Background. Representative population-based data on human papillomavirus (HPV) epidemiology are important for public health decision making but are difficult to obtain. Seroepidemiology is a valuable tool, although the relationship between HPV infection and seropositivity is incomplete.

Methods. We obtained a large representative sample using residual diagnostic test serum samples obtained from individuals aged 0–69 years (1247 samples from male patients and 1523 samples from female patients) in Australia. Serum antibody levels to HPV types 6, 11, 16, and 18 were measured using an immunoassay.

Results. Overall, seroprevalence of HPV types 6 and 16 was higher than seroprevalence of HPV types 11 and 18. Among female patients, peak HPV seropositivity occurred among those who were 30–39 years of age for types 6, 16, and 18 (22%, 22%, and 10.5%, respectively) and among those who were 40–49 years of age for HPV 11 (11.8%). Among male subjects, peak HPV seropositivity occurred among those who were 40–49 years of age for types 6 and 11 (15.4% and 9.1%, respectively) and among those who were 50–59 years of age for types 16 and 18 (14.3% and 8.2%, respectively). No cases of HPV seropositivity were detected in individuals <10 years of age.

Conclusions. Australian seroepidemiological data, showing differing age-specific patterns of HPV seropositivity in male and female patients, are likely to be generalizable to other developed countries and add to other data supporting completion of HPV vaccination before adolescence.

Human papillomavirus (HPV) infection is the most common of all sexually transmitted infections, with up to three-quarters of the general population infected at some time in their lives [1]. HPV is the causative agent in almost all cases of cervical cancer [2], and HPV types 16 and 18 are responsible for the majority (70%–80%) of cases of cervical cancer worldwide [3]. There are 2 main vaccine candidates, a bivalent vaccine targeted at HPV types 16 and 18 and a quadrivalent vaccine targeted at both the oncogenic HPV types 16, 18 and HPV types 6 and 11 (which are the HPV types primarily responsible for genital warts) [5]. Two recent studies have reported that the type-specific efficacy of the quadrivalent vaccine was 98% for the prevention of high-grade cervical lesions [6] and 100% for the prevention of anogenital disease, such as vulvar and vaginal intraepithelial neoplasia and genital warts [7], in women naive to the vaccine HPV types prior to vaccination.

The general population epidemiology of HPV infection is not well described. Most previous studies have used HPV DNA identified in genital specimens from sexually active women [8–13]. Although sexually active women are the target for prevention of cervical cancer, disease transmission occurs across the population, necessitating better understanding of the population epidemiology of HPV infection for optimal disease control. Measurement of the serum antibody response to HPV capsids or virus-like particles (VLPs) is a practical means of studying population-based HPV epidemiol-
ogy that has several advantages. First, cross-sectional seroprevalence can detect past HPV infection, whereas genital specimens measure only current infections, which are mostly transient and undetectable (via HPV DNA testing) within 2 years after infection [14], so that HPV seroprevalence is usually significantly higher than HPV DNA prevalence [15, 16]. Second, serological testing of a representative population provides information about both sexes and all ages without the need for collection of invasive genital specimens (which is associated with poor participation rates). Third, detection of HPV DNA from genital surfaces is prone to sampling errors [17]. Serological testing for HPV using VLPs has a sensitivity of 50%–60% and a high specificity (>90%), compared with genital HPV DNA testing [17].

The use of serological assays to measure HPV type-specific biomarkers by age provides a powerful way to estimate—and ultimately, monitor—the impact of HPV vaccines. The aim of this study was to determine the seroprevalence of HPV types 6, 11, 16, and 18 in Australian male and female subjects 0–69 years of age. The median age of first sexual intercourse in Australia is currently 16 years [18]. This is the first study to determine HPV seroprevalence in Australia and, to our knowledge, is the first serological study to estimate population prevalence in all ages against all 4 vaccine-preventable HPV types. These data are valuable for planning and monitoring, because the optimum control of HPV infection may require vaccination of both males and females at an early age. These data are likely to be applicable to many industrialized countries planning large-scale HPV vaccination programs.

METHODS

Study population. Serum samples were collected in the second 6 months of 2005 from public and private laboratories in the 3 most populous states of Australia (New South Wales, Victoria, and Queensland) with use of a validated sampling method for serosurveillance [19]. These states account for almost 80% of the population of Australia. We used a convenience sample of serum samples that were originally submitted for diagnostic testing and would otherwise have been discarded. Demographic data were limited to age group, sex, and date of sample collection. For the analysis, serum samples were stratified into the following age groups: 0–4, 5–9, 10–14, 15–19, 20–29, 30–39, 40–49, 50–59, and 60–69 years of age.

In all age groups, the sample size was calculated to achieve a point estimate of seroprevalence with 95% CIs of ±3%–5%, on the basis of the expected seroprevalence of HPV type 16 [20], and with consideration of the mean cumulative number of lifetime sexual partners by age cohort, as reported by the Australian Study of Health and Relationships [21]. Slightly more serum samples from female subjects (1523 samples) than from male subjects (1247 samples) were tested. Because no significant differences were noted between the age groups 0–4 years and 5–9 years, these age groups were combined for the analysis. Exclusion criteria were those established for the national serosurveys for vaccine preventable diseases [22]. Serum samples obtained from subjects who were immunosuppressed, had received multiple or recent transfusions (i.e., within 3 months), or were known to be infected with HIV were excluded on the basis of clinical information available to the pathology provider. The samples were tested for HPV type-specific antibodies at Merck Research Laboratories (Wayne, Pennsylvania). To estimate overall population HPV seroprevalence, the results were weighted to 2005 Australian midyear population estimates by age [23].

Serological measurements. Serum anti-HPV L1 6, 11, 16, and 18 antibody levels were measured using a competitive Luminex immunoassay (Merck) [24, 25] and were reported in arbitrary units (milli-Merk units per mL). Antibody titers were determined in a competitive format, in which known, type-specific, phycoerythrin-labeled, neutralizing antibodies compete with serum antibodies for binding to conformationally sensitive, neutralizing epitopes on the VLPs. The monoclonal antibodies used in the HPV competitive Luminex immunoassay included H6.M48, Kll.B2, H16.V5, and H18.J4 for HPV types 6, 11, 16, and 18, respectively. Seropositivity for HPV was defined as having anti-HPV titers ≥20, ≥16, ≥20, and ≥24 milli-Merk units per mL for HPV types 6, 11, 16, and 18, respectively. The seropositivity cutoff value is the level of response that distinguishes an antibody-negative sample from an antibody-positive sample.

Statistical methods. We defined the 15–19-year-old age group as a reference category to assess any significant differences in seropositivity for at least 1 HPV type (6, 11, 16, or 18) before (age, 10–14 years) and after (age, 20–24 years) the median age of sexual debut in the Australian population (16 years) [26]. Male and female subjects were unstratified separately.

Ethics approval. The study was approved by Western Sydney Area Health Service Human Research Ethics Committee. All samples were de-identified.

RESULTS

Results by sex, age group, and seropositivity to individual HPV types are presented in tables 1 and 2. In general, there was higher seropositivity for HPV types 6 and 16 across the whole population. The observed seropositivity for these HPV types was higher among female subjects than among male subjects. In female subjects, peak HPV seropositivity occurred in the 30–39-year-old age group for HPV types 6, 16, and 18 (22%, 22%, and 10.5%, respectively) and in the 40–49-year-old age group for HPV type 11 (11.8%). In male subjects, peak HPV seropositivity occurred in the 40–49-year-old age group for HPV types 6 and 11 (15.4% and 9.1%, respectively) and in the 50–
Table 1. Seropositivity for individual human papillomavirus (HPV) types in the female population, by age group.

<table>
<thead>
<tr>
<th>Age group</th>
<th>No. of samples tested</th>
<th>Proportion positive, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>HPV type 6</td>
</tr>
<tr>
<td>0–9 years</td>
<td>128</td>
<td>0.0 (0.0–2.8)</td>
</tr>
<tr>
<td>10–14 years</td>
<td>95</td>
<td>1.1 (0.5–5.7)</td>
</tr>
<tr>
<td>15–19 years</td>
<td>142</td>
<td>7.0 (3.4–12.6)</td>
</tr>
<tr>
<td>20–29 years</td>
<td>247</td>
<td>15.0 (10.8–20.1)</td>
</tr>
<tr>
<td>30–39 years</td>
<td>313</td>
<td>22.0 (17.6–27.1)</td>
</tr>
<tr>
<td>40–49 years</td>
<td>288</td>
<td>18.8 (14.4–23.7)</td>
</tr>
<tr>
<td>50–59 years</td>
<td>158</td>
<td>17.7 (12.1–24.6)</td>
</tr>
<tr>
<td>60–69 years</td>
<td>152</td>
<td>9.9 (5.6–15.8)</td>
</tr>
<tr>
<td>All*</td>
<td>1523</td>
<td>12.9 (11.4–14.6)</td>
</tr>
</tbody>
</table>

* Weighted population total, with estimates weighted by age distribution of the 2005 Australian midyear population estimates from the Australian Bureau of Statistics.

Table 2. Seropositivity for individual human papillomavirus (HPV) types in the male population, by age group.

<table>
<thead>
<tr>
<th>Age group</th>
<th>No. of samples tested</th>
<th>Proportion positive, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>HPV type 6</td>
</tr>
<tr>
<td>0–9 years</td>
<td>148</td>
<td>0.0 (0.0–2.5)</td>
</tr>
<tr>
<td>10–14 years</td>
<td>119</td>
<td>0.0 (0.0–3.1)</td>
</tr>
<tr>
<td>15–19 years</td>
<td>165</td>
<td>0.6 (0.0–3.3)</td>
</tr>
<tr>
<td>20–29 years</td>
<td>209</td>
<td>9.6 (5.9–14.4)</td>
</tr>
<tr>
<td>30–39 years</td>
<td>172</td>
<td>15.1 (10.1–21.4)</td>
</tr>
<tr>
<td>40–49 years</td>
<td>143</td>
<td>15.4 (9.5–22.4)</td>
</tr>
<tr>
<td>50–59 years</td>
<td>147</td>
<td>12.9 (8.0–19.4)</td>
</tr>
<tr>
<td>60–69 years</td>
<td>144</td>
<td>10.4 (5.9–16.6)</td>
</tr>
<tr>
<td>All*</td>
<td>1247</td>
<td>9.1 (7.5–10.8)</td>
</tr>
</tbody>
</table>

* Weighted population total, with estimates weighted by age distribution of the 2005 Australian midyear population estimates from the Australian Bureau of Statistics.

59-year-old age group for HPV types 16 and 18 (14.3% and 8.2%, respectively). The steepest increase in seroprevalence in any group was for HPV type 6 (figure 1A) in women, which increased from 7.0% among women aged 15–19 years to 15.0% among women aged 20–29 years. Similarly, seroprevalence of HPV type 16 more than doubled, from 7.0% among women in the 15–19-year-old age group to 14.6% among women in the 20–29-year-old age group. Women aged 20–29 years were further divided into those in the 20–24-year-old age group (123 subjects), among whom seroprevalence was 12.2%, 4.9%, 10.6%, and 3.3% for HPV types 6, 11, 16, and 18, respectively, and those in the 25–29-year-old age group (124 subjects), among whom seroprevalence was 17.7%, 4.0%, 18.5%, and 8.9% for HPV types 6, 11, 16, and 18, respectively. In male subjects, the steepest increase in seroprevalence was for HPV type 6 (figure 1B), which increased from 0.6% in the 15–19-year-old age group to 9.6% in the 20–29-year-old age group. No samples obtained from individuals <10 years of age were seropositive for any HPV type for either sex.

Results by sex, age group, and combinations of HPV seropositivity are presented in tables 3 and 4. These combinations are: (1) HPV types 16 or 18 (i.e., oncogenic) seropositivity; (2) HPV types 6 or 11 (i.e., genital warts–related) seropositivity; (3) seropositive to HPV types 6, 11, 16, or 18; (4) seropositive to both HPV type 16 and HPV type 18; and (5) seropositive to all 4 HPV types tested (HPV types 6, 11, 16, and 18). These combinations were included to assist in assessing the potential benefits of vaccination in different age and sex groups. Seropositivity for any HPV type (6, 11, 16, or 18) peaked at 38.7% among women aged 30–39 years and at 31.5% among men aged 40–49 years (figure 2). Seropositivity for all 4 HPV types was rare among both men and women, and it peaked at a later age (1.7% among 40–49-year-old women and 2.1% among 40–49-year-old men). For the weighted population total, seropo-
itivity for at least 1 of the oncogenic types (HPV types 16 or 18) was significantly more common among women (15.2%; 95% CI, 13.5%–16.9%) than it was among men (10.1%; 95% CI, 8.4%–11.9%) (tables 3 and 4). Seropositivity for at least 1 of the types causing genital warts (HPV types 6 and 11) was also significantly more common among women (15.3%; 95% CI, 13.6%–17.0%) than among men (11.4%; 95% CI, 9.6%–13.3%).

With use of those aged 15–19 years as the reference category (male or female subjects, as appropriate), seropositivity to at least 1 HPV type (6, 11, 16, or 18) was significantly higher for both male subjects (OR, 6.61; 95% CI, 1.86–25.63) and female subjects (OR, 1.92; 95% CI, 1.01–3.68) aged 20–24 years and was significantly lower among female subjects aged 10–14 years (OR, 0.18; 95% CI, 0.04–0.65). No statistically significant difference in the rate of HPV seropositivity was observed for male subjects aged 10–14 years (OR, 0.0; 95% CI, 0.0–2.11).

**DISCUSSION**

To our knowledge, this is the first seroepidemiologic study to measure the cross-sectional prevalence of antibodies to HPV types 6, 11, 16, and 18 at a population level in men, women, and children. Particular strengths of the study are data on seroprevalence in children and males, large sample size, and use of a validated assay identical to that used in phase III quadrivalent HPV vaccine trials [5–7]. We found that HPV seroprevalence among Australian women peaked in the 30–39-year-old age group and then decreased with age. This is consistent with cross-sectional data showing that the peak age in self-reported lifetime number of sexual partners for Australian women occurs in this age group [21]. A similar peak in middle age was also observed in the largest study of HPV seroprevalence among women to date [15], with the seroprevalence of most HPV types peaking in Costa Rican women at 35–44 years of age before decreasing. A recent seroprevalence study involving English females noted an earlier peak, with a decrease in seroprevalence after the mid-twenties [27]. This decline in seropositivity in older age groups could be the result of a cohort effect (i.e., in general, older women have had fewer lifetime sexual partners than younger women because of changing patterns of sexual behavior) or could reflect the eventual waning of antibody levels and resultant limitation of serological testing.
### Table 3. Seropositivity for combinations of human papillomavirus (HPV) types in the female population, by age group.

<table>
<thead>
<tr>
<th>Age group</th>
<th>No. of samples tested</th>
<th>HPV types 6 or 18</th>
<th>HPV types 6 or 11</th>
<th>Any HPV type 6, 11, 16, or 18</th>
<th>HPV type 16 and 18</th>
<th>All HPV types</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–9 years</td>
<td>128</td>
<td>0.0 (0.0–2.8)</td>
<td>0.0 (0.0–2.8)</td>
<td>0.0 (0.0–2.8)</td>
<td>0.0 (0.0–2.8)</td>
<td>0.0 (0.0–2.8)</td>
</tr>
<tr>
<td>10–14 years</td>
<td>95</td>
<td>2.1 (0.3–7.4)</td>
<td>1.1 (0.0–5.7)</td>
<td>3.2 (0.7–9.0)</td>
<td>0.0 (0.0–3.8)</td>
<td>0.0 (0.0–3.8)</td>
</tr>
<tr>
<td>15–19 years</td>
<td>142</td>
<td>10.6 (6.0–16.8)</td>
<td>7.7 (3.9–13.4)</td>
<td>15.5 (10.0–22.5)</td>
<td>1.4 (0.2–5.0)</td>
<td>0.7 (0.0–3.9)</td>
</tr>
<tr>
<td>20–29 years</td>
<td>247</td>
<td>18.2 (13.6–23.6)</td>
<td>18.2 (13.6–23.6)</td>
<td>30.0 (24.3–36.1)</td>
<td>2.4 (0.9–5.2)</td>
<td>0.4 (0.0–2.2)</td>
</tr>
<tr>
<td>30–39 years</td>
<td>313</td>
<td>26.8 (22.0–32.1)</td>
<td>23.6 (19.0–28.7)</td>
<td>38.7 (33.2–44.3)</td>
<td>5.8 (3.4–8.9)</td>
<td>0.6 (0.1–2.3)</td>
</tr>
<tr>
<td>40–49 years</td>
<td>288</td>
<td>23.3 (18.5–28.6)</td>
<td>24.0 (19.1–29.3)</td>
<td>35.1 (29.6–40.9)</td>
<td>4.2 (2.2–7.2)</td>
<td>1.7 (0.6–4.0)</td>
</tr>
<tr>
<td>50–59 years</td>
<td>158</td>
<td>15.8 (10.5–22.5)</td>
<td>19.0 (13.2–26.0)</td>
<td>25.9 (19.3–33.5)</td>
<td>4.4 (1.8–8.9)</td>
<td>1.3 (0.2–4.5)</td>
</tr>
<tr>
<td>60–69 years</td>
<td>152</td>
<td>11.8 (7.2–18.1)</td>
<td>15.1 (9.8–21.8)</td>
<td>23.0 (16.6–30.5)</td>
<td>1.3 (0.2–4.7)</td>
<td>0.0 (0.0–2.4)</td>
</tr>
<tr>
<td>Alla</td>
<td>1523</td>
<td>15.2 (13.5–16.9)</td>
<td>15.3 (13.6–17.0)</td>
<td>23.8 (21.8–25.8)</td>
<td>2.9 (2.0–3.7)</td>
<td>0.7 (0.3–1.1)</td>
</tr>
</tbody>
</table>

* Weighted population total, with estimates weighted by age distribution of the 2005 Australian midyear population estimates from the Australian Bureau of Statistics.

As a measurement of cumulative HPV exposure [15], although the humoral response to HPV infection is generally considered to be relatively stable [17, 28], there is evidence of a decrease in antibody titer in some women over time [29, 30].

Our finding that seroprevalence of HPV types 6 and 16 was higher among women than among men is consistent with other studies [20, 30, 31]. The most likely explanation is the extent of HPV exposure to the humoral immune system [20], because HPV infection in males usually involves keratinized epithelium, which is external, whereas infection in females involves the mucosal epithelium and a genital anatomy that may be more conducive to harboring the virus. However, this explanation does not account for the lack of difference in seropositivity for HPV types 11 and 18 between sexes. The lack of a statistically significant difference in seroprevalence between males and females for HPV types 11 and 18, which had lower overall seroprevalence than that of HPV types 6 and 16, may be attributable to a lack of statistical power. Consistent with US seroprevalence data for HPV type 16 only [20], seropositivity peaked slightly later in men (in the 40–49-year-old age group) than in women.

No seropositivity was found in children <10 years of age in the Australian population. Previous studies have found low levels of seropositivity in young children [32, 33]. Persistent maternal IgG may explain seropositivity when detected in infants [34, 35]. Vertical transmission, horizontal buccal transmission, or sexual abuse are more likely to account for the presence of HPV antibody positivity in older children [33, 36]. The lack of seropositivity found in this study suggests that these modes of transmission are rare or do not produce seroconversion.

When interpreting our data, it is important to note that cross-sectional HPV serological testing cannot differentiate between past or current HPV infection, nor can it differentiate between transient HPV infection and persistent HPV infection. However, prospective cohort studies show that the sensitivity of HPV serological testing is higher for persistent infection [37]. Among women in whom the presence of HPV DNA is verified

### Table 4. Seropositivity for combinations of human papillomavirus (HPV) types in the male population, by age group.

<table>
<thead>
<tr>
<th>Age group</th>
<th>No. of samples tested</th>
<th>HPV types 6 or 18</th>
<th>HPV types 6 or 11</th>
<th>Any HPV type 6, 11, 16, or 18</th>
<th>HPV type 16 and 18</th>
<th>All HPV types</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–9 years</td>
<td>148</td>
<td>0.0 (0.0–2.5)</td>
<td>0.0 (0.0–2.5)</td>
<td>0.0 (0.0–2.5)</td>
<td>0.0 (0.0–2.5)</td>
<td>0.0 (0.0–2.5)</td>
</tr>
<tr>
<td>10–14 years</td>
<td>119</td>
<td>0.0 (0.0–3.1)</td>
<td>0.0 (0.0–3.1)</td>
<td>0.0 (0.0–3.1)</td>
<td>0.0 (0.0–3.1)</td>
<td>0.0 (0.0–3.1)</td>
</tr>
<tr>
<td>15–19 years</td>
<td>165</td>
<td>1.2 (0.1–4.3)</td>
<td>1.2 (0.1–4.3)</td>
<td>2.4 (0.7–6.1)</td>
<td>0.0 (0.0–2.2)</td>
<td>0.0 (0.0–2.2)</td>
</tr>
<tr>
<td>20–29 years</td>
<td>209</td>
<td>8.6 (5.2–13.3)</td>
<td>13.4 (8.1–18.8)</td>
<td>19.1 (14.0–25.1)</td>
<td>0.5 (0.0–2.6)</td>
<td>0.0 (0.0–1.7)</td>
</tr>
<tr>
<td>30–39 years</td>
<td>172</td>
<td>15.1 (10.1–21.4)</td>
<td>17.4 (12.1–24.0)</td>
<td>27.3 (20.8–34.6)</td>
<td>2.3 (0.6–5.8)</td>
<td>0.6 (0.0–3.2)</td>
</tr>
<tr>
<td>40–49 years</td>
<td>143</td>
<td>18.2 (12.2–25.5)</td>
<td>20.3 (14.0–27.8)</td>
<td>31.5 (24.0–39.8)</td>
<td>3.5 (1.1–8.0)</td>
<td>2.1 (0.4–6.0)</td>
</tr>
<tr>
<td>50–59 years</td>
<td>147</td>
<td>19.0 (13.0–26.3)</td>
<td>15.6 (10.2–22.5)</td>
<td>25.9 (19.0–33.7)</td>
<td>3.4 (1.1–7.8)</td>
<td>1.4 (0.2–4.8)</td>
</tr>
<tr>
<td>60–69 years</td>
<td>144</td>
<td>8.3 (4.4–14.1)</td>
<td>11.8 (7.0–18.2)</td>
<td>18.8 (12.7–26.1)</td>
<td>2.1 (0.4–6.0)</td>
<td>0.0 (0.0–2.5)</td>
</tr>
<tr>
<td>Alla</td>
<td>1247</td>
<td>10.1 (8.4–11.9)</td>
<td>11.4 (9.6–13.3)</td>
<td>17.8 (15.7–20.0)</td>
<td>1.7 (0.9–2.4)</td>
<td>0.6 (0.1–1.1)</td>
</tr>
</tbody>
</table>

* Weighted population total, with estimates weighted by age distribution of the 2005 Australian midyear population estimates from the Australian Bureau of Statistics.
Figure 2. Cross-sectional seropositivity to any human papillomavirus type (6, 11, 16, and 18), by sex and age group

by 2 independent tests (i.e., among women with persistent HPV infection), >75% are seropositive, whereas among those women with discordant results (i.e., those women with transient infection), only 20% are seropositive for HPV [38]. Carter et al. [29] found, with use of a VLP-based ELISA, that 68.8%, 59.5%, and 54.1% of women experienced seroconversion for HPV types 6, 16, and 18, respectively, within 18 months after detection of type-specific HPV DNA in genital specimens. Other investigators have reported that seroconversion to HPV type 16 occurred most often 6–12 months after HPV DNA detection [39–41]. Transient HPV DNA (i.e., detected only at a single visit) has been associated with failure to experience seroconversion [37, 38, 41]. Thus, the HPV seroprevalence data reported here should be viewed as minimum measures of the prevalence of HPV infection; the likely proportions of the population who have been infected, including individuals with transient infection, are perhaps double the seroprevalence estimates presented here. Although the sensitivity of HPV serological testing for measuring past or current HPV infection is limited, the specificity is high (>90%) [17].

Comparison of data across studies should be done with caution, because the accuracy of HPV serological measures are affected by the type of assay used and the associated seropositivity cutoff values. Differences in seropositivity cutoff values can make comparison between epidemiological studies difficult [17]. In this study, we used serostatus cutoff values that are consistent with those used in a growing number of HPV seroprevalence studies [42, 43] and vaccine efficacy and immunogenicity studies [44–47]. There are currently efforts by the World Health Organization and the National Institute for Biological Standards and Controls to develop both HPV type 16 and HPV type 18 serological reference standards [48, 49]. The serum antibody response to HPV virions is polyclonal, with many cross-reactive antibodies generated. Generally, however, neutralizing antibodies against HPV are type-specific, with the exception of cross-reactive antibodies between HPV types 6 and 11 and low levels of cross-reactive antibodies between HPV types 31 and 33 and HPV types 45 and 18 [17, 50]. The assay used in this study measures antibodies to type-specific, conformational, neutralizing epitopes on the VLPs and shows little cross-reactivity [24]. It is not known whether naturally acquired HPV antibody response to an HPV type provides protection against reinfection or subsequent infection due to related types.

Although high levels of type-specific HPV antibodies generated through HPV vaccination have been shown to correlate with protection [4, 6, 7], there is, at present, no known minimum antibody level that confers protection. It is unclear whether those who have generated a natural antibody response through clearing a past HPV infection remain at risk of reinfection.

There are potential limitations to our study in relation to our sampling strategy. We obtained samples from only the most populous areas of Australia, and the results may not be applicable to specific subpopulations, particularly indigenous people, who are known to have a higher risk of sexually transmitted infection [51] and may have different HPV type distributions. Furthermore, samples were not collected from a random population sample but from serum samples submitted for diagnostic testing. This could affect the generalizability of our findings to the Australian population and, consequently, to other comparable populations. However, use of residual serum samples submitted for diagnostic testing has major cost and logistic advantages, and there is no reason to believe that individuals whose samples were tested would differ systematically from the general population with respect to lifetime number of sex partners, which is the major risk factor for HPV infection [39, 52–57]. The methodology used in the national serosurveillance program has previously been shown to yield results for diseases such as measles, mumps, rubella, varicella, and hepatitis B that are comparable to results obtained through cluster randomized
sampling [19]. Further, a direct comparison of opportunistic sampling with a prospectively collected community sample showed comparable seroprevalence estimates for measles [58].

Results of the study should be applicable to the populations of other developed countries, such as the United States and the United Kingdom. The median age of first sexual intercourse (currently 16 years of age in Australia [18], as in the United Kingdom [59] and Canada [60]) is similar in many developed countries [61]. Such sexual behavioral characteristics are likely to have a large impact on the risk of HPV exposure. HPV type 16 seroprevalence in our study was comparable to the findings of the only published population-based study of HPV seroprevalence in the United States [20], with overlapping confidence intervals for males and females in all matching age groups. The higher seroprevalence of HPV type 6 (compared with HPV type 11) and HPV type 16 (compared with HPV type 18) found in our study match similar findings in a recent US study of HPV DNA prevalence [10] and UK seroprevalence data [27], which again suggests the generalizability of our data.

Our findings have important implications for vaccine policy. Whereas previous Australian [8, 62] and US cross-sectional studies [10] of HPV DNA prevalence found low levels of vaccine-preventable types, we found, using serological testing, that exposure to the oncogenic HPV types 16 and 18 and genital warts associated with HPV types 6 and 11 is common. Our results confirm that primary prophylactic HPV vaccination programs should be targeted at preadolescents, because HPV seropositivity begins to increase markedly after 10 years of age. This is a powerful argument to counter the moral and religious opposition to vaccination of preadolescent girls [63]. The rapid increase in seropositivity in teenagers and young women suggests that vaccination after adolescence will be less effective, because many women will have already been infected with HPV, and some will already be chronically infected. Should HPV vaccines prove to be efficacious in males, our results also indicate that immunization before adolescence would be the preferred strategy for males. Previous experience with rubella immunization has demonstrated that optimal disease control at a population level, even if significant morbidity is confined to one sex, may require vaccination of both sexes and an early age of first vaccination [64, 65]. To ensure maximal impact, the age of vaccination will need to be weighed against the expected duration of vaccine efficacy, which is an issue of some uncertainty [66]. The unique population data provided by this study will inform disease transmission models assessing optimal vaccination strategies and will provide a baseline for monitoring the impact of current and future vaccination programs.

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