	68·6	66·9	69·8	<0·01
Median age (years)	75	74	75	
Age range (years)	0–101	0–99	0–101	
Mean LOS (days)	12·7	7·2	16·5	<0·0001
Median LOS (days)	6	5	7	<0·0001
LOS range (days)	1–8342	1–68	1–8342	
Total bed days (days)	60 055	5382	56 865	
Total bed days attributable to zoster†	26 266	5382	20 844†	
% male	43	41	44	<0·5
% in public hospitals	74	70	76	<0·0001
% acute care	91	97	87	<0·0001
% deaths	4 (186/4718)	1 (22/1903)	6 (164/2815)	<0·0001

* For difference between zoster as principal and secondary diagnosis.
† Bed days attributable to zoster for patients with a secondary diagnosis of zoster were calculated by using the mean LOS of people with zoster as a principal diagnosis, and multiplying it by the number of hospital episodes with zoster as a secondary diagnosis. Although possibly an underestimate, this allows comparison between the group with principal diagnosis of zoster.

Table 4. *Complications in hospitalized patients with a principal diagnosis of herpes zoster in Australia from July 1998 to June 1999*

Diagnosis	Number	%
Herpes zoster meningitis	15	0·8
Neurological complications	630	33·1
Ophthalmic complications	304	16·0
Other complications	165	8·7
Uncomplicated herpes zoster	789	41·5

Table 5. *Diagnosis Related Groups (DRG) for hospitalized patients with a secondary diagnosis of zoster in Australia from July 1998 to June 1999*

DRG description	Frequency
Rehabilitation	232 (8·2%)
Respiratory infection or inflammation	122 (4·3%)
Chronic obstructive airway disease	118 (4·2%)
Lymphoma and non-acute leukaemia	91 (3·2%)
Oesophagus, gastric and miscellaneous	82 (2·9%)
Heart failure and shock	77 (2·7%)
Stroke	57 (2·0%)
Other factors influencing health status	57 (2·0%)
Neurosurgery, neck and back + pain	50 (1·8%)
Cellulitis	47 (1·7%)
All other DRGs	1882 (66·9%)

community in that year, a rate of 830 per 100 000 population. The RPBS data suggest that about 40% of all cases of zoster in the community are treated with antivirals. Based on UK estimates [10] the community incidence of zoster in the age group >65 years would be 5075/100 000.

DISCUSSION

This study shows that the burden of herpes zoster, as measured by hospital bed days, is greater than that of varicella. From July 1998 to June 1999, there were at least twice as many hospitalizations in Australia for zoster than for varicella. Of those with a principal diagnosis of varicella, only 40% of episodes had complications compared with 59% for those with a principal diagnosis of zoster. The single most common complication for varicella was pneumonitis, and for zoster was neurological. Ophthalmic zoster was also frequent among hospitalized cases (16%). The overall case fatality rate of hospitalized zoster (4%) was eight times higher than that of varicella (0·5%). If only a principal diagnosis of zoster or varicella was considered, the case fatality was 2·5 times higher for

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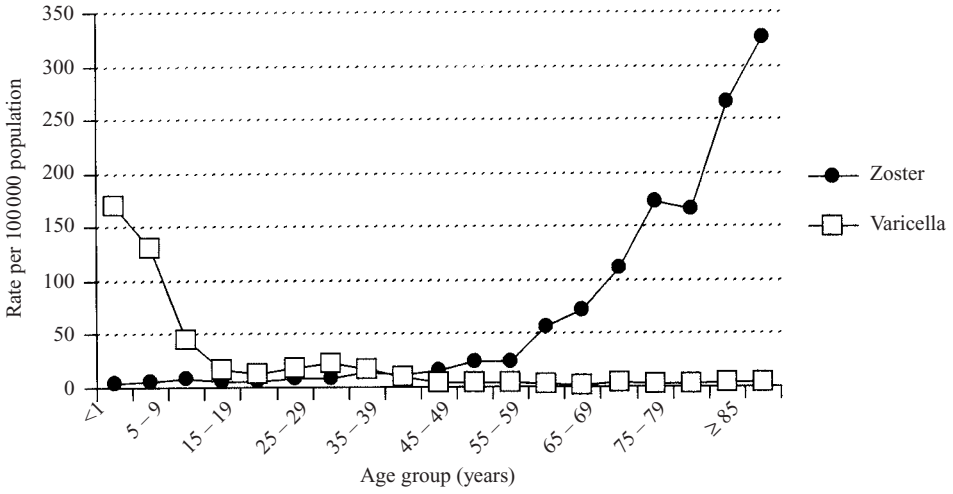

Fig. 3. Age specific rates of hospitalized zoster and varicella, Australia, 1998/99.

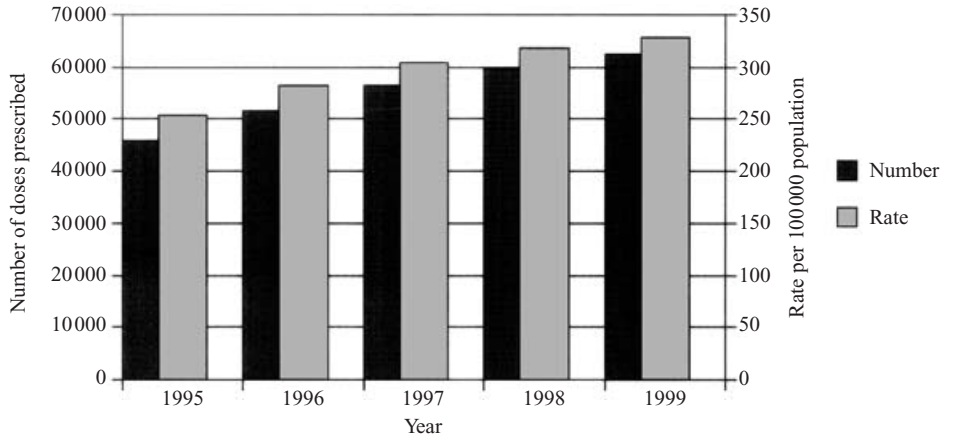

Fig. 4. Total doses and rate of antivirals prescribed for herpes zoster in the community, Australia, 1995–9.

zoster. It should be noted that if varicella or zoster was a secondary diagnosis, the principal diagnosis (for example, cellulitis or pneumonitis) may still be related to VZV infection.

Varicella mostly affected the young and led to shorter stays in hospital compared to zoster, which affected a much older population and led to longer stays in hospital.

An Australian study showed similar findings, with mortality from zoster (measured by routine cause of death data) being three times higher than that from varicella [18]. It also described six times as many hospital bed-days for zoster compared to varicella, using hospital data from two Australian States from 1988–94. This study also looked at GP visits for VZV disease using non-representative sentinel GP surveillance. They found that over 2 years, 0·18% of GP consultations were for varicella and 0·11% for herpes zoster [18].

Other studies have similarly described a higher burden of herpes zoster than varicella. A US study found that there were four times as many hospitalizations for zoster than varicella and the average cost of hospitalization was higher for zoster [5]. Similarly, in the UK and Canada, hospitalization rates for zoster were higher than for varicella [10]. A Canadian study found that the direct costs attributable to herpes zoster were higher than those attributable to varicella [15]. Only one study, based in a single US Health Maintenance Organisation (HMO), Kaiser Permanente, found similar hospitalization rates for varicella and zoster [19]. However, all study subjects were aged under 20 years, so that this study is not representative of the general community. In addition, the study only examined data for 1 year.

In our study, from July 1993 to June 1999, there was a trend for increasing rates of hospitalization for zoster, as well as an increasing rate of antiviral

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prescription for zoster. Although the increasing rate of antiviral prescription could reflect changes in medical practice, the data suggests that there may have been an overall increase in the number of zoster cases in the community, a proportion of which require hospitalization because of severe disease or complications. This may be due to the ageing of the population overtime, and due to better survival of people with chronic debilitating conditions.

The varicella vaccine was registered in Australia in 2000. There has been good analysis of the impact of the vaccine on varicella, particularly in paediatric age groups [20–23]. However, there has been less emphasis on the effect of varicella vaccination on older age groups and on herpes zoster epidemiology. The latter is important, as it has a higher burden of disease and mortality than varicella, and results in higher health care costs [15].

If natural varicella provides boosting against reactivation of herpes zoster, then there may be an increase in zoster incidence following universal varicella vaccination [24–26]. There is increasing evidence that varicella does boost immunity to herpes zoster, with two recent studies showing lower rates of zoster in groups who are exposed to varicella [27, 28]. In addition, vaccination is likely to shift the burden of varicella into older age groups and increase the average age of infection [24]. This may be a problem because of the higher morbidity and mortality of varicella in older age groups [3]. In the absence of surveillance data or other data on community incidence of herpes zoster, our estimates may be useful as a baseline measure, and are comparable to other estimates [9].

The limitations of this study include the use of routine hospital morbidity and prescribing data. Both may be subject to coding errors. A study of coding of hospital data in Australia found that errors in principal diagnosis occurred in 22% of separations, but were less likely for common conditions [29]. Both varicella and zoster are common conditions, and may be less likely to be miscoded. Prescribing data are also potentially subject to errors in coding. Although there have been no studies validating these data, the codes are linked directly to financial subsidies for drugs given for specified indications under the Australian Pharmaceutical Benefits Scheme, and may be less likely to be erroneous. Despite these limitations, in the absence of surveillance data, these routine datasets may be useful for monitoring trends in varicella and zoster.

At a time when this vaccine is being considered for the routine childhood vaccination schedule in Australia, baseline information on the burden of VZV infection, in particular herpes zoster, will assist in the formulation of the vaccine policy. It is sensible public health practice to monitor trends in both varicella and zoster, as VZV is a complex virus which causes both an acute disease, largely affecting children, and a reactivation illness, largely affecting the elderly. There is enough evidence to suggest that universal vaccination of infants may affect more than just the targeted paediatric population [24, 26–28, 30], and in light of this, it is reasonable to monitor trends in zoster. We believe that hospital morbidity data can be used for estimating the community incidence of herpes zoster. In the absence of routine surveillance for zoster, the pharmaceutical prescribing data could be used for surveillance of community-based cases of herpes zoster in the future, as it is a readily available source of information. No comprehensive, routine national surveillance currently exists for herpes zoster or varicella in Australia. Only one state, South Australia, has made varicella (but not herpes zoster) a notifiable disease since January 2002. Herpes zoster has a higher burden of disease than varicella, and must be a component of disease surveillance in order to determine the full impact of vaccination on the epidemiology of disease.

There is a need to utilize existing local data sources to monitor trends in both varicella and zoster until formal surveillance is established.

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