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The seroepidemiology and transmission dynamics of varicella in Australia

H. F. GIDDING[1]*, C. R. MACINTYRE[1], M. A. BURGESS[1] AND G. L. GILBERT[1,2]

[1] *National Centre for Immunization Research and Surveillance of Vaccine Preventable Diseases, Royal Alexandra Hospital for Children and University of Sydney, New South Wales 2145, Australia*
[2] *Centre for Infectious Diseases and Microbiology, Institute of Clinical Pathology and Medical Research, Westmead Hospital, Westmead, New South Wales 2145, Australia*

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SUMMARY

To enhance our understanding of the epidemiology and transmission dynamics of varicella in the pre-vaccine era we performed a serosurvey using opportunistically collected sera submitted to diagnostic laboratories across Australia during 1997–1999. A representative sample by state and sex of 2027 sera from persons aged 1–49 years was tested using an enzyme immunoassay method. The average age of infection and age-specific forces of infection (the probability that a susceptible individual acquires infection) were calculated using published methodologies. Seropositivity increased with age, with 83% of sera positive by ages 10–14 years. The highest force of infection was in the 5–9 years age group (0·195 per susceptible year) followed by the 0–4 years age group (0·139 per susceptible year) and the average age of infection was 8·15 years. These results provide valuable baseline information to measure the impact of vaccination and indicate that vaccination should be aimed at children less than 5 years of age, although further modelling using the serosurvey data is warranted.

INTRODUCTION

Varicella is an ubiquitous infection in Australia, with most adults immune due to previous exposure [1, 2]. During 1998–2000 chickenpox [3] and herpes zoster [4] caused an average of 6·7 and 19·3 deaths respectively each year (average annual birth cohort for period, 250 000; 1999 population, approximately 19 million), as well as significant hospital morbidity [1, 3]. However, there is a low incidence (1 per 107 000 pregnancies) of identified congenital varicella in Australia [5]. Studies of communicable diseases in the child-care setting have showed that varicella caused the largest outbreaks and had the longest mean outbreak duration compared to other common communicable diseases [6].

Following the example of the United States, Australia may introduce varicella vaccination as part of the routine immunization schedule in the near future. It is important to document the epidemiology and transmission dynamics of varicella and zoster in the unvaccinated Australian population, and use this as a baseline to observe trends after the introduction of vaccination.

A valuable source of epidemiological data, given that varicella and zoster are not notifiable at a national level in Australia, is population-based serosurveys. Serosurveillance data not only provide information about immunity but can also be used in conjunction with mathematical techniques to determine various epidemiological parameters associated with the transmission dynamics of the disease. These

* Author for correspondence: H. F. Gidding, National Centre for Immunization Research and Surveillance of Vaccine Preventable Diseases (NCIRS), Locked Bag 4001, Westmead, NSW 2145, Australia.

include the average age of infection and the age-specific forces of infection, where the force of infection is the probability that a non-immune individual will be infected over a short period of time.

In 1999 the National Centre for Immunization Research and Surveillance of Vaccine Preventable Diseases (NCIRS) conducted the first national serosurvey and measured immunity to the varicella zoster virus (VZV). In this paper we present the results of the serosurvey in order to provide an insight into the current epidemiology and transmission dynamics of VZV in Australia.

METHODS

Serosurvey

Sera were obtained from diagnostic laboratories throughout Australia. Laboratories were asked to contribute sera that had been submitted for diagnostic testing and would otherwise have been discarded. Sera from subjects who were immunocompromised, had received multiple transfusions in the past 3 months, were known to be infected with human immunodeficiency virus or had had serum collected for the diagnosis of measles were excluded. Samples were collected from 1997 to 1999, prior to the licensing of varicella vaccine in Australia.

Serum samples from people aged 1–49 years were stratified into the following age groups: 1–2, 3–4, 5–9, 10–14, 15–19, 20–24, 25–29, 30–39 and 40–49 years. Within each age group, states and territories were sampled proportionally to their population size. Sample sizes were calculated to achieve confidence intervals of approximately $\pm 5\%$ for each age group, based on the expected level of immunity to varicella. Approximately equal numbers of sera from males and females were tested.

Sera were identified at the referring laboratory by gender, age or date of birth, residential postcode, date of collection and a unique identifier, to ensure that only one sample from any subject was tested. Sera were de-identified before testing and coded by date of collection, state/territory of origin and referring laboratory.

Antibody assays

Sera were tested using the Enzygnost (Dade Behring Diagnostics, Marburg, Germany) anti-VZV IgG enzyme immunoassay (EIA), at the Institute of Clinical Pathology and Medical Research, Sydney, Australia. The results were interpreted, according to the manufacturer's instructions, as follows: optical density (OD) reading $<0{\cdot}1$, negative, 0·1–0·2, equivocal and $>0{\cdot}2$, positive. All sera for which the result was equivocal were retested and reclassified if positive or negative.

Ethics approval

The serosurvey was approved by the appropriate institutional ethics committees and the State-wide Health Confidentiality and Ethics Committee of the New South Wales Health Department.

Calculating the age-specific force of infection

Age-specific forces of infection, $\lambda(a)$, were calculated for the age groups 0–4, 5–9, 10–14, and 15+ years. The following equation describes the relationship between $\lambda(a)$ and the prevalence of antibodies/immunity to varicella, $z(a)$, at age 'a' [7]:

$$z(a) = 1 - \exp\left(- \int_0^a \lambda(a')\mathrm{d}a' \right).$$

Given age and the prevalence of antibodies to varicella obtained from the national serosurvey we can estimate $\lambda(a)$ assuming a binomial distribution for $z(a)$ and using maximum-likelihood methods [7]. In using this equation we assume that varicella is endemic, infection causes lifelong immunity, mortality of infected individuals does not increase, and finally that horizontal changes in the proportion immune mirror longitudinal changes for a specific cohort (i.e. age-specific forces of infection do not change over time). These assumptions broadly hold true for developed countries provided that the inter-epidemic period of the oscillations in disease incidence is short in relation to the age span over which the sera were collected – which is the case [8].

Calculating the average age of infection

The average age of infection, A, was calculated using the following equation [9]:

$$A = \sum_{i=1}^{n} [(1+\lambda_i a_{i-1})\exp(-\psi_{i-1}) - (1+\lambda_i a_i) \times \exp(-\psi_i)] / \{\lambda_i [1-\exp(-\psi_n)]\},$$

Table 1. *Number of sera tested and percentage positive for varicella IgG antibody by age group and sex, Australia pre-vaccination*

Age group (years)	Males		Females		
	No. tested	% positive	No. tested	% positive	*P* value*
1–2	69	16	69	23	0·3
3–4	110	29	104	38	0·2
5–9	202	71	201	60	0·01
10–14	172	78	175	87	0·03
15–19	147	85	139	87	0·6
20–24	129	82	136	88	0·2
25–29	100	89	95	96	0·08
30–39	54	98	50	100	1·0
40–49	40	95	35	100	0·5
Total	1023	72	1004	74	0·2

* *P* value for the comparison of proportions seropositive for males and females.

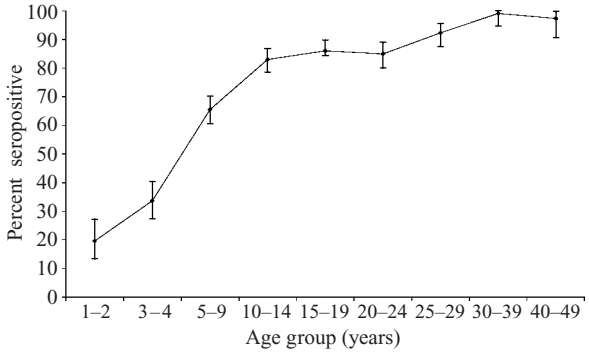

Fig. 1. Percentage of sera positive for varicella IgG antibody by age group (including 95% confidence intervals), Australia pre-vaccination.

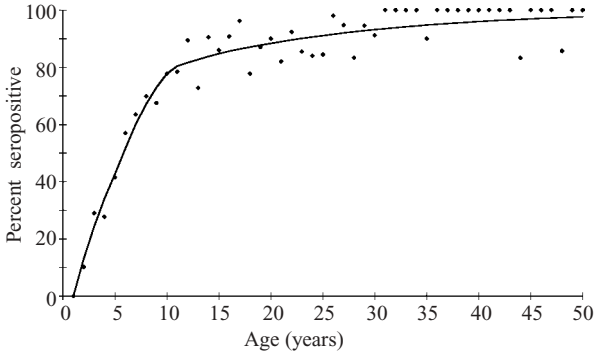

Fig. 2. Estimated and observed percentages of sera positive for varicella IgG antibody by age, Australia pre-vaccination. ◆, Data; —, model.

where ψ is defined as the age-independent constant

$$\psi_i = \sum_{j=1}^{i} \lambda_j (a_j - a_{j-1}) \quad \text{and} \quad \psi_0 = 0.$$

RESULTS

A total of 2027 sera were tested for varicella IgG; 73% were positive, 26% were negative and 0·7% remained equivocal after retesting. Seropositivity increased rapidly with increasing age up to the 10–14 years age group and then more gradually in older cohorts (Fig. 1). By age 10–14 years, 83% (95% CI 78·6–86·8) of sera were positive. A significant proportion of women of child-bearing age (15–44 years) were still susceptible to varicella (8·9%; 95% CI 6·4–12·0). There were slightly more females than males seropositive overall and in each age group, except 5–9 years, but most differences were non-significant (Table 1). Most (47%) of the 15 equivocal sera were from the 15–19 years age group and all were from ages less than 30 years.

The force of infection, $\lambda(a)$, was highest in the 5–9 years age group (0·195 per susceptible year; or 19·5% of susceptible individuals infected annually), followed by the 0–4 years age group (0·139 per susceptible year). The force of infection for age groups 10–14 years and $\geqslant$15 years was 0·063 and 0·053 per susceptible year respectively. The predicted levels of seroprevalence using these values for $\lambda(a)$ are a good approximation to the observed values (Fig. 2). The average age of infection was calculated to be 8·15 years.

DISCUSSION

We describe the results of the first national serosurvey for varicella conducted in Australia. Immunity

increased rapidly to 83% by the ages of 10–14 years and was above 97% by the age of 30 years. The rapid increase in immunity between the ages of 1 and 10 years correlates with the high forces of infection calculated for these age groups.

Our results show the same pattern as that described for other developed countries, with immunity rapidly increasing with age during childhood to a high level in adults [10–16]. However, adolescents in our study had a lower level of immunity than has been reported for some other countries. Swiss and North American studies have reported that over 90% of individuals in Europe and the United States acquire immunity before adolescence [11, 16] and a study in the United Kingdom using sera collected in 1991 reported that over 90% of children had been infected by the age of 15 years [12]. On the other hand, studies in Turkey and Italy reported levels of immunity by the ages of 10–14 years that were similar to ours (85 and 82% respectively) [10, 15]. Differences between countries are likely to be related to climactic conditions and mixing patterns, particularly in relation to child care and pre-school attendance. Further modelling is under way to determine how Australia's immunity profile could be affected by future vaccination programmes.

Except for the 5–9 years age group, immunity to varicella was higher in females than males (although not significantly so overall). However, for both sexes, immunity was consistently below 90% for the 15–24 years age group. In terms of the risk of congenital and neonatal varicella, the level of susceptibility in women of child-bearing age is a concern. Other Australian studies in women attending antenatal clinics gave similar results, with the proportion susceptible ranging from 6 to 8% [17, 18].

Studies using data from the United States [19], United Kingdom and Canada [20] also identified primary-school children as having the highest force of infection and the values reported for each age group were similar to ours. This suggests that, as in other countries, a vaccination programme in Australia would need to be targeted at children less than 5 years of age. That is, prior to the age groups with high transmission rates.

A cost-effectiveness analysis in the Australian context showed that universal infant vaccination against varicella was more cost-effective than an adolescent or catch-up programme [21], but failed to consider the impact of universal vaccination on the long-term epidemiology of varicella and herpes zoster. Universal vaccination of 12-month-old children will reduce the overall incidence and morbidity of varicella. However, modelling and epidemiological studies indicate that a possible detrimental effect of this strategy may be an increased incidence of herpes zoster, which causes greater morbidity and mortality than varicella [22–24]. Further research is required to better understand the relationship between varicella and zoster as this will have important implications for any potential varicella vaccination programme in Australia.

In this national serosurvey we used a convenience sample of sera. Ideally a population-based random sample of sera should be collected. However, this method is costly and time consuming and is prone to low response rates, which could lead to biases. Although convenience samples may also be biased, any selection biases are thought to be limited in our sample because first, in Australia everyone has free access to health care and therefore diagnostic laboratory services; and secondly, we enrolled most (87%) major laboratories in the country and these laboratories are unlikely to differ in the range of diagnostic services available. This means that the sera were collected for wide variety of reasons and were mostly from ambulatory patients who are unlikely to differ from the population as a whole in terms of their susceptibility to varicella. We have also been able to demonstrate that our convenience sample of sera gave similar results to that obtained from a prospectively collected, random sample from school-aged children in Victoria for immunity levels to measles, mumps, rubella, hepatitis B, and varicella [25].

This study enhances our understanding of the epidemiology of varicella in Australia in the pre-vaccine era. It provides valuable baseline data to evaluate the impact of future vaccination policies. Our results indicate future vaccination programmes need to target young children. However there is a role for further modelling, using these data, to estimate the effect of different vaccination programmes on the epidemiology of both varicella and herpes zoster so that appropriate policies are implemented.

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