Surveillance of viral pathogens in Australia

For many years, a sentinel laboratory system, the Laboratory Virology and Serology Reporting Scheme (LabVISE) has been collecting data on viral pathogens of public health importance in Australia. In future editions of Communicable Diseases Intelligence, *the editors will produce a series of articles focusing on the epidemiology of viruses and viral groups under surveillance through LabVISE which are of current public health interest.*

Varicella-zoster virus

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Introduction

This article summarises current knowledge and some of the implications the introduction of universal varicella vaccination may have on the epidemiology of varicella in Australia. Appropriate surveillance strategies for this changing epidemiology are also discussed.

Varicella-zoster virus causes two distinct clinical diseases. Primary infection causes varicella or chickenpox in children and reactivation of infection causes herpes zoster (shingles) mostly among the elderly. The virus is a member of the herpesvirus family, restricted in its infective range to humans. Although chickenpox and shingles have been recognised for centuries, changes in population demographics, increasing numbers of people living with immuno-compromising conditions and the recent introduction of effective varicella vaccines could change the epidemiology of the diseases. The recent recommendation of the Australian Technical Advisory Group on Immunisation (ATAGI) to introduce universal childhood immunisation against varicella has highlighted the need to understand the epidemiology and develop surveillance strategies appropriate for Australia.

Chickenpox

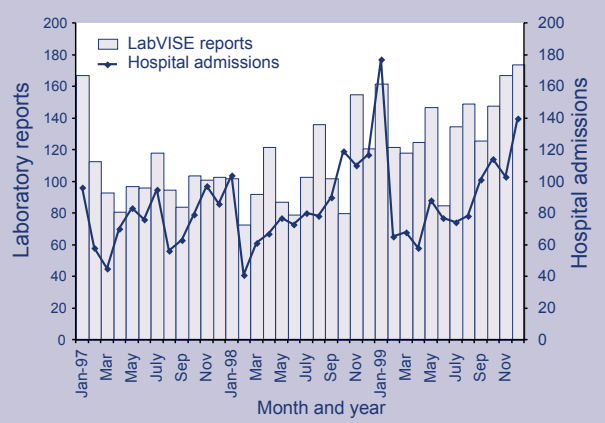
Chickenpox is a ubiquitous and highly contagious infection in children, usually affecting 90 per cent of children before adolescence.[1] Before the introduction of a varicella vaccine in the United States of America (USA) in 1995, there were approximately 4 million cases per annum of which around 500,000 sought medical care, 10,000 required hospitalisation and there were 100 deaths.[1,2] Varicella mortality declined between 1970 and 1994 overall, but rates among adults increased. Adults had a risk 25 times greater and infants had a risk 4 times greater of dying from varicella than children aged 1–4 years.[3] Although chickenpox is endemic in most populations, seasonal peaks may occur in late winter and early spring in temperate regions. Chickenpox may occur more frequently in adults in tropical regions than in temperate regions. Varicella infection during pregnancy may cause spontaneous abortion and intrauterine fetal infection may cause congenital abnormalities.[4] The risk of fetal infection and damage is small but clinical manifestations may include growth retardation, skin lesions, skeletal hypoplasia, encephalopathy, eye abnormalities and structural or functional abnormalities of the gastrointestinal and genitourinary tract.

Varicella infection in the newborn varies in severity according to the timing of infection. When maternal infection occurs from 3 weeks to 5 days before delivery neonates have mild varicella disease because of protective maternal antibodies. However, if maternal varicella occurs between 5 days before to 2 days after delivery, and the virus is transmitted across the placenta, potentially severe neonatal varicella may occur, since there is no protective effect of maternal antibody. In the latter, disease develops at between 5 and 10 days of age. A case fatality rate of 20–30 per cent has been reported.[4]

In Australia, national surveillance data on the incidence of chickenpox have not been routinely collected. Sentinel surveillance data are available from laboratory reports collected through the Laboratory Virology and Serology Surveillance System (LabVISE) since 1982 and the Australian Sentinel Practice Network (ASPREN) between 1995 and 2001.

The vast majority of cases of chickenpox are well recognised by parents. A diagnosis, if made by a medical practitioner, is based on clinical signs and symptoms and does not rely on laboratory tests. Nonetheless, there have been 16,153 laboratory reports of varicella virus identification collected through LabVISE since 1982. Such reports do not distinguish between cases of chickenpox and cases of shingles. During this period, reports have been received from a varying number (13 to 26) laboratories located in all states and territories except the Northern Territory. Since this is a sentinel system, it is difficult to discern trends over time, however, a seasonal peak in laboratory reporting in January (Figure 1) is apparent. This peak coincides with a peak in hospitalisations for varicella in Australia (Australian Institute of Health and Welfare National Hospital Morbidity Databases).[5]

Figure 1. Laboratory reports of varicella-zoster virus to LabVISE and hospitalisations with a principal diagnosis of varicella,* Australia, 1997 to 1999



* ICD–10-AM codes: B01.0, B01.1, B01.2, B01.8, B01.9 and ICD–9-CM codes 052.0, 052.1, 052.7, 052.8, 052.9

Laboratory testing is more often performed in age groups in whom varicella infections are unusual. Only 758 (7%) of the 11,052 patients in whom varicella was confirmed by laboratory testing between 1991 and 2000 were aged less than 5 years (Figure 2).

The ASPREN surveillance system is a network of about 120 general practitioners, mostly located in metropolitan areas, who together record between 7,000 and 8,000 consultations per week of specified conditions. ASPREN data are reported as rates per 1,000 consultations.[6] Between 1995 and 2001, cases of chickenpox, defined as 'an acute generalised viral disease with a sudden onset of slight fever, mild constitutional symptoms and a skin eruption which is maculopapular for a few hours, vesicular for 3 to 4 days and leaves a granular rash' were reported. An examination of these data between 1999 and 2001 showed little evidence of a seasonal peak in reporting (Figure 3). The annual average rate for chickenpox was 1.6 cases per 1,000 consultations per week.

Figure 2. Laboratory reports of varicella-zoster virus to LabVISE, 1991 to 2000, by age and sex

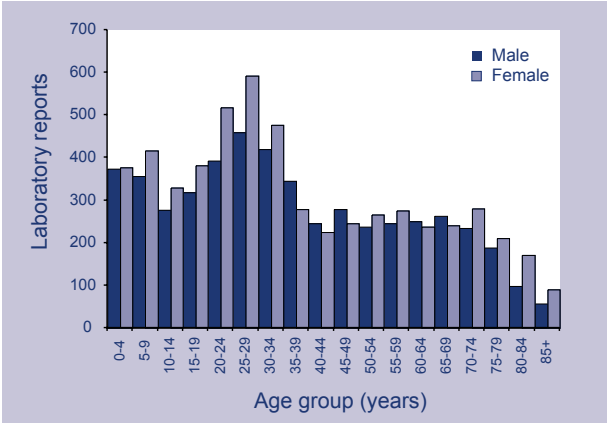
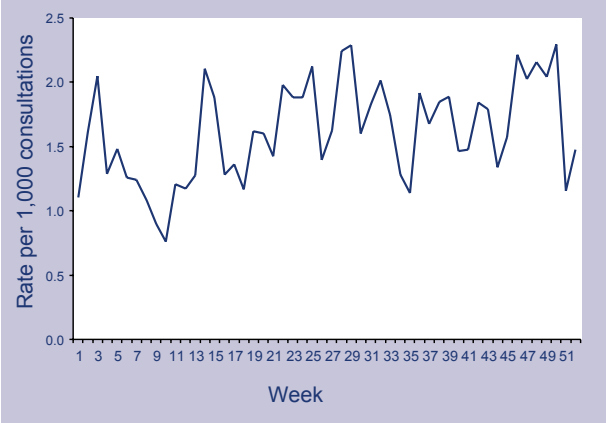


Figure 3. Average weekly consultations for chickenpox to sentinel practices (ASPREN), 1999 to 2001 combined, by week of consultation



There has been an average of 3–4 deaths each year since 1980.[7] Fifteen of the 20 deaths due to varicella between 1998 and 2000 were in people aged 60 years or more.[5] In the 2 years (July 1998 to July 2000), there were 3,725 hospitalisations, 60 per cent (2,241) of which had a principal diagnosis of varicella. Varicella infection required on average 7,823 hospital bed days per year with a median length of stay of 2 days. The highest rates of hospitalisation were in the 0–4 year age group and the length of stay was longest in the elderly. Of all varicella hospitalisations in this period, 3 per cent were cases of encephalitis and 8 per cent were cases of varicella pneumonia.[5]

A three-year survey, conducted by the Australian Paediatric Surveillance Unit (APSU) between 1995 and 1997, of more than 900 Australian paediatricians, detected 7 cases of congenital varicella, a rate of one per 107,000 pregnancies per year. Of these, 5 infants had congenital defects and 2 died.[8] The APSU survey also detected 44 infants with neonatal varicella, a rate of one case per 17,000 pregnancies per year. Of these, only two had severe disease and there were no deaths.[8]

Herpes zoster infection (shingles)

After infection with varicella virus in childhood, the virus remains latent in one or more dorsal root ganglia. Latency is maintained by specific cell-mediated immunity, which is boosted periodically by exposure to people with acute varicella. The varicella virus is reactivated in the elderly as cellular immunity decreases, and the virus spreads via the sensory nerves into the dermis to produce the characteristic vesicular lesions of herpes zoster (or shingles).[9] Individuals usually have single episodes of herpes zoster but an important sequela is post-herpetic neuralgia (PHN) which occurs in approximately 30 per cent of cases in the elderly.[9] PHN is defined as localised pain persisting for at least 3 months after the acute inflammatory phase of zoster in the skin. Symptoms may include severe pain or sensations of burning or itching and are refractory to conventional analgesics. Symptoms may continue for years and the frequency and intractability of PHN increases with age.[10]

Herpes zoster is estimated to affect 20 per cent of the population, particularly the elderly. In the USA there are estimated to be 500,000 cases of herpes zoster infections per year, resulting in 1.5 million visits to physicians.[1] Data on shingles in Australia are limited. Data for 1999/00 indicate that there were 1,918 admissions to Australian hospitals for herpes zoster (ICD–AM-10 code B02). These were composed of 776 zoster infections without complications and 1,142 infections with complications. The most common complication was nervous system involvement other than encephalitis and meningitis (ICD–10AM code B02.3, n=646), which included polyneuropathy, trigeminal neuralgia and geniculate ganglionitis.[11] Recent evidence suggests that adults with contacts with children and therefore with chickenpox have a lowered risk of developing zoster infections. This protective effect is greatest in those adults with many social contacts with children outside the home including contacts with sick children.[12]

Varicella vaccines

A live attenuated varicella vaccine was developed in Japan in the 1970s and introduced into the infant immunisation schedule in the USA in 1995. Currently, in the USA, all children aged between 12 months and 13 years are given a single dose of the vaccine, while, if seronegative, those aged more than 13 years should receive two doses of vaccine, separated by 4 weeks. Side effects and adverse events from the vaccine have been monitored and the vaccine appears in general to be well tolerated.[13] The vaccine virus strain can cause herpes zoster but does so at a significantly lower rate than the wild-type virus.[14]

Since the USA does not include varicella as a notifiable disease, the measurement of vaccine effectiveness has depended on case control studies and surveillance in sentinel sites. A case control study performed between 1997 and 2000, measured vaccine effectiveness at 85 per cent (95% CI 78–90%) for PCR-confirmed varicella and 97 per cent (95% CI 93–99%) against severe disease.[15] Recent reports from sentinel surveillance sites established to measure varicella vaccination effectiveness,[16] have shown declines in varicella cases of 71–84 per cent between 1995 to 2000 across all age groups, with the largest declines in children aged 1–4 years. Vaccine coverage by 2000 in these sentinel areas had reached between 74 and 84 per cent of the 19–35 month age group. Varicella vaccination of children with leukaemia[17] and recipients of haemopoietic cell transplants,[18] has been shown to protect against herpes zoster. Despite concerns of a rise in zoster, active surveillance for herpes zoster in the USA sentinel sites[16] has not shown any change in herpes zoster incidence to date (JF Seward, personal communication).

The cost-effectiveness of varicella vaccination

The cost-effectiveness of introducing varicella vaccination in Australia using a variety of strategies has been examined.[19] The study suggested that introduction of a vaccination program among infants would be the most cost-effective, but the possibility of a relative increase of disease among older children and adults means a 'catch up' program of vaccinating seronegative adolescents would have to be considered. There are considerable uncertainties about the duration of protective immunity induced by vaccination and models have assumed an undiminished effectiveness over 30

years, which may not be accurate. Varicella vaccination of infants in Australia has been estimated to avert 4.4 million cases, 3,500 hospitalisations and 30 fatalities over a 30–year period.[19]

Varicella vaccination and herpes zoster

More recent modelling of the impact of varicella vaccination has examined the effect on the incidence of herpes zoster (shingles). If reactivation of latent varicella infections is prevented by varicella immunity maintained by regular exposure to varicella, the reduction in circulating varicella virus might reduce immunity in the elderly and thereby increase the incidence of zoster. As noted above, zoster is a more serious illness than chickenpox with higher rates of hospitalisation and sequelae. Brisson and colleagues assessed the cost-effectiveness of introducing varicella vaccination in Canada[20] and concluded that if vaccination resulted in increases in zoster incidence, then vaccination became cost ineffective in the medium term. Subsequent modifications of their modelling led the authors to predict an epidemic of zoster affecting more than 50 per cent of those aged 10–44 years after the introduction of mass vaccination of children against varicella.[21] This epidemic would consist of an estimated 21 million cases of varicella and result in 5,000 deaths. However, the incidence of herpes zoster would decrease as a larger proportion of the population becomes vaccinated and 30 to 50 years after the introduction of varicella vaccination, would fall below pre-vaccination levels.[21]

In the cost-effectiveness study of varicella vaccination in Australia, the authors did not include the potential increase in the incidence of zoster in their calculations.[19] Neither this study nor the Canadian study[20] included the ultimate cost savings, from the eventual reduction in the incidence of herpes zoster to very low levels, by varicella vaccination. Despite the concerns about varicella vaccination and herpes zoster, the ATAGI has stood by their recommendation to give varicella vaccination to all 18-month-old children and to children aged 10–13 years without a history of varicella infection in Australia. The proposal will be considered by National Health and Medical Research Council in October 2002.

Surveillance of varicella disease in a new vaccine era

Given the expected changes in the epidemiology and control of varicella and zoster, what kinds of surveillance are needed in Australia? The large numbers of cases of chickenpox and the small proportion of cases who seek medical attention convinces most epidemiologists that making varicella a notifiable disease in Australia would be unworkable. However, to assess the impact of varicella vaccination, active sentinel surveillance such as that used in the USA, would be helpful.

In the USA, three counties have introduced active verification of every case using a standard case definition and the collection of vaccination history.[16] Active surveillance is expensive and labour-intensive, but is important in measuring vaccine effectiveness and changes in varicella epidemiology, particularly to detect increased prevalence of infections in pregnant women and in adolescents and adults where morbidity is more severe. The incidence of zoster infections in adults would need to be monitored to determine whether there is an increase in zoster, a change in severity or in the age-specific attack rate. This information would be vital to determine whether the introduction of varicella vaccination or re-vaccination of adults would be required to boost varicella immunity in an era of declining natural infection.

Alternately, surveillance might be based on hospitalisation data, which would measure the vaccine's impact on severe disease. Australian hospitalisation data are, however, only available with a 12 to 18 months delay which limits the timeliness of this surveillance. Surveillance through the ASPREN sentinel general practice scheme would give some measure of the impact on severe disease in a timely manner. The representativeness of the populations under surveillance is, however, of concern and the scheme is not able to collect more than a minimum of data on each case. Specialised laboratory surveillance to detect whether post-vaccination cases of varicella or herpes zoster are due to wild type or vaccine strains of varicella would be valuable. This would require sophisticated genetic testing of clinical isolates, isolated from a representative population.

The impact of varicella vaccination on the incidence of herpes zoster will be directly addressed by an ongoing clinical trial of varicella vaccination of adults previously infected with

varicella.[22] The study results, due in late 2004, will show whether or not varicella vaccination will prevent the development of herpes zoster in recipients. If varicella vaccination of the elderly boosts immunity to varicella and reduces the incidence of herpes zoster, vaccination of older age groups could be introduced. Control of both chickenpox and herpes zoster by a single vaccine would be an excellent public health outcome and highly cost-effective.

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