Varicella and herpes zoster hospitalizations before and after implementation of one-dose varicella vaccination in Australia: an ecological study

Anita E Heywood,[a] Han Wang,[b] Kristine K Macartney[b] & Peter McIntyre[b]

Objective To examine trends in varicella and herpes zoster (HZ) hospitalization following the availability and subsequent National Immunization Programme funding of one-dose varicella vaccination in Australia.

Methods Varicella vaccination coverage for children born between 2001 and 2009 was obtained from the Australian Childhood Immunization Register. Principal or any coded varicella or HZ hospitalizations were retrieved from the national hospital morbidity database from 1998 to 2010. Trends in hospitalization rates in different age groups and indigenous status were assessed. Incidence rate ratios (IRR) were calculated between periods before and after implementation of immunization programme funding.

Findings In the first year of the funded immunization programme, varicella vaccine coverage reached 75% in children aged 24 months and more than 80% in children aged 60 months. Compared with the pre-vaccine period, varicella hospitalization rates during the funded programme were significantly lower for age groups younger than 40 years; with the greatest reduction in children aged 18–59 months (IRR: 0.25; 95% confidence interval, CI: 0.22–0.29). Indigenous children had a higher varicella hospitalization rate compared with non-indigenous children before vaccine implementation (IRR: 1.9; 95% CI: 1.4–2.7), but afterwards reached equivalence (IRR: 1.1; 95% CI: 0.7–1.6). The age-standardized HZ hospitalization rate declined between the periods (IRR: 0.95; 95% CI: 0.92–0.97).

Conclusion Rapid attainment of high coverage reduced varicella hospitalizations in the targeted age group, particularly for indigenous children, but also in non-targeted age groups, with no increase in HZ hospitalizations. This suggests high one-dose varicella vaccine coverage can have a substantial impact on severe disease.

Abstracts in عربي, 中文, Français, Русский and Español at the end of each article.

Introduction

Prior to the introduction of varicella vaccination in Australia, primary infection with the varicella-zoster virus (VZV) was a common childhood disease, with the majority (88%) of the population experiencing infection by adolescence.[1] Although the varicella vaccine has been available since 1995, few countries have recommended universal childhood vaccination, and even fewer have implemented publicly funded national varicella vaccination programmes.[2] Most of the data on the impact of varicella vaccination come from studies conducted in the United States of America (USA), where, since 1996, vaccination has been recommended for children older than 12 months. However, vaccine uptake was slow, with one-dose coverage at 19–35 months of age not reaching more than 80% until 2002.[3] During the USA one-dose era, significant declines in varicella ambulatory visits, hospitalizations and deaths were documented, including non-targeted age groups, consistent with a herd immunity effect.[4,5] Nonetheless, continued disease transmission and outbreaks in highly vaccinated populations prompted the move from a one-dose to a two-dose schedule in both Germany[6] and the USA.[3]

The World Health Organization has requested evidence for the impact of varicella and herpes zoster (HZ, a reactivation of latent VZV) vaccination programmes from countries with robust data to use for developing evidence-based recommendations.[7] To date, evidence of programme impact on varicella zoster disease outside the USA is predominantly regional or limited to small population samples; no data are available for subpopulations with higher incidences. Additionally, increases in HZ are hypothesized to occur from a reduction in natural immunological boosting in previously infected individuals. However, data are limited and inconclusive.

Vaccines listed on Australia's National Immunization Programme schedule are fully funded at a national level for eligible age groups, with programme delivery managed by each state and territory.[8,9] The experience that followed the availability of varicella vaccines in Australia (Table 1) is unique in several aspects. Both licensed vaccines, Varivax® and Varilrix®, have been available since 2000, with Varilrix® used almost exclusively in the National Immunization Programme since November 2005. Furthermore the programme includes one-dose routine vaccination at 18 months of age and a single catch-up dose delivered via Australia's school-based immunization programme at 12–13 years. Data on childhood vaccination coverage are available from the Australian Childhood Immunization Register and complete national hospitalization data are available by age for Aboriginal and Torres Strait Islanders and non-indigenous people. It is known that indigenous Australians have higher varicella hospitalization rates compared to non-indigenous Australians. These higher rates are possibly related to poorer access to primary care, particularly in remote areas, and/or higher rates of skin/soft tissue complications related to environmental living conditions.[11]

Using national data records on varicella immunization and hospitalization, we evaluated age-related trends in both varicella and HZ hospitalizations during periods of differing varicella vaccine coverage. We also aimed to assess the out-

[a] School of Public Health and Community Medicine, University of New South Wales, Level 3, Samuels Building, Botany Road, Kensington, NSW 2052, Australia.
[b] National Centre for Immunisation Research and Surveillance, The Children's Hospital at Westmead, Sydney, Australia.
Correspondence to Anita E Heywood (email: a.heywood@unsw.edu.au).
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Table 1. **Periods of varicella vaccine availability and varicella hospitalization data, Australia 1998 to 2010**

Period	Varicella vaccine availability	Included hospitalization data[a]
Pre-vaccine (before 2000)	No licensed vaccine	July 1998–December 1999 (1.5 years)
Licensed (2000–2003)	Vaccine licenced but no formal recommendations	January 2000–December 2003 (4 years)
Recommended (2004–2005)	Vaccine recommended[b] but not funded through NIP	January 2004–December 2005 (2 years)
Funded (2006–current)	Single dose vaccine public funded through NIP[c]	January 2006–June 2010 (4.5 years)

NIP: national immunization programme.
[a] Includes hospitalizations by date of hospital admission.
[b] Recommended as a single dose at 18 months of age. Vaccine recommendations.[10]
[c] One-dose vaccination was funded from November 2005 for children of 18 months of age and from February 2006 for the school-based catch-up programme.

come of the immunization programme on varicella hospitalizations in Australia's indigenous population.

Methods

Data sources

The Australian Childhood Immunization Register records vaccines given to all Medicare-enrolled children younger than seven years of age,[12] which includes 99% of Australia's annual births of approximately 300 000 children.[13] Data on the proportion of eligible children who received the varicella vaccine were obtained quarterly, including indigenous status. Coverage data at 24 months of age were available for children born between October 2001 and September 2009. To determine timeliness of vaccination, we also assessed coverage at 60 months of age for children born between January 2003 and June 2008. State and territory summary data on the proportion of school enrolments vaccinated in the adolescent school-based catch-up programme in 2009 were provided by jurisdiction health departments. The school-based catch-up was conducted at 12 to 13 years of age. For these adolescents, parental reports of previous natural infection or vaccination are accepted as valid reasons for non-vaccination in the school-based vaccination programme. However, parental report data were not available for analysis.[14]

National, de-identified demographic and diagnostic data for individual hospitalizations (private and public hospitals) for varicella and HZ were obtained from the National Hospital Morbidity database for the period from July 1998 to June 2010.[15] All episodes coded as varicella or its complications (codes B01-B01.9 in the International Statistical Classification of Diseases, 10th Revision, Australian Modification, ICD-10-AM) and HZ or its complications (codes B02-B02.9) in the principal or any diagnostic fields were obtained. Dual hospitalization coding for varicella and HZ were excluded (0.6% of all VZV-coded hospitalizations). Mid-year population estimates by age and indigenous status were obtained from the Australian Bureau of Statistics.[13]

We conducted a search in the Medline database for studies assessing the impact of National Immunization Programmes using the search terms "varicella" or "zoster" and "hospitalizations" and "vaccination" or "immunization". The search was limited to English language articles published or available online from 1 January 1996 to 1 March 2013. The initial search identified 101 potential studies on varicella hospitalizations and 53 potential studies on HZ hospitalizations. After excluding studies that did not report average annual hospitalization rates for pre- and post-programme periods, eight varicella and three HZ studies were included in the review.

Data analysis

Annual crude and age-specific hospitalization rates for varicella and HZ in the population were calculated by Australian financial year of hospital discharge (1 July to 30 June). Average hospitalization rates for the periods of vaccine availability (Table 1) were calculated by date of hospital admission to reflect changes in vaccine availability. Reported rates refer to principal hospitalizations, unless otherwise stated. To account for temporal changes in population age structure, age-adjusted hospitalization rates were calculated, using direct standardization to the population of the publicly funded period when comparing vaccine availability periods and 2009/2010 financial year population when comparing annual changes.[13] Analysis of hospitalization rates for Aboriginal and Torres Strait Islander peoples was restricted to four jurisdictions (Western Australia, South Australia, Queensland and the Northern Territory) due to known incomplete hospital records of indigenous status in other jurisdictions in earlier years.[11] Indigenous Australians represent 2.4% of the total Australian population, with 60.1% residing in these four states and territories.[13,16] Poisson regression was used to analyse yearly trends in crude, age-standardized and age-specific hospitalizations and to calculate average annual percentage change and accompanying *P*-values. Hospitalizations averted were calculated by applying pre-vaccination hospitalization rates to the funded immunization programme population. Ninety-five per cent confidence intervals (CIs) were calculated using the Poisson distribution for hospitalization counts and the log transformation method was used to obtain incidence rate ratios (IRR). Analysis was undertaken using SAS version 9.2 (SAS Institute, Cary, USA).

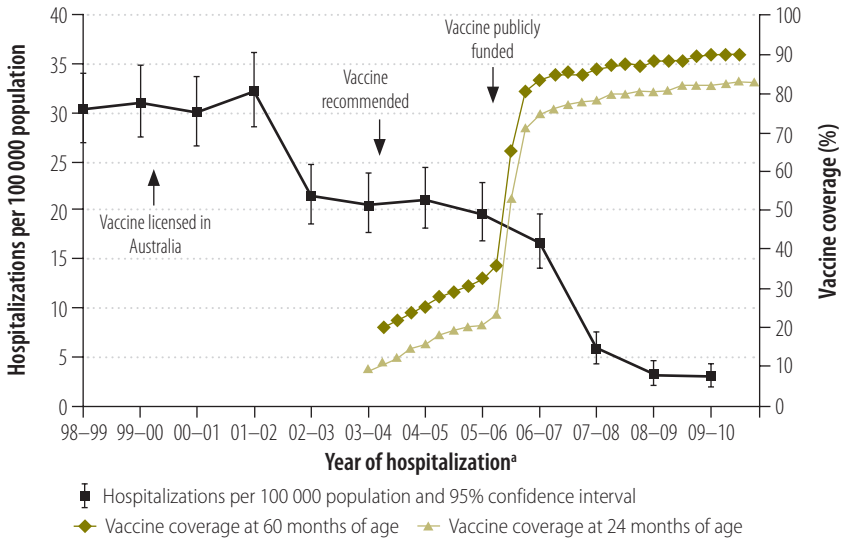
Results

Vaccination coverage

Before the immunization programme funding was introduced, the varicella vaccination coverage increased slowly (Fig. 1). According to the Australian Childhood Immunization Register, 9.7% of children aged 24 months had been vaccinated before the unfunded recommendations in late 2003. By the end of 2005, the second year of the unfunded recommendations, 20.9% vaccination coverage was achieved. After immunization programme funding, coverage at 24 months of age increased to 74.8% within the first year and exceeded 80% 2.5 years into the programme in 2008 (Fig. 1).

Vaccine coverage at 60 months of age was consistently higher, reaching 90.0% by the end of 2012. Among the indigenous population, coverage was 1.2% and 5.4% lower at the age of 24

Fig. 1. **Annual varicella hospitalization rates (principal diagnosis) for children aged 18–59 months and varicella vaccination coverage in children aged 24 and 60 months, Australia, July 1998 to June 2010**



[a] Australian financial year from 1 July to 30 June.

Note: Coverage for 24 and 60 months are assessed for the same cohort of children, e.g. for the cohort born January–June 2002, 24-month coverage was assessed at January–June 2004 (12.1%) and 60-month coverage at January–June 2007 (21.0%).

months in 2003 and 2005, respectively, compared with the non-indigenous population before the immunization programme funding. However, after the funding, vaccination increased rapidly to an estimated 81.9% of indigenous children aged 24 months by the end of 2010 and 91.6% of indigenous children aged 60 months by the end of 2011. School-based vaccination programmes had variable one-dose coverage across jurisdictions, ranging from 19% to 42% of enrolled students in 2009, which was similar to previous years.[14]

Varicella hospitalizations

Between 1 July 1998 and 30 June 2010, 16 261 varicella hospitalizations were recorded for all ages, including 10 632 (65.4%) principally coded as varicella. The annual crude principal hospitalization rates declined by an average of 21.4% (95% CI: 17.8–25.0) per year following the immunization programme funding. During the funded period, the age-standardized varicella hospitalization rate was 49.6% (95% CI: 47.3–51.9) lower than the pre-vaccine period and 40.3% (95% CI: 37.4–43.1) lower than in the recommended, unfunded period (Table 2). Significant average annual declines in hospitalization rates were observed for all age groups under 40 years ($P < 0.001$). The greatest reduction in rates was detected in children from 1 to 4 years old, with 72.5% (95% CI: 68.8–75.7) lower rates during the funded immunization programme period, compared with the pre-vaccine period and 58.6% (95% CI: 52.9–63.6) lower compared with the recommended, unfunded period. Notably, the age group of 1 to 4 years was the only one to show a statistically significant decline during the recommended, unfunded period (Table 2).

For the age group specifically targeted under the funded immunization programme, i.e. children aged 18–59 months (Fig. 1), the average hospitalization rate during the programme was a quarter of the average pre-vaccine rate (IRR 0.25, 95% CI: 0.22–0.29). For infants (under one year), not eligible for vaccination, hospitalization rates during the funded immunization programme were significantly lower than during the pre-vaccine and recommended, unfunded periods, 62.1% (95% CI: 54.7–68.3) and 53.3% (95% CI: 44.5–60.7), respectively. When applying pre-vaccine hospitalization rates to the funded period population, an estimated 686 varicella hospitalizations, including 369 in children younger than five years, were annually averted in Australia following the immunization programme funding.

Over the study period, there were 560 varicella hospitalizations, 333 (59.5%) of which were with a principal diagnosis, and where the patient was recorded as being Aboriginal and/or Torres Strait Islander. Prior to vaccine availability, indigenous Australians were hospitalized at a minimum of twice the rate of the non-indigenous population (IRR 2.6, 95% CI: 2.0–3.2). Following the funded immunization programme, overall hospitalization rates remained higher for the indigenous people (Fig. 2).

For indigenous children aged 0–4 years, the hospitalization rates were also higher during the pre-vaccine period compared with non-indigenous children (IRR: 1.9; 95% CI: 1.4–2.7). However, the rate declined from 71.8 (95% CI: 51.1–98.2) per 100 000 population in the pre-vaccine period to 16.6 (95% CI: 11.1–24.1) per 100 000 population in the immunization programme period (IRR: 0.23; 95% CI: 0.14–0.38), reaching similar rates for both groups of children (IRR: 1.1; 95% CI: 0.7–1.6) (Fig. 2).

Herpes zoster hospitalizations

Between 1 July 1998 and 30 June 2010, 59 660 hospital episodes were coded as HZ, and 25 198 (42.2%) as the principal diagnosis. Crude principal HZ hospitalization rates increased by an average of 0.53% (95% CI: 0.18–0.89) per year. However, when rates were age-standardized, HZ hospitalization declined at an average of 0.57% (95% CI: 0.24–0.91%) per year (Fig. 3). Temporal changes for all HZ-coded hospitalizations were similar to principal HZ hospitalizations (Fig. 3). Compared with earlier time periods, age-standardized HZ rates were significantly lower during immunization programme funding and age-specific principal HZ hospitalization rates remained stable or lower (Table 3).

Discussion

Australia is one of the few countries that has included varicella vaccination under its national immunization programme, distinctively funding one-dose routine childhood vaccination and an adolescent catch-up programme. Many European countries – despite a European consensus recommendation – have not introduced universal varicella vaccination.[17] For example, the United Kingdom of Great Britain and North-

Table 2. **Varicella-coded hospitalizations during the periods of different varicella vaccine availability, Australia, July 1998 to June 2010**

Age (years)	Varicella hospitalization								
	Pre-vaccine period		Vaccine licensed period		Vaccine recommended period		Vaccine funded period		IRR[c] (95% CI)
	No.[a]	Rate[b] (95% CI)	No.[a]	Rate[b] (95% CI)	No.[a]	Rate[b] (95% CI)	No.[a]	Rate[b] (95% CI)	
Principal varicella									
<1	143	57.1 (49.7–65.3)	111	44.5 (40.4–48.8)	119	46.4 (40.7–52.7)	62	21.7 (19.2–24.4)	0.38 (0.32–0.45)
1–4	353	34.0 (31.1–37.0)	325	31.6 (29.9–33.4)	233	22.6 (20.6–24.8)	102	9.4 (8.5–10.3)	0.28 (0.24–0.31)
5–9	147	11.0 (9.6–12.6)	121	8.9 (8.2–9.8)	113	8.4 (7.4–9.6)	75	5.5 (5.0–6.2)	0.50 (0.42–0.60)
10–19	115	4.4 (3.8–5.1)	88	3.2 (2.9–3.6)	85	3.0 (2.6–3.5)	61	2.1 (1.9–2.4)	0.48 (0.40–0.59)
20–39	291	5.1 (4.6–5.6)	291	5.1 (4.8–5.4)	308	5.3 (4.9–5.8)	192	3.1 (2.9–3.3)	0.61 (0.55–0.69)
40+	94	1.2 (1.0–1.4)	103	1.2 (1.1–1.3)	128	1.4 (1.2–1.6)	124	1.3 (1.2–1.4)	1.07 (0.89–1.29)
All ages	1142	6.1 (5.8–6.4)	1038	5.3 (5.2–5.5)	985	4.9 (4.6–5.1)	616	2.9 (2.8–3.0)	0.47 (0.45–0.50)
Age standardized	–	5.7 (5.6–5.9)	–	5.1 (5.0–5.3)	–	4.8 (4.7–5.0)	–	2.9 (2.8–3.0)	0.50 (0.48–0.53)
All varicella-related									
<1	208	83.3 (74.3–93.1)	149	59.6 (54.9–64.5)	162	63.4 (56.7–70.7)	83	29.3 (26.4–32.5)	0.35 (0.30–0.41)
1–4	636	61.3 (57.5–65.3)	489	47.5 (45.5–49.8)	357	34.7 (32.2–37.3)	154	14.2 (13.2–15.3)	0.23 (0.21–0.26)
5–9	261	19.5 (17.7–21.7)	181	13.4 (12.5–14.5)	174	13.0 (11.7–14.5)	112	8.3 (7.7–9.1)	0.43 (0.37–0.49)
10–19	177	6.8 (6.0–7.7)	129	4.7 (4.4–5.2)	122	4.4 (3.9–5.0)	86	3.0 (2.7–3.4)	0.44 (0.38–0.52)
20–39	489	8.6 (8.0–9.2)	415	7.3 (7.0–7.7)	429	7.4 (6.9–7.9)	272	4.4 (4.2–4.7)	0.52 (0.47–0.57)
40+	161	2.1 (1.9–2.4)	174	2.0 (2.0–2.3)	213	2.3 (2.2–2.7)	237	2.4 (2.3–2.6)	1.19 (1.03–1.37)
All ages	1933	10.3 (10.0–10.7)	1536	7.9 (7.7–8.1)	1455	7.2 (7.0–7.5)	946	4.4 (4.3–4.6)	0.43 (0.41–0.45)
Age standardized	–	9.7 (9.5–9.9)	–	7.6 (7.5–7.9)	–	7.1 (7.0–7.4)	–	4.4 (4.3–4.6)	0.46 (0.44–0.47)

CI: confidence interval; IRR: incidence rate ratio.

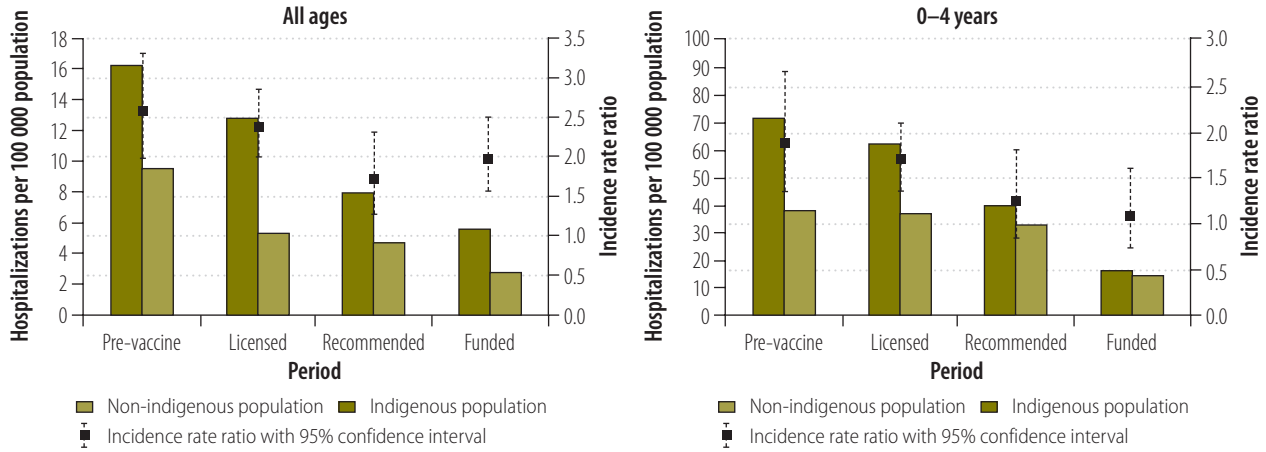
[a] Average annual number of hospitalizations.

[b] Average annual hospitalization rate per 100 000 population.

[c] The ratio between funded period rate and the pre-vaccine period rate.

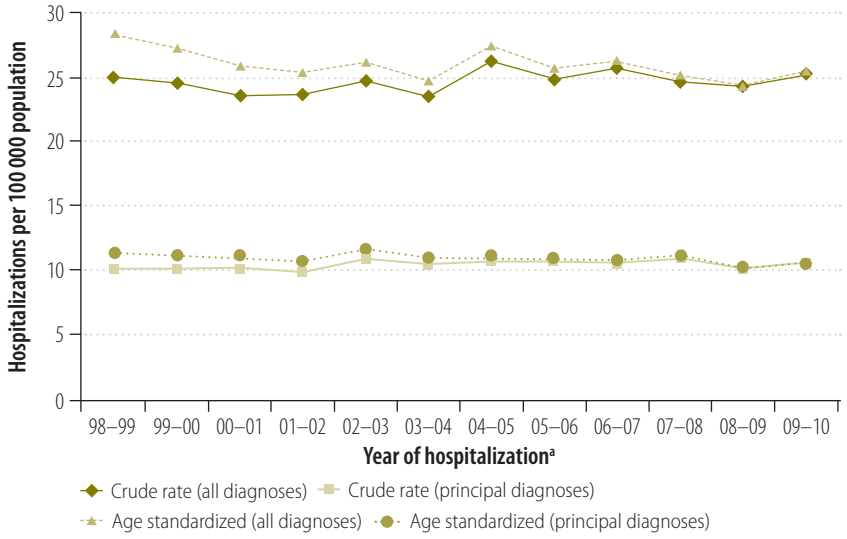
Note: Totals may not add up due to rounding.

Fig. 2. **Varicella hospitalization rates[a] (principal diagnosis) and incidence rate ratios for indigenous and non-indigenous population by varicella vaccine availability and age group in four Australian jurisdictions,[b] July 1998 to June 2010**



[a] Average annual hospitalization rate per 100 000 population.
[b] Western Australia, South Australia, Northern Territory and Queensland.

Fig. 3. **Annual crude and age-standardized hospitalization rates for herpes zoster, Australia, 1998 to 2010**



[a] Australian financial year from 1 July to 30 June.

ern Ireland recently decided to fund an HZ immunization programme, but rejected a population-based varicella vaccination based on concerns about breakthrough varicella, a potential shift in varicella to older age groups and potential increases in HZ.[18] However, we found no evidence for a shift in varicella hospitalization to older age groups in Australia after the implementation of universal varicella vaccination. Instead, we observed significant reductions in varicella hospitalizations for persons younger than 40 years. In line with our results, studies from other countries with universal varicella vaccination have shown marked declines in varicella hospitalizations in both targeted age groups and indirect effects to non-targeted age groups (Table 4). We also observed that the pre-existing twofold disparity in varicella hospitalization between indigenous and non-indigenous children was eliminated under the funded immunization programme. Demonstration of this broad beneficial outcome across population groups in Australia suggests that our experience is likely to be applicable to other countries with disparities in varicella disease.

Our data show evidence of herd immunity during the funded immunization programme. In Australia, similar to other countries, data on adult varicella vaccination coverage is not available. However, it is presumed to be low and would not account for the decline in hospitalizations observed in adults younger than 40 years of age. Our results show more than a 60% decline in hospitalizations for infants – not eligible for vaccination – which can only be attributed to herd immunity effects. This finding is consistent with declines in neonatal (68%) and congenital (79%) varicella from enhanced surveillance both in Australia[26] and in the USA.[22] Furthermore, concerns regarding increased risk of infection during pregnancy[18] are not supported by our results, which show a decline in varicella hospitalizations in the 20–39 year age group which include women of child-bearing age. Furthermore, data from the USA one-dose programme show declines in hospitalisations across all age groups and no upward age shift in varicella hospitalizations.[4,21,27,28] Overall, available data provide evidence that pregnant women and their infants benefitted from a universal childhood varicella vaccination programme due to herd immunity effects.

It was estimated that an Australian varicella immunization programme would directly avert 450 hospitalizations annually, saving up to 21 532 Australian dollars per hospitalization averted.[29] Our results exceeded that prediction, with an average of 686 hospitalizations prevented annually in the first four and a half years of the

Table 3. **Herpes zoster-coded hospitalizations during the periods of different varicella vaccine availability, Australia, July 1998 to June 2010**

Age (years)	HZ hospitalization								
	Pre-vaccine period		Vaccine licensed period		Vaccine recommended period		Vaccine funded period		IRR[c] (95% CI)
	No.[a]	Rate[b] (95% CI)	No.[a]	Rate[b] (95% CI)	No.[a]	Rate[b] (95% CI)	No.[a]	Rate[b] (95% CI)	
Principal HZ									
0–4	19	1.5 (1.0–2.2)	27	2.1 (1.7–2.5)	20	1.5 (1.1–2.1)	14	1.0 (0.8–1.3)	0.69 (0.45–1.07)
5–19	71	1.8 (1.5–2.2)	86	2.1 (1.9–2.3)	72	1.7 (1.5–2.1)	75	1.8 (1.6–2.0)	1.00 (0.80–1.24)
20–49	217	2.6 (2.3–2.9)	226	2.6 (2.5–2.8)	229	2.6 (2.4–2.9)	236	2.6 (2.4–2.7)	0.99 (0.88–1.13)
50–59	165	7.9 (7.0–9.0)	175	7.5 (6.9–8.1)	206	8.1 (7.3–8.9)	205	7.6 (7.1–8.1)	0.96 (0.83–1.10)
60–69	268	18.7 (16.9–20.6)	255	16.7 (15.7–17.7)	312	18.6 (17.2–20.1)	355	18.4 (17.5–19.3)	0.98 (0.88–1.10)
70–79	581	52.8 (49.4–56.4)	565	48.9 (46.9–51.0)	585	49.9 (47.0–52.8)	535	44.1 (42.3–45.9)	0.83 (0.77–0.90)
80+	547	104.6 (97.5–112.0)	663	109.2 (105.1–113.5)	726	105.7 (100.3–111.2)	814	105.1 (101.7–108.5)	1.00 (0.93–1.08)
All ages	1867	9.9 (9.6–10.3)	1997	10.2 (10.0–10.5)	2148	10.6 (10.3–10.9)	2234	10.4 (10.2–10.6)	1.05 (1.01–1.09)
Age standardized	–	11.0 (10.8–11.2)	–	10.8 (10.6–11.1)	–	10.9 (10.7–11.1)	–	10.4 (10.2–10.6)	0.95 (0.92–0.97)
All HZ-related									
0–4	29	2.3 (1.7–3.1)	36	2.8 (2.3–3.3)	25	1.9 (1.4–2.5)	19	1.4 (1.1–1·7)	0.62 (0.43–0.89)
5–19	119	3.0 (2.6–3.5)	126	3.1 (2.8–3.4)	119	2.9 (2.5–3.3)	116	2.8 (2.5–3.0)	0.92 (0.77–1.09)
20–49	502	6.0 (5.5–6.4)	479	5.6 (5.3–5.9)	495	5.6 (5.3–6.0)	465	5.1 (4.8–5.3)	0.85 (0.78–0.92)
50–59	366	17.6 (16.2–19.2)	398	17.0 (16.2–17·8)	468	18.3 (17.2–19.6)	441	16.4 (15.7–17.1)	0.93 (0.85–1.02)
60–69	664	46.3 (43.4–49.2)	592	38.7 (37.2–40.3)	709	42.3 (40.1–44.6)	818	42.4 (41.0–43.8)	0.92 (0.86–0.98)
70–79	1422	129.3 (123.9–134.9)	1390	120.2 (117.1–123.4)	1367	116.5 (112.2–121.0)	1286	105.9 (103.2–108.7)	0.82 (0.78–0.86)
80+	1550	296.1 (284.2–308.4)	1644	271.0 (265.4–277.6)	1926	280.4 (271.6–289.4)	2104	271.5 (266.1–277.1)	0.92 (0.88–0.96)
All ages	4652	24.8 (24.2–25.4)	4664	23.9 (23.5–24.2)	5107	25.2 (24.7–25.7)	5251	24.5 (24.2–24.8)	0.99 (0.96–1.02)
Age standardized	–	27.8 (27.4–28.1)	–	25.4 (25.1–25.8)	–	26.0 (25.7–26.3)	–	24.5 (24.2–24.8)	0.88 (0.87–0.90)

CI: confidence interval; HZ: herpes zoster; IRR: incidence rate ratio.
[a] Average annual number of hospitalizations.
[b] Average annual hospitalization rate per 100 000 population.
[c] The ratio between funded period rate and the pre-vaccine period rate.
Note: Totals may not add up due to rounding.

Table 4. **Published studies[a] on varicella hospitalizations before and after funded one-dose varicella immunization programmes**

Site	Data source and data type (pre-vaccine versus funded period)	One-dose vaccine coverage funded period (%)[b]	Age group (years)	Pre-vaccine hospitalization rate (95% CI)[c,d]	Funded programme hospitalization rate (95% CI)[c,d]	Per cent reduction in hospitalization % (95% CI)[d]
Australia (this study)	National hospital database, principal diagnosis population rates (1998–1999 versus 2006–2010)	74.8–83.2	All 1–4	6.1 (5.8–6.4) 34.0 (31.1–37.0)	2.9 (2.8–3.0) 9.4 (8.5–10.3)	52.7 (49.8–55.5) 72.5 (68.8–75.7)
Victoria, Australia[19]	State-wide hospital database, principal diagnosis population rates (1995–1999 versus 2006–2007)	~70 000[e]	All 0–4	4.0 (3.8–4.2) 21.0 (18.9–23.2)	3.1 (2.6–3.7) 12.9 (11.4–14.2)	22.5 38.6
New South Wales, South Australia, Victoria, Western Australia, Australia[20]	Active surveillance at four paediatric hospitals, all-varicella diagnoses hospitalization count (1999–2001 versus 2007–2010)	ND	0–15	598[f]	160[f]	73.2
USA[4]	NHDS, estimated principal diagnosis population rates (1993–1995 versus 1996–2004)	ND	All 0–4	15.9 (11.3–20.5) 42.9 (19.6–66.3)	7.0 (5.4–8.5) 15.3 (8.0–22.6)	56[g] 64.3[g]
USA[21]	NHDS, estimated all-varicella diagnoses population rates (1988–1995 versus 2000–2006)	> 65	All 0–4	4.2 (3.3–5.0) 25	1.2 (0.8–1.6) 7	71[g] 72
USA[22]	MarketScan database, all-varicella diagnoses. Rate per enrolee (1994–1995 versus 2001–2002)	81	0–49 < 10	2.3 9.9	0.3 0·9	88 91
Ontario, Canada[23]	State-wide hospital database, all-varicella diagnoses, population rates (1992–1998 versus 2004–2007)	> 200 000[h]	All < 1 1–4	4.0 (3.9–4.2) 39.4 (35.7–43.5) 6.7 (25.2–28.3)	1.7 (1.6–1.9) 18.6 (13.7–24.5) 10.2 (8.4–12.3)	57 (53–62) 53 (39–67) 62 (54–69)
Canada[24]	National paediatric active hospital surveillance, all-varicella diagnoses hospitalization count					
5 provinces	(2000–2001 versus 2008)	ND	0–16	59[j]	7[j]	88
8 provinces	(2004–2007 versus 2008)	ND	0–16	263[j]	51[j]	81
Veneto, Italy[25]	Regional hospital database, all-varicella diagnoses, population rates (2000 versus 2008)	78.6	0–14	18.7	8.4	55.1

CI: confidence interval; ND: not determined; NHDS: National Hospital Discharge Survey.

[a] Studies of national population-based hospitalizations or multi-site sentinel hospital-based surveillance in countries with universal funded varicella vaccination programmes and reporting pre-vaccine and post-funding rates or counts.

[b] Reported coverage by 12–35 months of age (reported age range differs by country). Vaccine sales data presented where coverage not reported.

[c] Rate per 100 000 population for principal hospitalizations unless otherwise stated.

[d] Not all studies reported a confidence interval.

[e] Represents 2008 sales, which were greater than the birth cohort that year.

[f] Values represent total patients during the period.

[g] No confidence intervals were reported for the reduction in hospitalization.

[h] Represents the annual sales between 2004–2007, which were greater than the annual birth cohorts.

[i] Values represent patients/year.

funded programme. A re-evaluation of programme cost-effectiveness, including herd immunity effects, is therefore warranted. Funded catch-up vaccination is likely to be central to reducing the pool of susceptible adolescents and adults for whom varicella disease outcomes are more severe.[30] However, few countries that have implemented a universal varicella vaccination programme have also implemented formal catch-up programmes. In our adolescent programme, the uptake matched our expectations, based on varicella seroprevalence data indicating more than 80% seropositivity in individuals aged 10–14 years before the vaccine was available.[1,14] We also show incremental increases in coverage between 24 and 60 months of age, which indicate lack of timeliness and suggest uptake may be prompted by vaccination requirements at the time of school or childcare entry. The importance of vaccine availability

Table 5. **Published studies[a] on all ages herpes zoster hospitalization rates before and after funded one-dose varicella immunization programmes**

Site	Data source and data type (pre-vaccine versus funded period)	Pre-vaccine hospitalization rate (95% CI)[b,c]	Funded programme hospitalization rate (95% CI)[b,c]	Per cent change in hospitalizations (95% CI)[c]
Australia (this study)	National hospital database, age-standardized population rates (1998–1999 versus 2006–2010)	11.0 (10.8–11.2)	10.4 (10.2–10.6)	−5.3 (2.6–7.8)
Victoria, Australia[19]	State-wide hospital database, population rates (1995–1999 versus 2006–2007)	13.4 (12.6–14.1)	20.5 (20.0–21.0)	+34.6 ($P < 0.05$)
USA[34]	Nationwide inpatient sample, estimated population rates (1993–1995 versus 2004)	ND	25 (23.8–26.2)	$P < 0.05$ increase
Ontario, Canada[23]	State-wide hospital database, age-standardized population rates (1992 versus 2009)	8.7	4.1	−53

CI: confidence interval; ND: not determined.
[a] Studies of national population-based hospitalizations in countries with universal funded varicella vaccination programmes and reporting pre-vaccine and post-funding rates.
[b] Rate per 100 000 population for all zoster-related hospitalizations.
[c] Not all studies reported confidence intervals, some reported *P*-values.

for older children has been emphasized in progressively expansive catch-up recommendations in the USA.[3] Similar to data from Ontario, Canada,[23] we observed that a low universal vaccination coverage during the recommended but unfunded period had a minimal effect on the reported disease burden which was limited to the target age group. Accomplishing a rapid, high vaccination coverage and mechanisms for catch-up appear to be important components of a successful one-dose funded universal immunization programme.

Modelling studies have predicted higher HZ incidence among unvaccinated previously infected individuals (based on absence of immune boosting from exposure to circulating varicella zoster virus).[30] Instead, we show that age-adjusted and age-specific HZ hospitalization rates did not increase over time, despite a high varicella vaccination coverage in Australia for almost five years. Our coverage approached the 90% coverage included in studies modelling the impact of varicella vaccination on the epidemiology of varicella and HZ. This is the scenario that is included in studies modelling the impact of varicella vaccination on the epidemiology of varicella and HZ.[30–32] Some epidemiological studies have reported temporal increases in the crude HZ hospitalization rates.[19,33] However, only two other studies have assessed trends in age-standardized HZ rates before and after vaccine introduction, including hospitalizations and health care utilization, and showed no temporal increase in HZ (Table 5).[35,36]

Increasing age is the greatest risk factor for VZV reactivation, due to age-related decline in cellular immunity, high prevalence of chronic disease and use of immune-compromising medication.[37] HZ hospitalization rates in persons older than 80 years are more than twice that of persons aged 70–79 years. Over the study period, the percentage of the Australian population over 80 years of age increased from 2.8% to 3.7%.[13] Statistical adjustments for ageing populations are required in epidemiological studies to adequately determine temporal changes in HZ. A combined childhood varicella and older adult HZ vaccination programme is a potential comprehensive strategy for the prevention of VZV disease in the entire population, and vaccination against HZ has been recommended for Australians aged over 60 years.[8] However, due to manufacturer supply issues, virtually no HZ vaccine has been available and there is currently no funding from the national immunization programme.

The strengths of our study include the use of comprehensive national population-based databases: 12 years of hospital admissions data, not limited by under-reporting, sampling or regional differences; and national vaccine coverage data where under-reporting for immunization programme-funded vaccines is minimal.[12] Although several studies[4,19–21,23–25,27,28] have demonstrated the early effect of a universal varicella immunization programme (Table 4), we included national data assessing both population-adjusted varicella and HZ over the pre- and post-programme periods. We used principal-coded hospitalizations, which potentially underestimates the total hospitalized disease burden, but reduces reporting of incidental hospitalizations and miscoding and is therefore likely to be a more accurate method than the use of all HZ-related hospitalizations. Although this is an ecological study, there is no evidence that other factors that could affect hospitalization rates have changed over time, such as better access to health care or changes in hospital admissions or coding practices. The high positive predictive value (95.7%) for varicella coding demonstrated in a hospitalized Australian paediatric population[38] supports the robustness of using varicella-coded data. However, varicella hospitalization data in older adults may be limited by miscoding of HZ.[35] The majority of HZ-related hospitalizations are likely to have been complicated by complex co-morbidities, particularly in the frail elderly and/or immunocompromised populations and may not reflect the principal cause for admission.[39]

Our study is limited to the inclusion of VZV infection requiring hospitalization. Varicella results in severe morbidity in only a minority of cases, for which hospitalization is a proxy measure. While the risk of complications is greater in adults and children with

immunocompromising conditions, the highest absolute numbers of varicella hospitalizations are in otherwise healthy children.[38] Approximately 2% of cases in children younger than two years require hospitalization.[40] Hospitalization rates for HZ are two to four times the rate for varicella.[41] VZV-related disease also significantly impacts health care utilization at the primary care level, but this was not assessed in our study. Assessing trends in non-hospitalized VZV disease will become more important as Australia's varicella immunization programme matures, including monitoring outbreaks and breakthrough varicella.

Although one-dose programmes have been effective in preventing severe varicella disease, as further confirmed by our study, evidence suggests that a two-dose schedule is required to interrupt virus transmission. Ongoing school outbreaks and high rates of breakthrough varicella, although usually mild, have prompted some countries to implement a two-dose schedule.[3,6] A submission to fund two-dose varicella vaccination under the Australian National Immunization Programme was rejected in 2008 due to uncertainty regarding the incremental cost-effectiveness of the second dose.[42] However, emerging data on further declines during the two-dose programme in the USA[43,44] and recent evidence indicating that breakthrough varicella was almost seven times less likely to occur in two- compared with one-dose vaccine recipients[45] provide empirical evidence of the potential benefits of a two-dose schedule.

This study is a comprehensive analysis of national Australian population-based data comparing both varicella and HZ hospitalizations during periods of varicella vaccine availability, using robust national vaccine coverage data and the largest study reporting experience with Varilrix®. There are several differences in the approach to implementing varicella vaccination programmes internationally, including the age at vaccination, one or two-dose schedules, and inclusion of catch-up vaccination.

Australia's experience with a one-dose funded varicella vaccination programme with rapidly attained high coverage is relevant to countries considering a universal programme. The beneficial outcome of the vaccination programme is expected to increase as the programme matures and re-examination of the cost-effectiveness of incorporating a second dose may be warranted over time. ■

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ملخص

حالات الإدخال إلى المستشفى جراء الإصابة بالحماق والهربس النطاقي قبل تنفيذ تطعيم الحماق أحادي الجرعة في أستراليا وبعده: دراسة بيئية

الغرض دراسة الاتجاهات في الإدخال إلى المستشفى جراء الإصابة بالحماق والهربس النطاقي بعد إتاحة تطعيم الحماق أحادي الجرعة عن طريق التمويل من برنامج التمنيع الوطني لهذا التطعيم في أستراليا وبعده.

الطريقة تم الحصول على التغطية بتطعيم الحماق للأطفال مواليد الفترة من 2001 إلى 2009 من سجل تمنيع الطفولة الأسترالي. وتم استرجاع حالات الإدخال إلى المستشفى جراء الإصابة بالحماق أو الهربس النطاقي الرئيسية أو المرمزة من قاعدة بيانات المراضة بالمستشفيات الوطنية في الفترة من عام 1998 إلى عام 2010. وتم تقييم الاتجاهات في معدلات الإدخال إلى المستشفى في مختلف الفئات العمرية وحالة الأطفال من السكان الأصليين. وتم حساب نسب معدل الإصابة بين الفترات قبل تنفيذ تمويل برنامج التمنيع وبعده.

النتائج وصلت التغطية بلقاح الحماق في العام الأول من برنامج التمنيع الممول إلى 75 ٪ في الأطفال الذين يبلغ عمرهم 24 شهراً وما يزيد عن 80 ٪ في الأطفال الذين يبلغ عمرهم 60 شهراً. ومقارنة بفترة ما قبل التطعيم، انخفضت معدلات الإدخال إلى المستشفى جراء الإصابة بالحماق خلال البرنامج الممول بدرجة كبيرة في الفئات العمرية الأصغر من 40 عاماً؛ وكان أكبر انخفاض في الأطفال الذين تراوح عمرهم من 18 إلى 59 شهراً (نسبة معدل الإصابة: 0.25؛ فاصل الثقة 95 ٪، فاصل الثقة: 0.22 – 0.29). وازداد معدل الإدخال إلى المستشفى جراء الإصابة بالحماق لدى الأطفال من السكان الأصليين مقارنة بالأطفال من السكان غير الأصليين قبل تنفيذ التطعيم (نسبة معدل الإصابة: 1.9؛ فاصل الثقة 95 ٪، فاصل الثقة: 1.4 – 2.7) غير أنه وصل بعدها إلى التكافؤ (نسبة معدل الإصابة: 1.1؛ فاصل الثقة 95 ٪، فاصل الثقة: 0.7 – 1.6). وانخفض معدل الإدخال إلى المستشفى جراء الإصابة بالهربس النطاقي الموحد حسب السن بين الفترات (نسبة معدل الإصابة: 0.95؛ فاصل الثقة 95 ٪، فاصل الثقة: 0.92 – 0.97).

الاستنتاج أدى الوصول السريع للتغطية المرتفعة إلى تقليل حالات الإدخال إلى المستشفى جراء الإصابة بالحماق في الفئة العمرية المستهدفة، لا سيما لدى الأطفال من السكان الأصليين، وكذلك في الفئات العمرية غير المستهدفة، مع عدم زيادة في حالات الإدخال إلى المستشفى جراء الإصابة بالهربس النطاقي. ويشير هذا إلى وجود أثر كبير للتغطية المرتفعة بلقاح الحماق أحادي الجرعة على حالات المرض الحادة.

摘要

澳大利亚实施一剂水痘疫苗接种之前和之后水痘和带状疱疹的住院情况：生态研究

目的 研究澳大利亚在提供一剂水痘疫苗接种和获得后续国家免疫规划资助之后水痘和带状疱疹 (HZ) 住院治疗趋势。

方法 从澳大利亚儿童免疫登记处获取 2001 年至 2009 年间出生的儿童水痘疫苗接种覆盖率。从国立医院发病率数据库检索 1998 年到 2010 年主要或任何编码水痘或 HZ 住院情况。对不同年龄组和原住状态的住院率趋势进行了评估。计算实施免疫规划资助之前和之后的发病率比率 (IRR)。

结果 在得到资助的免疫规划的第一年中，在 24 月龄儿童中水痘疫苗覆盖率达到 75%，年龄个 60 个月的儿童则达到 80% 以上。较之接种之前，在资助规划期间，40 岁以下人群中的水痘住院率大大降低，在 18-59 个月的儿童中降低最大 (IRR:0.25;95% 置信区间，CI:0.22 – 0.29)。较之非原住儿童，在实施疫苗之前，原住儿童水痘住院率较高 (IRR:1.9;95% CI:1.4 – 2.7)，但之后则趋于相等 (IRR:1.1;95% CI:0.7 – 1.6)。两个期间之间年龄标准化 HZ 住院率降低 (IRR:0.95;95% CI:0.92 – 0.97)。

结论 快速实现高覆盖率可减少目标年龄群的水痘住院率，原住民儿童尤其如此，在非目标年龄群中也是如此，同时 HZ 住院率没有增加。这表明高的一剂水痘疫苗覆盖率可以对严重疾病产生重大影响。

Résumé

Hospitalisations dues à la varicelle et l'herpès zoster avant et après la mise en œuvre de la vaccination monodose contre la varicelle en Australie: une étude écologique

Objectif Examiner les tendances dans les hospitalisations dues à la varicelle et l'herpès zoster (HZ) après la disponibilité et le financement du programme de vaccination national qui a suivi, pour la vaccination monodose contre la varicelle en Australie.

Méthodes La couverture vaccinale contre la varicelle pour les enfants nés entre 2001 et 2009 a été obtenue à partir du registre australien de vaccination des enfants. Toutes les hospitalisations dues principalement à ou codifiées comme étant dues à la varicelle ou au HZ ont été extraites de la base de données nationale de morbidité hospitalière pour la période 1998–2010. Les tendances dans les taux d'hospitalisation des différents groupes d'âge et le statut d'autochtone ont été évaluées. Les rapports de taux d'incidence (RTI) ont été calculés entre les périodes avant et après la mise en œuvre du financement du programme de vaccination.

Résultats Pendant la première année du programme financé de vaccination, la couverture vaccinale contre la varicelle a atteint 75% chez les enfants âgés de 24 mois et plus de 80% chez les enfants âgés de 60 mois. Par rapport à la période prévaccinale, les taux d'hospitalisation due à la varicelle pendant le programme financé étaient significativement plus faibles dans les groupes d'âges de moins de 40 ans; avec la plus grande réduction chez les enfants âgés de 18-59 mois (RTI: 0,25; intervalle de confiance de 95%, IC 95%: 0,22–0,29). Les enfants autochtones avaient un taux d'hospitalisation due à la varicelle plus élevé que les enfants non autochtones avant la mise en œuvre du vaccin (RTI: 1,9; IC 95%: 1,4–2,7), mais ce taux est devenu équivalent par la suite (RTI: 1,1; IC 95%: 0,7–1,6). Le taux d'hospitalisation due au HZ normalisé selon l'âge a baissé entre les deux périodes (RTI: 0,95; IC 95%: 0,92–0,97).

Conclusion La réalisation rapide de la couverture élevée a réduit le nombre d'hospitalisations dues à la varicelle dans le groupe d'âge ciblé, en particulier pour les enfants autochtones, mais également dans les groupes d'âge non ciblés, sans augmentation du nombre d'hospitalisations dues au HZ. Cela suggère que la couverture vaccinale monodose contre la varicelle peut avoir un impact important sur cette maladie grave.

Резюме

Госпитализации из-за ветряной оспы и опоясывающего герпеса до и после однодозной схемы вакцинации против ветряной оспы в Австралии: экологическое исследование

Цель Изучить тенденции в госпитализации из-за ветряной оспы и опоясывающего герпеса (ОГ) после выделения текущего и последующего финансирования в рамках Национальной программы иммунизации для однодозовой схемы вакцинации против ветряной оспы в Австралии.

Методы Данные об охвате вакцинацией против ветряной оспы детей, родившихся в период с 2001 по 2009 гг, были получены из Австралийского реестра иммунизации детей. Основные или иные кодированные сведения о госпитализации из-за ветряной оспы и ОГ были взяты из национальной базы данных о заболеваемости в больницах в период с 1998 по 2010 гг. Была проведена оценка тенденций в сфере госпитализации представителей разных возрастных групп и лиц с разным статусом принадлежности к коренному населению. Сотношения коэффициентов заболеваемости (СК3) были рассчитаны за периоды до и после выделения финансирования в рамках программы иммунизации.

Результаты В первый год реализации финансируемой программы иммунизации охват вакцинацией против ветряной оспы достиг 75% детей в возрасте 24 месяцев и более 80% детей в возрасте 60 месяцев. По сравнению с периодом до вакцинации показатели госпитализации из-за ветряной оспы в период реализации финансируемой программы были значительно ниже для возрастных групп в возрасте до 40 лет; при этом наибольшее снижение показателя выявлено у детей в возрасте 18-59 месяцев (СК3: 0,25; 95%-й доверительный интервал (ДИ): 0,22-0,29). У детей коренных народов отмечался более высокий уровень госпитализации из-за ветряной оспы по сравнению с детьми некоренного населения до проведения вакцинации (СК3: 1,9; 95% ДИ: 1,4-2,7), но впоследствии был достигнут паритет (СК3: 1,1; 95% ДИ: 0,7-1,6). Нормализованный с учетом возраста показатель госпитализации из-за ОГ снизился между указанными периодами (СК3: 0,95; 95% ДИ: 0,92-0,97).

Вывод Быстрое достижение высокого уровня охвата привело к снижению показателя госпитализаций из-за ветряной оспы не только в целевой возрастной группе, особенно в группе детей

коренных народов, но и в нецелевых возрастных группах, без увлечения числа госпитализаций из-за ОГ. Это указывает на то, что высокий охват однодозовой вакциной против ветряной оспы может оказывать существенное положительное влияние на противодействие этому тяжелому заболеванию.

Resumen

Hospitalizaciones por varicela y herpes zóster antes y después de la implementación de la vacunación monodosis de la varicela en Australia: un estudio ecológico

Objetivo Examinar las tendencias de la hospitalización por varicela y herpes zóster (HZ) siguiendo la disponibilidad y la subsecuente financiación del Programa Nacional de Vacunación de la vacuna monodosis de la varicela en Australia.

Métodos La cobertura de la vacunación contra la varicela para los niños nacidos entre 2001 y 2009 se obtuvo del Registro Australiano de Vacunación Infantil (Australian Childhood Immunization Register). Las hospitalizaciones por varicela o HZ principales o codificadas fueron sacadas de la base de datos del hospital nacional sobre morbilidad en el periodo comprendido entre 1998 y 2010. Se evaluarion las tendencias de las tasas de hospitalización en diferentes grupos de edad y estados indígenas. Las tasas de incidencia (TI) se calcularon entre los periodos previos y posteriores a la implementación de la financiación del programa de vacunación.

Resultados En el primer año del programa de vacunación financiado, la cobertura de la vacuna de la varicela llegó al 75% en los niños de 24 meses y a más del 80% en los niños de 60 meses. En comparación con el periodo previo a las vacunas, las tasas de hospitalización por varicela durante el programa financiado fueron significativamente menores en grupos de edad menores de 40 años, con la reducción más importante en los niños de entre 18–59 meses (TI: 0,25; 95% intervalo de confianza, IC: 0,22–0,29). Los niños indígenas tenían una tasa de hospitalización por varicela más alta que los no indígenas antes de la implementación de la vacuna (TI: 1,9; 95% IC: 1,4–2,7), pero tras esta se alcanzó una igualdad (TI: 1,1; 95% IC: 0,7–1,6). La tasa de hospitalización por herpes zóster estandarizada por edad disminuyó entre los periodos (TI: 0,95; 95% IC: 0,92–0,97).

Conclusión La rápida consecución de la cobertura alta redujo las hospitalizaciones por varicela en el grupo de edad al que se dirigía, especialmente en niños indígenas aunque también en grupos de edad a los que no iba dirigido, sin incrementar las hospitalizaciones por herpes zóster. Esto sugiere que la cobertura de la vacuna monodosis de la varicela puede tener un impacto importante en la grave enfermedad.

References

1. Gidding HF, MacIntyre CR, Burgess MA, Gilbert GL. The seroepidemiology and transmission dynamics of varicella in Australia. Epidemiol Infect. 2003;131(3):1085–9. doi: http://dx.doi.org/10.1017/S0950268803001134 PMID: 14959774
2. WHO vaccine-preventable diseases: monitoring system. 2014 global summary [Internet]. Geneva: World Health Organization; 2014. Available from: http://apps.who.int/immunization_monitoring/globalsummary/schedules [cited 2013 Oct 24].
3. Marin M, Güris D, Chaves SS, Schmid S, Seward JF. Advisory Committee on Immunization Practices, Centers for Disease Control and Prevention (CDC). Prevention of varicella: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2007;56(RR-4):1-40.
4. Shah SS, Wood SM, Luan X, Ratner AJ. Decline in varicella-related ambulatory visits and hospitalizations in the United States since routine immunization against varicella. Pediatr Infect Dis J. 2010;29(3):199–204. doi: http://dx.doi.org/10.1097/INF.0b013e3181bbf2a0 PMID: 19949362
5. Nguyen HQ, Jumaan AO, Seward JF. Decline in mortality due to varicella after implementation of varicella vaccination in the United States. N Engl J Med. 2005;352(5):450–8. doi: http://dx.doi.org/10.1056/NEJMoa042271 PMID: 15689583
6. Wiese-Posselt M, Hellenbrand W. Changes to the varicella and pertussis immunisation schedule in Germany 2009: background, rationale and implementation. Euro Surveill. 2010;15(16) PMID: 20429999
7. SAGE Working Group on Varicella and Herpes Zoster Vaccines [Internet]. Geneva: World Health Organization; 2012. Available from: http://www.who.int/immunization/sage/sage_wg_varicella_zoster_may12/en/index.html [cited 2012 Dec 18].
8. National Health and Medical Research Council. Australian Technical Advisory Group on Immunisation. The Australian Immunisation Handbook. 10th ed. Canberra: Australian Government Department of Health; 2013.
9. Nolan TM. The Australian model of immunization advice and vaccine funding. Vaccine. 2010;28 Suppl 1:A76–83. doi: http://dx.doi.org/10.1016/j.vaccine.2010.02.038 PMID: 20413003
10. National Health and Medical Research Council. The Australian Immunisation Handbook. 9th ed. Canberra: Australian Government Department of Health; 2003.
11. Menzies R, Turnour C, Chiu C, McIntyre P. Vaccine preventable diseases and vaccination coverage in Aboriginal and Torres Strait Islander people, Australia 2003 to 2006. Commun Dis Intell Q Rep. 2008;32 Suppl:S2–67. PMID: 18711998
12. Hull BP, Deeks SL, McIntyre PB. The Australian Childhood Immunisation Register – A model for universal immunisation registers? Vaccine. 2009;27(37):5054–60. doi: http://dx.doi.org/10.1016/j.vaccine.2009.06.056 PMID: 19576945
13. 3201.0 Population by age andsSex, Australian states and territories, June 2010 [Internet]. Canberra: Australian Bureau of Statistics; 2010. Available from http://www.abs.gov.au/AUSSTATS/abs@.nsf/Lookup/3201.0Main+Features1Jun%2010?OpenDocument [cited 2014 May 2].
14. Ward K, Dey A, Hull B, Quinn HE, Macartney K, Menzies R. Evaluation of Australia's varicella vaccination program for children and adolescents. Vaccine. 2013;31(10):1413–9. doi: http://dx.doi.org/10.1016/j.vaccine.2012.12.052 PMID: 23290837
15. Australian hospital statistics 2007-08. AIHW Cat. no. HSE 71. Canberra: Australian Institute of Health and Welfare; 2009.
16. 3238.0 Experimental Estimates and Projections, Aboriginal and Torres Strait Islander Australians, 1991 to 2021. Canberra: Australian Bureau of Statistics; 2009. Available from: http://www.abs.gov.au/Ausstats/abs@.nsf/0/A03584675FA93CECCA25762A001D0701 [cited 2014 Mar 13].
17. Sengupta N, Booy R, Schmitt HJ, Peltola H, Van-Damme P, Schumacher RF, et al. Varicella vaccination in Europe: are we ready for a universal childhood programme? Eur J Pediatr. 2008;167(1):47–55. doi: http://dx.doi.org/10.1007/s00431-007-0424-0 PMID: 17334784
18. Joint Committee on Vaccination and Immunisation: Statement on varicella and herpes zoster vaccines. London: the National Archives; 2010. Available from: http://webarchive.nationalarchives.gov.uk/20130107105354/http:/www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@ab/documents/digitalasset/dh_133599.pdf [cited 2014 Mar 13].
19. Carville KS, Riddell MA, Kelly HA. A decline in varicella but an uncertain impact on zoster following varicella vaccination in Victoria, Australia. Vaccine. 2010;28(13):2532–8. doi: http://dx.doi.org/10.1016/j.vaccine.2010.01.036 PMID: 20117265
20. Marshall HS, McIntyre P, Richmond P, Buttery JP, Royle JA, Gold MS, et al. Changes in patterns of hospitalized children with varicella and of associated varicella genotypes after introduction of varicella vaccine in Australia. Pediatr Infect Dis J. 2013;32(5):530–7. doi: http://dx.doi.org/10.1097/INF.0b013e31827e92b7 PMID: 23249914
21. Lopez AS, Zhang J, Brown C, Bialek S. Varicella-related hospitalizations in the United States, 2000–2006: the 1-dose varicella vaccination era. Pediatrics. 2011;127(2):238–45. doi: http://dx.doi.org/10.1542/peds.2010-0962 PMID: 21199857

22. Chaves SS, Lopez AS, Watson TL, Civen R, Watson B, Mascola L, et al. Varicella in infants after implementation of the US varicella vaccination program. Pediatrics. 2011;128(6):1071–7. doi: http://dx.doi.org/10.1542/peds.2011-0017 PMID: 22123875
23. Kwong JC, Tanuseputro P, Zagorski B, Moineddin R, Chan KJ. Impact of varicella vaccination on health care outcomes in Ontario, Canada: effect of a publicly funded program? Vaccine. 2008;26(47):6006–12. doi: http://dx.doi.org/10.1016/j.vaccine.2008.08.016 PMID: 18761386
24. Tan B, Bettinger J, McConnell A, Scheifele D, Halperin S, Vaudry W , et al. The effect of funded varicella immunization programs on varicella-related hospitalizations in IMPACT centers, Canada, 2000-2008. Pediatric Infectious Disease Journal 2012; 31(9): 956-63
25. Pozza F, Piovesan C, Russo F, Bella A, Pezzotti P, Emberti Gialloreti L. Impact of universal vaccination on the epidemiology of varicella in Veneto, Italy. Vaccine. 2011;29(51):9480–7. doi: http://dx.doi.org/10.1016/j.vaccine.2011.10.022 PMID: 22015389
26. Khandaker G, Marshall H, Peadon E, Zurynski Y, Burgner D, Buttery J, et al. Congenital and neonatal varicella: impact of the national varicella vaccination programme in Australia. Arch Dis Child. 2011;96(5):453–6. doi: http://dx.doi.org/10.1136/adc.2010.206037 PMID: 21349886
27. Reynolds MA, Watson BM, Plott-Adams KK, Jumaan AO, Galil K, Maupin TJ, et al. Epidemiology of varicella hospitalizations in the United States, 1995–2005. J Infect Dis. 2008;197(s2) Suppl 2:S120–6. doi: http://dx.doi.org/10.1086/522146 PMID: 18419384
28. Zhou F, Harpaz R, Jumaan AO, Winston CA, Shefer A. Impact of varicella vaccination on health care utilization. JAMA. 2005;294(7):797–802. doi: http://dx.doi.org/10.1001/jama.294.7.797 PMID: 16106004
29. Scuffham PA, Lowin AV, Burgess MA. The cost-effectiveness of varicella vaccine programs for Australia. Vaccine. 1999;18(5-6):407–15. doi: http://dx.doi.org/10.1016/S0264-410X(99)00261-3 PMID: 10519929
30. Gidding HF, Brisson M, Macintyre CR, Burgess MA. Modelling the impact of vaccination on the epidemiology of varicella zoster virus in Australia. Aust N Z J Public Health. 2005;29(6):544–51. doi: http://dx.doi.org/10.1111/j.1467-842X.2005.tb00248.x PMID: 16366065
31. Gao Z, Gidding HF, Wood JG, MacIntyre CR. Modelling the impact of one-dose vs. two-dose vaccination regimens on the epidemiology of varicella zoster virus in Australia. Epidemiol Infect. 2010;138(4):457–68. doi: http://dx.doi.org/10.1017/S0950268809990860 PMID: 19781116
32. Brisson M, Edmunds WJ, Gay NJ, Law B, De Serres G. Modelling the impact of immunization on the epidemiology of varicella zoster virus. Epidemiol Infect. 2000;125(3):651–69. doi: http://dx.doi.org/10.1017/S0950268800004714 PMID: 11218215
33. Jardine A, Conaty SJ, Vally H. Herpes zoster in Australia: evidence of increase in incidence in adults attributable to varicella immunization? Epidemiol Infect. 2011;139(5):658–65. doi: http://dx.doi.org/10.1017/S0950268810001949 PMID: 20727248
34. Patel MS, Gebremariam A, Davis MM. Herpes zoster-related hospitalizations and expenditures before and after introduction of the varicella vaccine in the United States. Infect Control Hosp Epidemiol. 2008;29(12):1157–63. doi: http://dx.doi.org/10.1086/591975 PMID: 18999945
35. Jumaan AO, Yu O, Jackson LA, Bohlke K, Galil K, Seward JF. Incidence of herpes zoster, before and after varicella-vaccination-associated decreases in the incidence of varicella, 1992–2002. J Infect Dis. 2005 ;191(12):2002–7. doi: http://dx.doi.org/10.1086/430325 PMID: 15897984
36. Tanuseputro P, Zagorski B, Chan KJ, Kwong JC. Population-based incidence of herpes zoster after introduction of a publicly funded varicella vaccination program. Vaccine. 2011;29(47):8580–4. doi: http://dx.doi.org/10.1016/j.vaccine.2011.09.024 PMID: 21939721
37. Schmader K, Gnann JW Jr, Watson CP. The epidemiological, clinical, and pathological rationale for the herpes zoster vaccine. J Infect Dis. 2008;197(s2) Suppl 2:S207–15. doi: http://dx.doi.org/10.1086/522152 PMID: 18419399
38. Carapetis JR, Russell DM, Curtis N. The burden and cost of hospitalised varicella and zoster in Australian children. Vaccine. 2004;23(6):755–61. doi: http://dx.doi.org/10.1016/j.vaccine.2004.07.025 PMID: 15542199
39. Jackson LA, Reynolds MA, Harpaz R. Hospitalizations to treat herpes zoster in older adults: causes and validated rates. Clin Infect Dis. 2008;47(6):754–9. doi: http://dx.doi.org/10.1086/591132 PMID: 18680413
40. Brisson M, Edmunds WJ, Law B, Gay NJ, Walld R, Brownell M, et al. Epidemiology of varicella zoster virus infection in Canada and the United Kingdom. Epidemiol Infect. 2001;127(2):305–14. doi: http://dx.doi.org/10.1017/S0950268801005921 PMID: 11693508
41. de Melker H, Berbers G, Hahné S, Rümke H, van den Hof S, de Wit A, et al. The epidemiology of varicella and herpes zoster in The Netherlands: implications for varicella zoster virus vaccination. Vaccine. 2006;24(18):3946–52. doi: http://dx.doi.org/10.1016/j.vaccine.2006.02.017 PMID: 16564115
42. Public summary document for Measles, mumps, rubella and varicella vaccine, powder for injection vial with diluent syringe, 0.5 mL, Priorix-Tetra©, November 2007 [Internet]. Canberra: Australian Government Department of Health; 2007. Available from: http://www.health.gov.au/internet/main/publishing.nsf/Content/pbac-psd-measles-nov07 [cited 2014 Mar 13].
43. Kattan JA, Sosa LE, Bohnwagner HD, Hadler JL. Impact of 2-dose vaccination on varicella epidemiology: Connecticut–2005–2008. J Infect Dis. 2011;203(4):509–12. doi: http://dx.doi.org/10.1093/infdis/jiq081 PMID: 21199882
44. Bialek SR, Perella D, Zhang J, Mascola L, Viner K, Jackson C, et al. Impact of a routine two-dose varicella vaccination program on varicella epidemiology. Pediatrics. 2013;132(5):e1134–40. doi: http://dx.doi.org/10.1542/peds.2013-0863 PMID: 24101763
45. Prymula R, Bergsaker MR, Esposito S, Gothefors L, Man S, Snegova N, et al. Protection against varicella with two doses of combined measles-mumps-rubella-varicella vaccine versus one dose of monovalent varicella vaccine: a multicentre, observer-blind, randomised, controlled trial. Lancet. 2014;383(9925):1313–24. doi: http://dx.doi.org/10.1016/S0140-6736(12)61461-5 PMID: 24485548