

Changes in Patterns of Hospitalized Children With Varicella and of Associated Varicella Genotypes After Introduction of Varicella Vaccine in Australia

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Background: Varicella in children, although usually mild, can cause hospitalization and rarely death. This study examined patterns of hospitalized children with varicella, and associated varicella genotypes, in 4 tertiary children's hospitals throughout Australia before and after varicella vaccine was introduced.

Methods: We obtained coded data on discharge diagnoses from each hospital before (1999 to 2001) and after (2007 to 2010) varicella vaccine introduction in 2005, adding active surveillance to capture clinical features, complications and immunization history in the latter period. Varicella vesicles were swabbed, and genotyping of varicella strains was performed by real-time polymerase chain reaction amplification.

Results: Overall, a 68% reduction in coded hospitalizations (varicella, 73.2% [$P < 0.001$]; zoster, 40% [$P = 0.002$]) occurred post-vaccine introduction. Of children with detailed clinical data (97 varicella and 18 zoster cases), 46 (40%) were immunocompromised. Only 6 of 32 (19%) age-eligible immunocompetent children were immunized. Complications, most commonly secondary skin infections ($n = 25$) and neurologic conditions ($n = 14$), occurred in 44% of children. There were no deaths; but 3 immunocompetent unimmunized children had severe multiple complications requiring intensive care. All strains genotyped were "wild-type" varicella, with Clade 1 (European origin) predominating.

Conclusions: After the introduction of varicella vaccine, coverage of greater than 80% at 2 years of age was achieved, with varicella hospitalizations reduced by almost 70%. Of hospitalized children age-eligible for varicella vaccine, 80% were unimmunized, including all cases requiring intensive care.

Key Words: varicella, immunization, immunocompromised, hospitalization, pediatric

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Varicella is a highly contagious infection spread by air-borne transmission or contact with vesicle fluid from skin lesions.¹ Varicella is often more severe in immunocompromised children who are at risk of complications due to increasing use of immunosuppressive therapies.^{2,3} In the prevaccine era, more than 5% of children hospitalized with complicated varicella developed long-term sequelae.⁴ Congenital and neonatal varicella are uncommon, but may have severe consequences.⁵ Before the availability of varicella vaccine in Australia from 2001, an estimated 240,000 varicella cases, 1500 hospitalizations and 1–16 deaths from varicella occurred annually.^{6–8} Decline in varicella hospitalizations⁹ and deaths¹⁰ has been observed in the United States, as have reductions in community and hospitalized cases in Australia,¹¹ since introduction of the vaccine.

Two varicella vaccines, Varilrix (GlaxoSmithKline Biologicals, London, UK) and VARIVAX (Merck & Co., Inc., Whitehouse Station, NJ), have been licensed in Australia since 2001. Both contain preparations of the live attenuated Oka strain, first isolated in Japan.⁷ Although varicella vaccine was recommended for universal use in children from 2003,⁷ it was not made available free of charge on Australia's National Immunisation Program until November

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2005. Under the National Immunisation Program, varicella vaccine is available as a single dose for children at 18 months of age or 10–13 years of age, the latter as a school-based program for children who have not previously been infected or immunized.⁷

Accurate surveillance of varicella postvaccine is challenging as disease is common and usually diagnosed clinically rather than by laboratory tests such as viral isolation or nucleic acid testing. Hospitalization data based on discharge diagnoses coded as varicella are available retrospectively,^{8,12} but have limitations and do not include data on immunization status.

In 2007, the Paediatric Active Enhanced Disease Surveillance project was established to conduct active surveillance of children hospitalized with conditions of public health importance, including varicella. The design of the Paediatric Active Enhanced Disease Surveillance project was modeled on the Canadian CPS Immunization Monitoring Program, Active system, but additionally includes capacity to obtain diagnostic specimens after consent.^{13,14}

The occurrence of “vaccine escape” genotypes of varicella is a key question in immunized breakthrough cases,^{15,16} with little information available on the distribution of varicella genotypes and their relationship to virulence in Australia or elsewhere.¹⁷

The aim of this study was to obtain detailed clinical data on varicella cases after introduction of a funded program with high coverage in Australia, for comparison with historical data, with a special focus on immunization status and genotypes of varicella.

MATERIALS AND METHODS

Case Definition and Ascertainment

Active surveillance for varicella was established in major tertiary pediatric hospitals in 4 Australian states (Royal Children’s Hospital, Victoria; The Children’s Hospital at Westmead, New South Wales; Women’s and Children’s Hospital South Australia; and Princess Margaret Hospital for Children, Western Australia, Australia). A research nurse at each hospital prospectively monitored varicella admissions and laboratory requests for inpatient varicella testing for a 3-year period from August 1, 2007, by reviewing admission records and from contact with clinical staff, as described elsewhere.¹⁴

The case definition was hospitalization related to varicella or zoster and age from 1 month to 15 years. Cases were enrolled after parental consent was obtained. Only cases deemed to have in-hospital complications were enrolled in the first year of the study; thereafter ascertainment was expanded to include all hospitalizations. Demographic and clinical data, including medical and immunization history, were verified using the Australian Childhood Immunisation Register (ACIR)¹⁸ and complications identified in hospital were obtained using a standardized questionnaire.

In addition, data on discharge diagnoses with *International Classification of Diseases, 10th revision* codes (B01, B02 and subcategories) at the 4 hospitals during the study period and for a 3-year comparison period (1999 to 2001) before the availability of varicella vaccine in Australia were obtained. The period 1999 to 2001 coincided with a previous study of clinical features of varicella hospitalizations at one of the participating hospitals.¹²

Clinical Specimens

Vesicular fluid was obtained by swabbing the base of a deroofed vesicle. Samples were analyzed at the Center for Infectious Disease and Microbiology Laboratory Services, a State-based reference virology laboratory at Westmead Hospital, Sydney, New South Wales, Australia. Genotyping of varicella strains was conducted by real-time polymerase chain reaction amplification using Evagreen (Biotium, Hayward, CA) on the Corbett Rotor-Gene 6000 (Qiagen, Victoria, Australia). The wild-type strains and

vaccine strain (vOka) were differentiated by single-nucleotide polymorphism detection using high resolution melt analysis of 5 gene targets (Orf1, 21, 37, 60 and 62) and DNA sequence analysis of ORF22, using a method previously described.^{17,19} Varicella-zoster genotypes were classified according to the new universal nomenclature proposed for varicella-zoster virus clades and compared with previously reported circulating varicella genotypes.^{19,20}

Statistical Analysis

Data were analyzed and presented as summary descriptive statistics using Stata (version 10.1; StataCorp, College Station, TX). Comparison of proportions between groups was made using the χ^2 test and Kruskal–Wallis test. Statistical tests were two-tailed with a significance level of 5%.

RESULTS

Hospitalizations Coded as Varicella or Zoster Pre- and Post-vaccine Introduction

In Australia, all children have equal access to the public hospital system through a government-supported fund, Medicare. The number of hospitalizations was stable over the study time period at the 4 participating centers.

In the 4 hospitals, 710 hospital episodes had a discharge diagnosis of varicella (598) or zoster (112) in the 3-year period 1999 to 2001. In the 3 years of active surveillance, 2007 to 2010, after introduction of funded varicella immunization at 18 months of age at the end of 2005, 227 hospital episodes (varicella, 160 and zoster, 67) were identified from *International Classification of Diseases* discharge codes at the same hospitals (Fig. 1). This was a reduction of 73.2% for varicella ($P < 0.001$) and 40% for zoster ($P = 0.002$) hospitalizations. Post-vaccine introduction, 70.5% of total varicella-related hospitalizations were coded as varicella, compared with 84.2% in the prevaccine era ($P < 0.001$).

Characteristics of Study Patients

Of 880 children screened prospectively for varicella or zoster, 137 met the case definition and 115 (varicella, 97 and zoster, 18) were enrolled, which was 60.6% and 26.9% of the number of *International Classification of Diseases*-coded varicella and zoster cases, respectively. The median age of hospitalized children was 6 years and 6 months with a range of 33 days to 15 years and 7 months (interquartile range [IQR]: 2.1–9.0 years; Fig. 2). The median age at diagnosis for varicella was 6 years and 1 month with an age range of 1 month to 15 years and for zoster was 10 years and 9 months with an age range of 4–14 years. There was an equal distribution of males (51%, $n = 59$) and females (49%, $n = 56$).

Children Less Than 18 Months of Age

Twenty-four children (24.7%) too young to be eligible for the funded immunization program were identified—8 were aged 1–6 months, 10 were aged 7–12 months and 6 were aged 13–17 months. The length of stay ranged from 1 to 10 days, and none required admission to an intensive care unit. However, most (79%, $n = 19$) had complications during their hospitalization. These included a 5-month-old infant diagnosed with encephalopathy by the treating physician, and hospitalized for 8 days, and an 8-month-old child who required debridement of infected skin lesions. Two children were immunocompromised, one with neutropenia of unknown cause and the other was postchemotherapy for a neuroblastoma.

Immune Status

Immunodeficiency or immunosuppression after therapy was identified in 46 children (40%) including children with

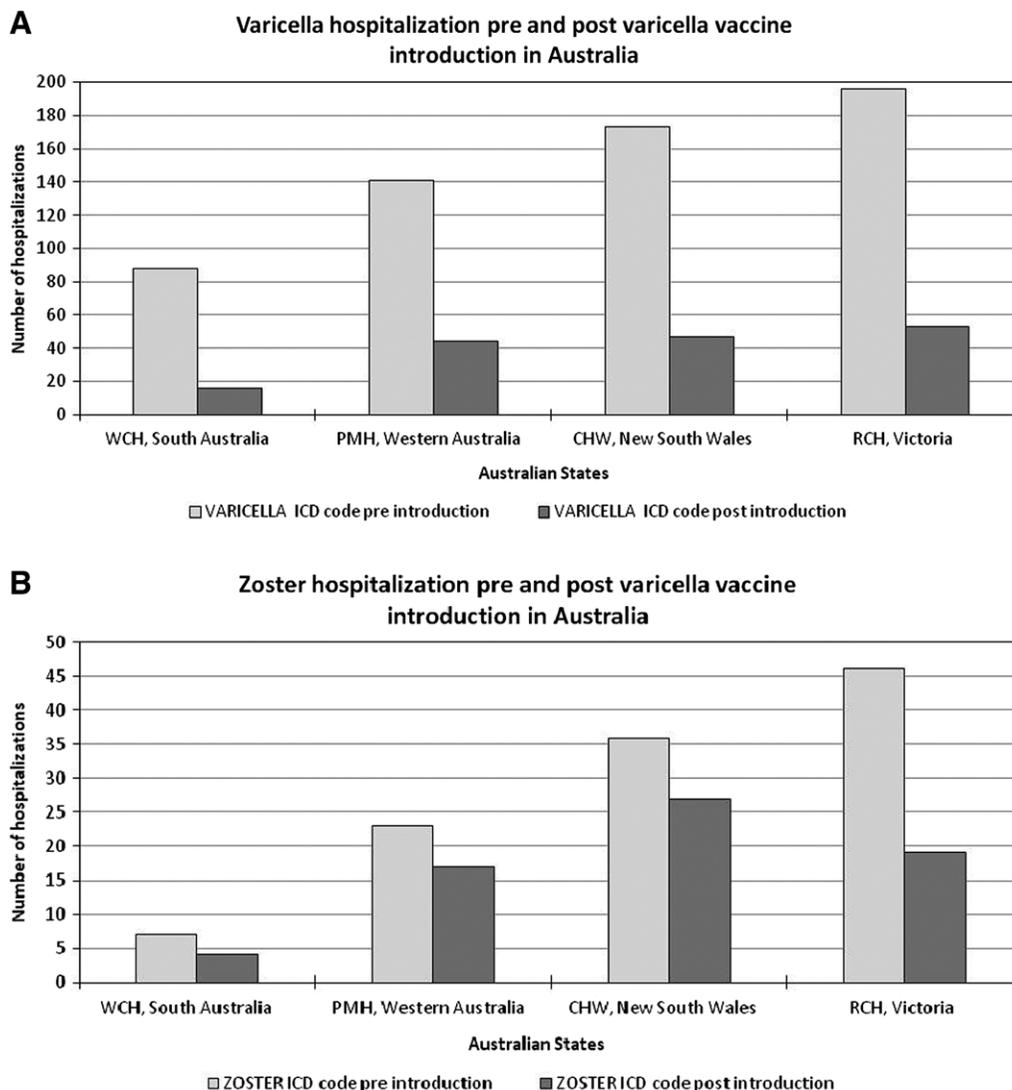


FIGURE 1. (A) Varicella and (B) zoster hospitalizations in the pre- and post-varicella vaccine era as recorded by *International Classification of Diseases, 10th revision (ICD 10)* codes. WCH indicates Women's and Children's Hospital, South Australia; PMH, Princess Margaret Hospital for Children, Western Australia; CHW, The Children's Hospital at Westmead, New South Wales; RCH, Royal Children's Hospital, Victoria.

a malignancy (acute lymphoblastic leukemia, Ewing tumor), receiving chemotherapy, post-bone marrow transplantation or long-term steroid use. These children had a median age of 8.1 years (IQR: 5.4–10.9) and were significantly older than immunocompetent children who had a median age of 5.1 years (IQR: 1.3–7.7; Kruskal–Wallis $P < 0.001$). A higher proportion of children with a diagnosis of zoster (77.8%) were immunodeficient compared with those with varicella (33%).

Varicella Immunization

Confirmed varicella vaccines included Varilrix vaccine ($n = 11$) and VARIVAX vaccine ($n = 1$) in 12 (10.4%) of the 115 hospitalized children (Fig. 3). No child had received 2 doses of vaccine.

Of the immunocompetent children, 32 were eligible by age for the funded varicella vaccine, but only 6 (18.8%) were immunized, including a child who received varicella vaccine aged 16 months rather than at the scheduled 18-month immunization time point. The 6 vaccinated children were aged 16 months to

7 years and 4 months. None of the 6 immunized children required intensive care management, but 3 developed cellulitis. All were discharged between 2 and 6 days (median = 2 days) postadmission compared with 1–58 days (median = 2 days) for unimmunized children. No child more than 9 years of age was immunized against varicella.

Of the 46 immunocompromised children, 6 (13%) had previously received a varicella vaccine. In previously immunized children, the median interval between varicella immunization and hospitalization was 2.2 years with an age range of 42 days to 7 years; longer intervals were observed for immunocompromised children (Fig. 4). The mean duration of hospitalization for all children was 5.6 days (6.5 days for previously immunized children and 5.6 days for children not immunized against varicella). The median duration of hospitalization was 3.0 days irrespective of immunization status, but the range was wider for children who were not immunized (1–58 days) compared with those who were immunized (2–34 days). The median length of stay for immunocompromised children

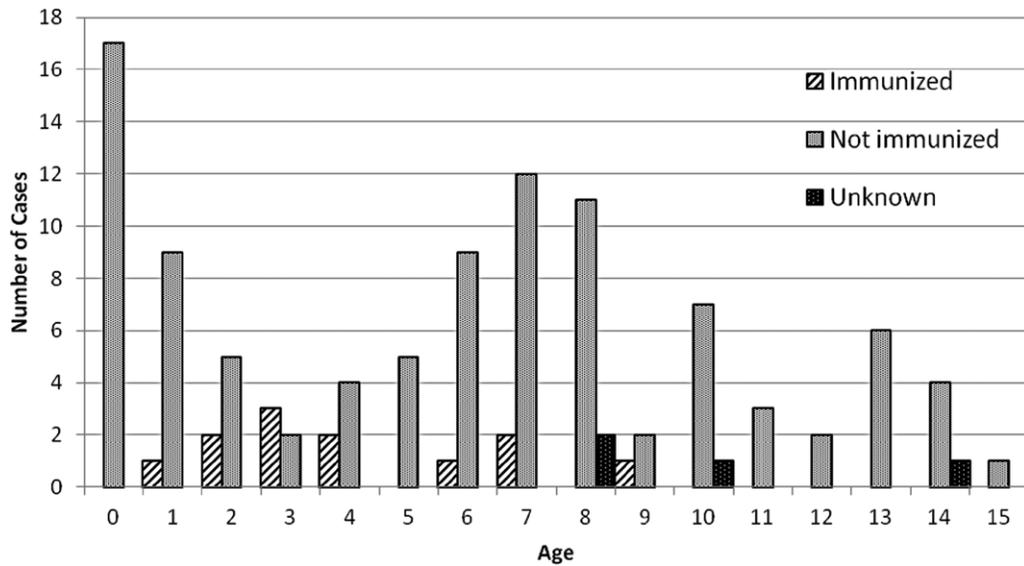


FIGURE 2. Total number of varicella/zoster hospitalizations by age and immunization status.

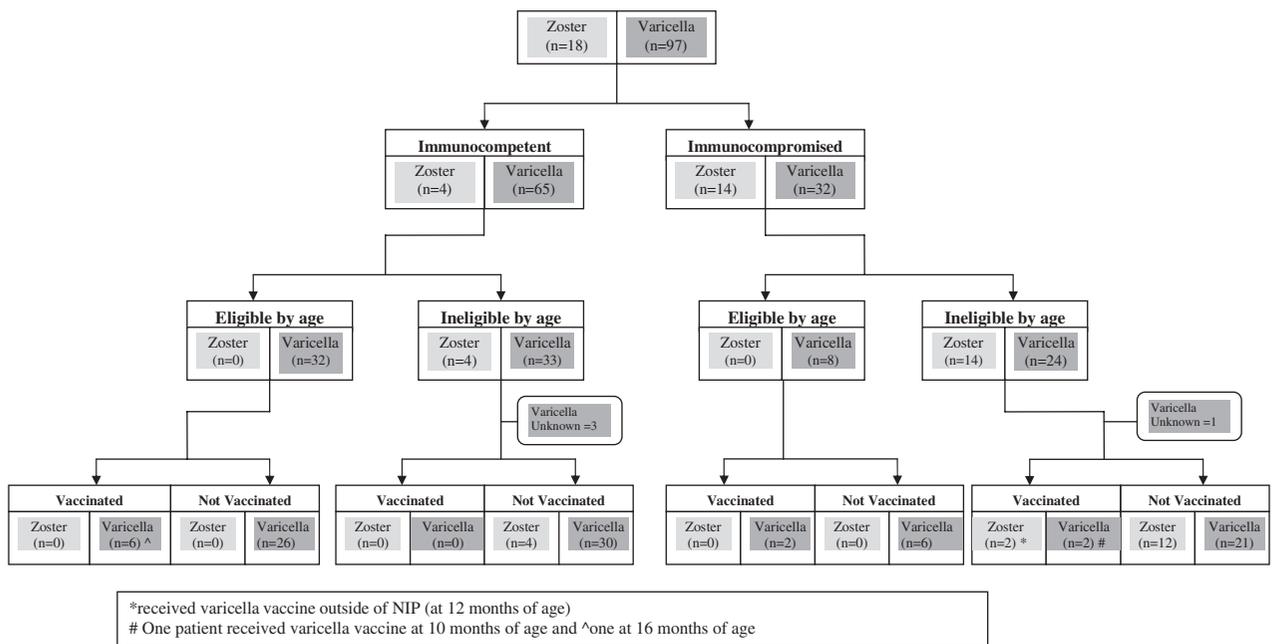


FIGURE 3. Previous varicella immunization by diagnosis and immune status. Eligible children included those eligible by age to have received varicella vaccine at 18 months of age according to the Australian National Immunisation Schedule. NIP indicates National Immunisation Program.

was 5 days compared with 2 days in immunocompetent children (Kruskal–Wallis test $P < 0.001$).

Varicella Contacts

A history of contact with other infected children was obtained for 67 children (58.3%). Where documented (n = 46), the majority of contacts (n = 25) were at school or preschool, or family members (n = 21).

Antiviral Therapy

A total of 65 children (56.5%) received antiviral therapy, including aciclovir (n = 60), valaciclovir (n = 3) and famciclovir

(n = 2); 93% of immunocompromised children (43/46) versus 32% (22/69) of immunocompetent children (χ^2 test; $P < 0.001$). Nine immunocompromised children received zoster immunoglobulin. The median duration of hospitalization for immunocompetent children who received antiviral therapy was not significantly higher (3 days; IQR: 2–6 days) than for those who did not receive antivirals (median = 2 days; IQR: 2–3 days; Kruskal–Wallis test $P = 0.276$).

Varicella Complications

Complications were identified more commonly in varicella (44%, n = 43/97) than zoster (27.8%, n = 5/18) hospitalizations, with a total of 73 complications recorded by treating physician

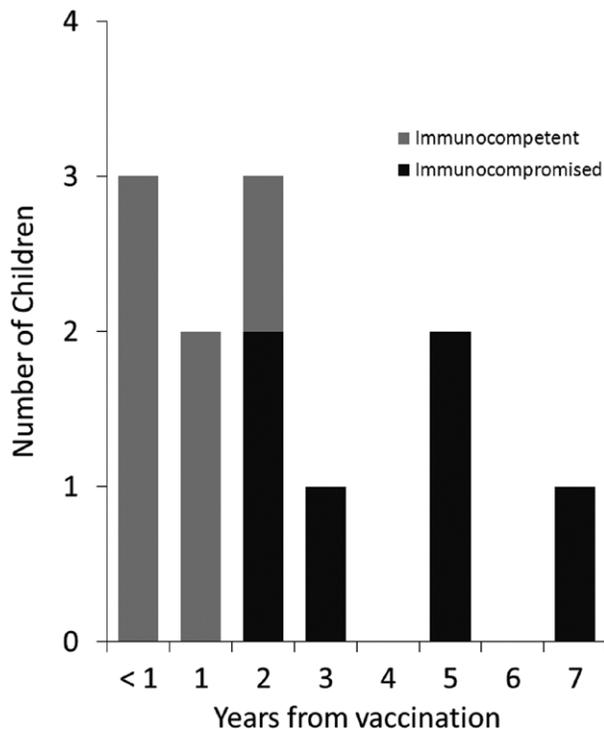


FIGURE 4. Length of time from varicella immunization to hospitalization in previously immunized children.

(Table 1). The most common varicella complications were secondary skin infection (25, 25.8 %) and neurological problems (14, 14.4%), including 8 children with seizures. All 3 children admitted to intensive care were immunocompetent and had severe multiple complications and ongoing problems at discharge (Table, Supplemental Digital Content 1, <http://links.lww.com/INF/B427>); 2 were infected by siblings, all survived.

Recurrent Varicella

Of children hospitalized with varicella, 15 (15.5%) were reported by parents as having had varicella at an earlier age of whom 11 of 15 (73%) had an underlying immunodeficiency condition, significantly more than for immunocompetent children (Fisher exact $P = 0.027$).

Varicella Genotyping

Vesicular fluid collected for varicella virus isolation in 58% ($n = 66$) of cases was used for genotyping to identify circulating varicella virus genotypes and any mutations of the vaccine strain. In some cases, no vesicle fluid could be obtained because the vesicles had healed by the time the child was hospitalized. Varicella genotyping showed all viruses isolated were “wild-type” strains. Clade 1 was the most prevalent genotype, occurring in all 4 states, followed in frequency by Clades 5 and 3. A single recombinant genotype was identified in Western Australia (Fig. 5).

DISCUSSION

In all participating hospitals, a reduction of more than 70% in hospital admissions coded as related to varicella was found. The accuracy of coded data for varicella and zoster has previously been demonstrated in a study at one of the hospitals,¹² and this reduction is in keeping with the vaccine coverage of 81.8% among children eligible for the funded dose of varicella vaccine

at 18 months of age in 2009.²¹ However, it is in stark contrast to the 18% of children hospitalized with varicella in the eligible age group who had received varicella vaccine, which suggests a high effectiveness of the vaccine in preventing hospitalization as documented in the United States.^{9,10} The reduction in cases coded as zoster at discharge was less at 40% but many of these were either immunocompromised (78%) or too old to be eligible for the funded vaccine program.

Complicated varicella in hospitalized cases occurred less frequently (43%) than the only detailed clinical report from the prevaccine era in Australia (57%)¹² and a similar report from the Netherlands (76%).²² A larger proportion of children hospitalized for varicella had underlying immunodeficiency (40%) compared with the 16% reported from the pre-varicella vaccine era in this previously reported study from one of the participating hospitals, but the proportion of zoster cases who were immunocompromised did not change (78% versus 74%).¹²

Compared with this same report, the average age of children on admission in our study increased to 5 years 6 months from 4 years 2 months for varicella and for zoster to 10 years 9 months compared with 9 years 9 months.¹² We also identified recurrent varicella, based on parental report, in 15 children, most of whom were immunocompromised, compared with no reported recurrent varicella cases in the prevaccine era study. Contributing factors to the high proportion of immunocompromised children admitted with varicella include increased susceptibility to severe disease, coupled with a lower threshold for admission²³ and in some cases varicella vaccine being contraindicated. Enhancing protection for this vulnerable group will require both increased immunization coverage and herd immunity to varicella, in addition to encouraging household contacts to be immunized.

No varicella deaths were reported during the study period at any of the 4 hospitals compared with 2 deaths from the one hospital in the 1999 to 2001 prevaccine period, but the proportion of previously healthy children admitted to intensive care (3/69, 4.6% versus 5/123, 4.1%) was similar.¹² It is known that exposure to varicella in a sibling may lead to more severe disease, and 2 of the 3 cases requiring intensive care acquired varicella from household contacts.²⁴

Varicella genotype diversity remains unchanged since the introduction of varicella vaccine. Several studies have demonstrated a regional dominance of specific varicella genotypes, most likely influenced by environmental factors, travel and migration.²⁵ We found much greater strain diversity than that reported from Europe, Africa and North America. In previous Australian studies, Clade 1 (European) predominated (46–53%) followed by Clade 3 (21–24%), Clade 5 (8–12%), Clade 2 (6–12%), Clade 4 (3–10%) and Clade VI (5%).^{17,26} Although these previous studies were not as nationally representative as our study, our results are consistent with these findings and show no evidence of “vaccine pressure.” A higher diversity of genotypes was evident in New South Wales and Western Australia compared with Victoria and South Australia, although the number of samples collected in these latter states was low. There is a potential for recombination events between wild-type and vaccine viruses¹⁷ and the possibility of circulating “vaccine escape” genotypes, emphasizing the importance of continuing surveillance and monitoring of varicella genotypes in the postvaccine era. A newly recognized single-nucleotide polymorphism in ORF0 of varicella vaccine strains (including VARIVAX and Varilrix), that is not present in wild-type strains has recently been identified.²⁷ ORF0 is a likely determinant of attenuation and should be incorporated into classification schemes identifying putative clades. Continued surveillance with varicella genotyping to identify new mutations is

TABLE 1. Complications Associated With Hospitalized Cases of Varicella and Zoster by Immune Status With At Least One Complication per Hospitalized Case

| Complication | Immunocompromised (n = 32) | Immunocompetent (n = 65) | Total (n = 97) |
|----------------------------------|----------------------------|--------------------------|----------------|
| Varicella | | | |
| Skin/cutaneous/soft tissue | | | |
| Secondary skin infection | 2 | 23 | 25 |
| Orbital cellulitis | | 1 | 1 |
| Total | 2 | 24 | 26 |
| Systemic | | | |
| Bacteremic varicella* | 2 | 1 | 3 |
| Toxic shock syndrome | 0 | 1 | 1 |
| Reye syndrome | 1 | 0 | 1 |
| Lymphadenitis | 0 | 1 | 1 |
| Dehydration | 0 | 7 | 7 |
| Total | 3 | 10 | 13 |
| Neurologic | | | |
| Seizures | 1 | 7† | 8 |
| Cerebellitis/cerebritis | 0 | 2 | 2 |
| Meningitis | 0 | 1 | 1 |
| Transverse myelitis | 0 | 1 | 1 |
| Guillaine-Barre syndrome | 0 | 1 | 1 |
| Diplopia | 1 | | 1 |
| Total | 2 | 12 | 14 |
| Bone/joint | | | |
| Septic arthritis/arthritis | 2 | 2 | 4 |
| Osteomyelitis | 0 | 2 | 2 |
| Total | 2 | 4 | 6 |
| ENT/Respiratory | | | |
| Otitis media | 0 | 1 | 1 |
| Respiratory infection | 1 | 2 | 3 |
| Pneumonia (radiograph confirmed) | 0 | 1 | 1 |
| Total | 1 | 4 | 5 |
| Other | | | |
| Pancreatitis/hepatitis | 0 | 1 | 1 |
| Pericardial effusion | 0 | 1 | 1 |
| Pyelonephritis | 0 | 1 | 1 |
| Gastroenteritis | 0 | 1 | 1 |
| Total | 0 | 4 | 4 |
| Zoster | | | |
| N | 14 | 4 | 18 |
| Dehydration | 1 | 0 | 1 |
| Pneumonia | 1 | 0 | 1 |
| Secondary skin infection | 2 | 1 | 3 |
| Total | 4 | 1 | 5 |

*Bacteremic varicella denotes varicella infection with associated bacteremia, for example, *Staphylococcus aureus*.

†Six were febrile convulsions

of importance in informing immunization strategies. Continued molecular surveillance provides an opportunity to identify genotypes associated with more severe disease or affecting immunocompromised children. Importantly, there were no hospitalized cases due to vaccine-related genotypes, suggesting that any vaccine-associated disease is subclinical or mild.

Less than 20% of immunocompetent children hospitalized with varicella had previously received a varicella vaccine. Although one dose of varicella vaccine provides good protection against severe disease,²⁸ our study found that cases that were severe enough to require hospitalization can occur despite immunization, as described by others.^{29,30}

Giving varicella vaccine at 12 months instead of 18 months of age could have potentially prevented an additional 5% of cases in our series. There was a history of contact with other infected children for more than half of the children hospitalized, and there is unrealized potential for prevention of these cases if they had been offered varicella vaccine postexposure,³¹ or if there had been a catch-up immunization for children aged more than 18 months and less than 10 years in Australia. Encouraging varicella immunization

for all immunocompetent children with an emphasis on timeliness should reduce the number of hospitalized cases in Australia and better protect those who are vulnerable to the infection but unable to be immunized. From 2013, a combination measles-mumps-rubella-varicella vaccine will be given at 18 months of age in the Australian National Immunisation Program, linked to receipt of family tax benefits and this could improve coverage of one dose of varicella vaccine.

Not all breakthrough varicella cases are mild, as demonstrated in our data with 6 hospitalized cases among 68 hospitalized immunocompetent children and 4 cases in immunocompromised children. Breakthrough disease is considered to be the result of waning immunity after single-dose immunization. A second dose of vaccine is likely to provide a robust immune memory response in immunized children whose initial response was inadequate and provide additional protection to primary nonresponders.^{32,33} As most breakthrough disease occurred within 3 years of immunization, our data suggest the timing of the second dose should be soon after the first dose (1–2 months). Although recommended in Australia, a two-dose schedule for children is not currently funded,

Varicella genotypes by state, Australia

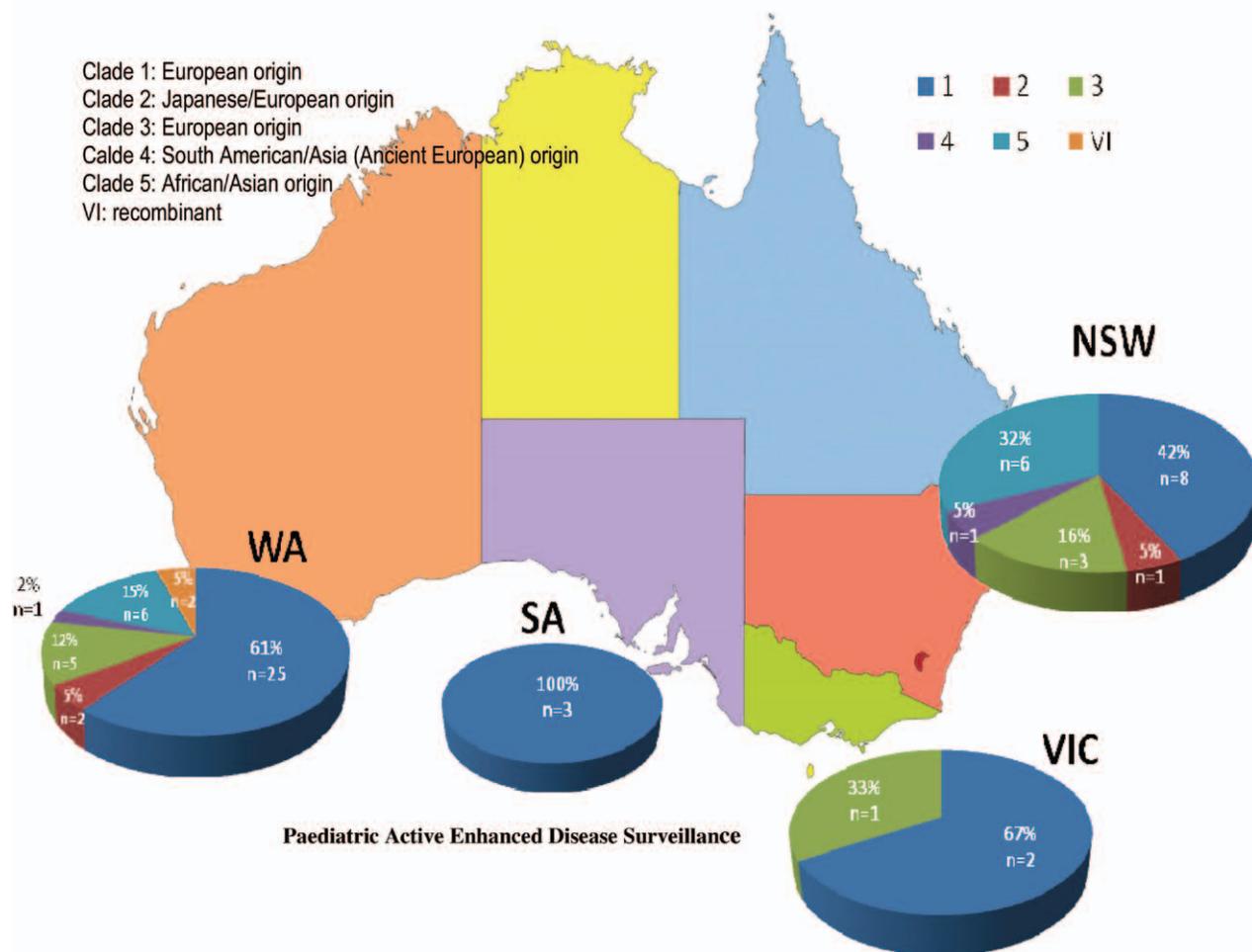


FIGURE 5. Varicella genotypes by state at participating hospitals, Australia.

and our data suggest that the most important objective should be to improve 1-dose coverage.

The results of our study support the need for increased awareness about severe varicella in the community and vaccination providers. Previous studies have shown a lack of parental knowledge about varicella vaccination, but considerable concern about children acquiring the infection.³⁴ Immunization of children who were ineligible by age or missed out on the funded program should be encouraged.³⁵

Surveillance of varicella after introduction of the vaccine is important for investigating changes in epidemiology, viral evolution, host–virus interactions and the role of travel in importation of new viral strains, as well as for identifying possible vaccine escape genotypes.^{26,36} This information can inform changes to immunization policy, practice and immunization schedules to benefit the health of children and particularly those most vulnerable to severe disease.

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