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Prevalence of infection with herpes simplex virus types 1 and 2 in Australia: a nationwide population based survey

A L Cunningham, R Taylor, J Taylor, C Marks, J Shaw, A Mindel

Background: Studies demonstrating previous herpes simplex virus (HSV) type 2 infection as a risk factor for HIV transmission, and the development of a HSV vaccine candidate, have emphasised the need for worldwide population based studies of HSV seroprevalence. The only nationwide seroprevalence studies have been conducted in the United States.

Methods: An Australia-wide, population based study of HSV-1 and HSV-2 seroprevalence was conducted, using serum and sociodemographic data collected between 1999–2000, for a representative study of risk factors for diabetes in over 11 000 adults. A stratified random sample of 4000 was tested for HSV-2 and 1000 for HSV-1, with sampling and weighting for various demographic factors.

Results: Seroprevalence of HSV-2 in Australian adults was 12%. Prevalence in women (16%) was twice that in men (8%). Rural populations had a lower prevalence (9%) than metropolitan (13%), and Indigenous had a higher prevalence (18%) than the non-Indigenous populations (12%). The seroprevalence of HSV-1 was 76% with significant differences by age group, sex and Indigenous status.

Conclusion: These are the first nationwide data to compare with US studies. HSV-2 infection is less common in Australia than the United States, and this will allow planning for combating HIV transmission in high prevalence populations in northern Australia. In addition, the high HSV-1 seroprevalence will be important for future deployment of genital herpes vaccines.

METHODS
The study used serum and sociodemographic data already collected for AusDiab, a nationwide, representative study designed to investigate diabetes and related risk factors in the Australian population (age ≥25 years), derived from subjects residing in 42 randomly selected urban and non-urban areas, based on 1996 census collection districts in each state and territory. The study was conducted between 1999 and 2000 and included over 11 000 participants (0.05% of the Australian population). The survey involved a short household interview, followed by a biomedical examination at a local survey centre. Householders not available at the initial interview were approached again, on up to four occasions. Household questionnaires were completed in 67% of the households (n = 11 479) that could be contacted and contained at least one eligible person. A total of 20 347 eligible individuals were interviewed in these 11 479 households. The final survey sample (those attending the biomedical examination) included 11 247 adults (5049 men and 6298 women), representing 55% of those completing the household interview; 44% were male, with the mean age being 51.5 years. This compares with 49.0% male in the 1998

Abbreviations: ELISA, enzyme linked immunosorbent assay; HSV, herpes simplex virus; NHANES, National Health and Nutrition Survey; OR, odds ratio; RR, relative risk; STI, sexually transmitted infections
Table 1 Demographic variation in HSV-2 seroprevalence in Australia

<table>
<thead>
<tr>
<th>HSV-2</th>
<th>No</th>
<th>Weighted†</th>
<th>Univariate RR</th>
<th>Multivariate RR*</th>
</tr>
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<tr>
<td>Age (years)</td>
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<td></td>
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<td></td>
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<tr>
<td>25–34</td>
<td>496</td>
<td>10.7 (8.0 to 13.4)</td>
<td>0.61 (0.44 to 0.84)</td>
<td>1.00</td>
</tr>
<tr>
<td>35–44</td>
<td>935</td>
<td>16.4 (14.0 to 18.7)</td>
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<td>45–54</td>
<td>1020</td>
<td>15.8 (13.6 to 18.0)</td>
<td>0.61 (0.44 to 0.84)</td>
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<td>55–64</td>
<td>678</td>
<td>11.9 (9.5 to 14.4)</td>
<td>0.61 (0.44 to 0.84)</td>
<td>1.00</td>
</tr>
<tr>
<td>65–74</td>
<td>571</td>
<td>9.3 (6.9 to 11.7)</td>
<td>0.61 (0.44 to 0.84)</td>
<td>1.00</td>
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<td>≥75</td>
<td>300</td>
<td>7.7 (4.7 to 10.7)</td>
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<td>1739</td>
<td>8.9 (7.6 to 10.3)</td>
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<td>Female</td>
<td>2261</td>
<td>16.3 (14.8 to 17.8)</td>
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<td>Capital city</td>
<td>2162</td>
<td>14.4 (12.9 to 15.9)</td>
<td>0.61 (0.44 to 0.84)</td>
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<td>Rural and remote</td>
<td>1034</td>
<td>8.7 (7.0 to 10.4)</td>
<td>0.61 (0.44 to 0.84)</td>
<td>1.00</td>
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<td>Indigenous status</td>
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<tr>
<td>Non-Indigenous</td>
<td>3885</td>
<td>12.8 (11.8 to 13.9)</td>
<td>0.61 (0.44 to 0.84)</td>
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<td>Indigenous</td>
<td>115</td>
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<td>Australia</td>
<td>4000</td>
<td>13.1 (12.1 to 14.2)</td>
<td>0.61 (0.44 to 0.84)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

95% confidence interval (CI) of rates calculated by the normal approximation of the binomial. CIs for weighted rates are based on weighted proportions but actual n (given in the table). Relative risk (RR) calculated from a Poisson regression analysis. 95% CIs of RR calculated from the Wald method using SAS.

†Weighted to the age, sex, geographic, and Indigenous structure of the 2001 Australian census population.

Analysis

In AusDiab, the proportion of participants living in state capitals, other metropolitan, and non-metropolitan areas were 65%, 7%, and 28% respectively, whereas in this study, the proportions were 54%, 20%, and 26% and the Indigenous proportion was 1%; in comparison, in this study, it is 3%. In addition, the age/sex distribution of the sample was found to differ marginally from the 1996 census because of differential response rates by age and sex.

For production of prevalence rates of HSV-1 and HSV-2, weights were calculated to adjust for: (a) purposeful oversampling of Indigenous and "other metropolitan" groups, and (b) the skewed age/sex distribution in AusDiab (compared to the census) from differential response by age and sex. Weight factors were calculated as the ratio of the proportion of a stratum in the 2001 Australian census to the proportion in the same stratum in the study population of sera. For the non-Indigenous population, the strata were age group (6), sex (2), and geographic area (3). For the Indigenous population, because of the small numbers, the strata were age group (6) and sex (2). Strata specific weights were applied to cases before tabulations of weighted prevalences.

Analysis commenced by cross tabulation of HSV-2 and HSV-1 seroprevalence with age group, sex, geography of residence, and Indigenous status. Confidence intervals (95%) were calculated using the normal approximation of the binomial, except for instances where numerators were small (<30) and the exact binomial was used. The $\chi^2$ test was used to assess heterogeneity between categories of variables. p Values are provided, and p<0.05 used to establish statistical significance. Prevalences weighted to the 2001 census are given for comparison. In this instance, 95% confidence intervals were calculated using the weighted proportions, but the actual number in each stratum (given in the tables) was given to estimate the standard error.

To examine the effects of possible confounding, Poisson regression was undertaken with each variable separately, then together in a model. Poisson regression, rather than logistic regression, was used because prevalences were considerable and the odds ratio (OR) from logistic regression only approximates the relative risk (RR) when proportions are small. In this analysis, the RR derives from the weighted prevalences. RRs are given with 95% confidence intervals. Statistical analyses were carried out in SPSS, SAS, and Stata.
TABLE 2  Demographic variation in HSV-1 seroprevalence in Australia

<table>
<thead>
<tr>
<th>HSV-1</th>
<th>No</th>
<th>Rate (%)</th>
<th>95% CI</th>
<th>Weighted†</th>
<th>Univariate RR</th>
<th>Multivariate RR*</th>
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<td>Age</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>25–34</td>
<td>124</td>
<td>68.5 (60.3 to 76.7)</td>
<td>67.0 (58.7 to 75.3)</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
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<tr>
<td>35–44</td>
<td>233</td>
<td>77.3 (71.9 to 82.7)</td>
<td>75.1 (69.6 to 80.7)</td>
<td>1.13 (0.98 to 1.29)</td>
<td>1.12 (1.00 to 1.26)</td>
<td>1.12 (1.00 to 1.26)</td>
</tr>
<tr>
<td>45–54</td>
<td>232</td>
<td>81.0 (76.0 to 86.1)</td>
<td>80.1 (75.0 to 85.2)</td>
<td>1.18 (1.03 to 1.35)</td>
<td>1.19 (1.06 to 1.34)</td>
<td>1.19 (1.06 to 1.34)</td>
</tr>
<tr>
<td>55–64</td>
<td>176</td>
<td>75.6 (69.3 to 82.0)</td>
<td>75.5 (69.2 to 81.9)</td>
<td>1.10 (0.95 to 1.27)</td>
<td>1.11 (0.98 to 1.25)</td>
<td>1.11 (0.98 to 1.25)</td>
</tr>
<tr>
<td>65–74</td>
<td>170</td>
<td>85.9 (80.7 to 91.1)</td>
<td>85.2 (79.9 to 90.5)</td>
<td>1.25 (1.09 to 1.44)</td>
<td>1.25 (1.11 to 1.41)</td>
<td>1.25 (1.11 to 1.41)</td>
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<tr>
<td>≥75</td>
<td>65</td>
<td>75.4 (64.9 to 85.9)</td>
<td>76.6 (66.3 to 86.9)</td>
<td>1.10 (1.10 to 1.33)</td>
<td>1.09 (0.93 to 1.28)</td>
<td>1.09 (0.93 to 1.28)</td>
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<tr>
<td>Sex</td>
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</tr>
<tr>
<td>Male</td>
<td>516</td>
<td>71.3 (67.4 to 75.2)</td>
<td>71.3 (67.4 to 75.2)</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
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<tr>
<td>Female</td>
<td>480</td>
<td>80.4 (76.9 to 84.0)</td>
<td>80.4 (76.9 to 84.0)</td>
<td>1.13 (1.05 to 1.21)</td>
<td>1.12 (1.05 to 1.19)</td>
<td>1.12 (1.05 to 1.19)</td>
</tr>
<tr>
<td>Geography</td>
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<td></td>
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</tr>
<tr>
<td>Capital city</td>
<td>536</td>
<td>73.7 (72.1 to 79.3)</td>
<td>73.6 (69.9 to 77.3)</td>
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<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Other metropolitan</td>
<td>193</td>
<td>82.4 (77.0 to 87.8)</td>
<td>78.9 (73.1 to 84.7)</td>
<td>1.09 (0.98 to 1.20)</td>
<td>1.08 (1.00 to 1.18)</td>
<td>1.08 (1.00 to 1.18)</td>
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<tr>
<td>Rural and remote</td>
<td>271</td>
<td>79.7 (74.9 to 84.5)</td>
<td>78.6 (73.7 to 83.5)</td>
<td>1.05 (0.96 to 1.15)</td>
<td>1.04 (0.97 to 1.12)</td>
<td>1.04 (0.97 to 1.12)</td>
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<td>Indigenous status</td>
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<td></td>
</tr>
<tr>
<td>Non-Indigenous</td>
<td>972</td>
<td>77.6 (75.0 to 80.2)</td>
<td>75.4 (72.7 to 78.1)</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Indigenous</td>
<td>28</td>
<td>96.8 (81.7 to 99.9)*</td>
<td>100.0 (87.7 to 100.0)***</td>
<td>1.24 (1.01 to 1.53)</td>
<td>1.24 (1.04 to 1.47)</td>
<td>1.24 (1.04 to 1.47)</td>
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<tr>
<td>Australia</td>
<td>1000</td>
<td>78.1 (75.5 to 80.1)</td>
<td>75.7 (73.0 to 78.4)</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
</tbody>
</table>

95% confidence interval (CI) of rates calculated by the normal approximation of the binomial except for those indicated. CIs for weighted rates are based on weighted proportions but actual n (given in the table). 95% CI of rates calculated by the normal approximation of the binomial. Relative risk (RR) calculated from a Poisson regression analysis. 95% CIs of RR calculated from the Wald method using SAS.

*Age group, sex, geography, Indigenous status.
†Weighted to the age, sex, geographic, and Indigenous structure of the 2001 Australian census population.
‡Two sided test *Exact binomial χ2(n) chi square at x degrees of freedom.

HSV antibody testing

All sera were tested for antibody to HSV-2 using an indirect enzyme linked immunosorbent assay (ELISA), specifically the HerpeSelect 2 ELISA IgG (Focus Technologies). The manufacturer recommends that an index value of >1.10 is presumptive for the presence of antibody to HSV-2. However, we have found that using this cut-off value yields a high rate of false positive results (unpublished). To overcome this problem, a cut-off value of 3.5 was used to determine HSV-2 seropositive sera. Sera that gave an equivocal result in the HerpeSelect 2 ELISA (index values 0.9–3.5) were resolved using western blot.27

A subset of the sera (see above) was tested for antibodies to HSV-1. Depending on the HSV-2 serostatus of these sera, they were tested by one of two strategies as previously described.28 If HSV-2 antibody was negative, serum was tested using the Enzygnost anti-HSV IgG ELISA (Behring) for detection of total antibody to HSV. If HSV-2 antibody was positive, serum was tested using HSV-1 western blot. This strategy was used owing to the lack of a low cost, sufficiently sensitive ELISA for antibody to HSV-1.

RESULTS

HSV-2 seroprevalence

The prevalence of HSV-2 in this large Australian population was 12%, and there were statistically significant differences by age group, sex, geography, and Indigenous status (table 1). Prevalence of HSV-2 was highest in the 25–34 year age range (14–19%) and in comparison with the youngest age group (25–34 years), the RR of HSV-2 seropositivity was 1.5 (p<0.001), adjusted for sex, geography, and Indigenous status (table 1). Women (16%) had a significantly higher prevalence of HSV-2 than men (8%) (adjusted RR 1.8). The age specific pattern of HSV-2 prevalence was similar for women and men, although the excess prevalence in women was greatest in the youngest age group (fig 1). Rural and remote populations had lower HSV-2 prevalence (9%) than capital city or other metropolitan populations (adjusted RR 0.6 compared to the capital city referent group). The Indigenous population had a significantly higher prevalence of HSV-2 (18%) than the non-Indigenous (12%) (the RR was 1.5 adjusted for age, sex, and geography).

HSV-1 seroprevalence

The prevalence of HSV-1 was 76%, and there were statistically significant differences by age group, sex, and Indigenous status (table 2). Prevalence of HSV-1 was highest in the 65–74 year age range (85%) and in comparison with the youngest age group (25–34 years), the RR of HSV-1 seropositivity was 1.25, adjusted for sex, geography, and Indigenous status. Women (80%) had significantly higher prevalence of HSV-1 than men (71%) (adjusted RR 1.12). The age specific pattern of HSV-1 prevalence was broadly similar for women and men (fig 2). There were no statistically significant differences in HSV-1 prevalence by geography. However, the Indigenous population had a higher prevalence of HSV-1 (close to 100%) than the non-Indigenous population (75%) (RR 1.24 adjusted for age, sex and geography) (table 2).

DISCUSSION

This is the first representative, nationwide, population based survey of HSV-1 and HSV-2 seroprevalence undertaken.
outside the United States and showed that the prevalence of HSV-1 and HIV-2 antibodies in Australia were 76% and 12%, (at a mean age of 45–50). Analysis of HSV-1 and HSV-2 seroprevalence for available demographic factors; age, geography, sex, and Indigenous status revealed marked and significant differences for HSV-2, but much smaller differences for HSV-1 seroprevalence. Thus, the HSV-2 seroprevalence increased to a peak of 16% at ages between 35 and 44, and declined thereafter to ~8% in those over 65 years. Females had a significantly higher seroprevalence than males, again peaking at 35–44 and subjects in metropolitan areas, especially capital cities, had a significantly higher seroprevalence compared with those in rural areas. There was also a significantly higher HSV-1 (100% v 75%) and HSV-2 seroprevalence (18% v 12%), comparing Indigenous and non-Indigenous Australians.

The higher prevalence of HSV-2 antibody in Indigenous populations is consistent with a relatively high incidence of sexually transmitted infections in some of these populations. The relatively small number of Indigenous people in our survey did not allow further distinction between rural and metropolitan communities. Further studies should focus specifically on Indigenous people, particularly in census districts where they predominate.

This study and our previous studies in pregnant women in western Sydney confirm that Australia has a relatively low HSV-2 seroprevalence compared with most other countries. Conversely, HSV-1 seroprevalence in Australia is higher than in the United States and many parts of Europe. In some developed countries, there has been a reduction in overall HSV-1 seroprevalence over recent decades as a result of decreased acquisition in infancy. In contrast, worldwide, there is a trend towards increasing sexual acquisition of HSV-1 in adolescence and early adulthood, and this trend is also apparent in Australia. Therefore, HSV-2 seroprevalence is now less accurate as a predictor of the overall burden of genital herpes. This is offset by the fact that genital HSV-1 recurs much less frequently than HSV-2. HSV-1 seroprevalence and early infant acquisition is much higher in many developing countries, where adult seroprevalence nears 100%. This is similar to the HSV-1 seroprevalence documented in the Indigenous people in our survey. Such high levels of HSV-1 acquisition probably reflect extensive infant salivary spread in poorer hygienic conditions. Nevertheless, the reasons for higher overall HSV-1 seroprevalence in Australia, compared with the United States, require further studies of acquisition in infancy and in adolescence.

Unfortunately, this study lacked data from people aged 25 or younger. Information from NHANES II and III and other studies in high risk individuals, or selected populations around the world, have shown that HSV-2 seroprevalence increases rapidly from the mid-teens to the mid-twenties and then continues to slowly increase in the older age groups. The few studies that have looked at HSV-2 seroprevalence in younger adolescents and children, have shown that this infection is uncommon in people below the age of 15. In Australia, further studies will be required to determine HSV-2 seroprevalence in these younger age groups.

Many studies and a meta-analysis of them, have indicated that previous genital HSV-2 infection is a risk factor for spread of HIV. The contribution to spread (attributable risk) is proportional to seroprevalence. Thus, in some African countries, where HSV-2 seroprevalence is more than 80%, the attributable risk may rise to 40%. This provides a rationale for the current trials of suppression of recurrences of genital HSV-2 with aciclovir in an attempt to reduce HIV transmission. Knowledge of variations of HSV-2 seroprevalence and hence susceptibility to HIV between populations or countries, should allow closer monitoring and early detection of HIV in these populations. Spread of HIV from Papua New Guinea to populations in northern Australia could be facilitated by previous HSV-2 infection among high risk (Indigenous) Australians.

As previous HSV-1 infection reduces the severity of disease and may or may not protect against HSV-2 infection, differences in seroprevalence between countries may alter the patterns of genital HSV-2 disease or even infection. Differences in HSV-1 seroprevalence are likely to influence the efficacy of the HSV-2 glycoprotein D2-dMPL vaccine manufactured by GSK (Simplirix), as efficacy has only been demonstrated in women with no previous antibodies to HSV-1 or HSV-2. Therefore, in preparing for potential deployment of the vaccine in each country, it is important that there is an accurate estimate of HSV-1 seroprevalence in adolescent and adult populations. In some countries, or even some populations in other countries, very high HSV-1 seroprevalence might make deployment very difficult.

ACKNOWLEDGMENTS
We thank Dr P Zimmet for assistance facilitating the study and invaluable advice about access to the AusDiab database and to the serum bank.

CONTRIBUTORS
ALC, RT, and AM, concept and design; ALC, AM, RT and JT, manuscript writing; JS, epidemiological data collection; JT, HIV serological testing; RT, CM, data analysis; all authors, manuscript review.

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Conflict of interest: none.

REFERENCES