Full length Article

HPV genotype prevalence in Australian women undergoing routine cervical screening by cytology status prior to implementation of an HPV vaccination program

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Abbreviations: HPV: human papillomavirus; CIN: cervical intraepithelial neoplasia; LSIL: low-grade squamous intraepithelial lesion; HSIL: high-grade intraepithelial lesion.

Abstract: 237 words

No. words in text: 2494
Abstract:

Background: Data on the prevalence of cervical HPV genotypes in Australia by age and by grade of cytological abnormality are sparse.

Objective: Measure prevalence of HPV genotypes among 2620 Australian women by age and cytology status.

Study Design: Women presenting for routine Pap smear screening were recruited from diverse regions, including a significant sample of Indigenous women. DNA extracts prepared from Thinprep specimens were HPV genotyped by Roche LINEAR ARRAY HPV.

Results: HPV prevalence and genotype distribution were stratified by age (mean 32.6y) and Pap smear result (cytology normal in 86.7%). Overall HPV prevalence was 38.7% with high-risk HPV prevalence of 26.5%. Prevalence of HPV (66.3% in women <21y to 15.3% in women >40y), multiple HPV infection (45.5% in <21y to 5.8% in >40y) and vaccine-targeted genotypes (HPV 6/11/16/18) (34.1% in <21y to 2.4% in >40y) declined significantly with age. The six most common genotypes were: HPV 16 (8.3%), 51 (5.1%), 53 (4.7%), 62 (4.3%), 89 (3.9%) and 52 (3.8%). HR-HPV prevalence increased from 21.1% in women with normal cytology to 80.9% in those with cytologically predicted high-grade abnormalities (HGAs) (p <0.001). The most common genotypes in women with HGAs were HPV 16 (51.1%), 18 (14.9%), 52 (12.8%), 31 (10.6%), and 33 (10.6%): all HR-types.

Conclusion: Pre-vaccination cross-sectional prevalence of HR-HPV infection was high in this sample of Australian women attending for screening. HPV 16 was the commonest high-risk type detected at all ages and cytological grades.
24   **Keywords:** human papillomavirus, genotype, cervical cytology, cervical cancer, CIN,
25   linear array
1. Background:

Carcinoma of the cervix is a significant cause of mortality in women, accounting for around 275,000 deaths worldwide annually. Mortality rates have significantly reduced over time in developed countries due to successful cervical screening programs using the Papanicolaou test, aimed at early detection of cytological abnormalities.

Infection with an oncogenic or high-risk human papillomavirus (HPV) genotype is the major causative factor for development of precancerous high-grade cervical intraepithelial lesions (CIN2/3) and ultimately cervical cancer. However, the majority of cervical HPV infections are transient, asymptomatic and cleared by host immunity. There are approximately 40 known genotypes that specifically target the anogenital mucosa which are divided into low-risk (LR) and high-risk types, through epidemiological association with anogenital cancers.

Virtually all cases of cervical cancer and/or high-grade CIN2/3 are preceded by persistent HR-HPV infection(s).

Currently, there are two licensed prophylactic HPV vaccines; a bivalent HPV 16/18 (Cervarix) vaccine and a quadrivalent HPV 6/11/16/18 (Gardasil®) one. Both vaccines prevent infection with the two major oncogenic types causing 70% of cancers of the cervix, while the quadrivalent vaccine also targets HPV types causing over 90% of genital wart cases. In Australia, the quadrivalent HPV vaccine was approved for use in 2006, with free vaccination being made available for school-aged girls from April 2007 through the national HPV vaccination program (12–18 years-old). Between July 2007 and December 2009 the vaccine
was also offered free to all women under the age of 27 years through community vaccination providers. The free school-based program for 12 to 13-year-old girls is ongoing, with adolescent males being added from February 2013.

Prior to HPV vaccination in Australia, information on HPV type-specific prevalence across the general population was limited. Most HPV genotyping studies in Australia focused on the analysis of biopsies/liquid-based samples from patients with CIN2/3 and/or cervical cancer\(^{(13-17)}\). From these studies, HPV 16 and 18 were identified as the most common genotypes among women with higher grade disease, in line with international findings. However, very little is known about the prevalence of other HPV genotypes. To address, a nationwide study of HPV prevalence in sexually active Australian women presenting for Pap testing at 34 sites across the country was established: the Women Human papillomavirus Indigenous Non-indigenous Urban Rural Study (WHINURS)\(^{(18)}\). The aim of WHINURS was to ascertain HPV genotype prevalence rates among Australian women presenting for routine Pap smears across Australia, prior to rollout of the HPV prophylactic vaccines. Population based estimates adjusted for risk factors for women up to age 40 have been presented elsewhere and address the primary research questions regarding possible differences between Indigenous and remote dwelling women compared to other Australian women\(^{(18)}\).
2. Objectives

To provide more comprehensive data on the age-related distribution of HPV genotypes in Australian women prior to vaccination by including women up to age 60, and to determine the association between genotypes and cytological changes on Pap smears.
3. Study Design

3.1 Study population

Participants were recruited between April 2005 and February 2008 from all Australian jurisdictions, with deliberate over-sampling of specimens from more remote locations and from Indigenous women \(^{(18)}\). After consultation with Indigenous communities, medical services, healthcare workers, family planning and well women’s clinics across Australia, women 18-60 years of age were recruited. Cervical specimens were ecto/endocervical brush samples collected by clinicians into PreservCyt for ThinPrep cytology. A two ml aliquot was sent to the Regional HPV Labnet at the Royal Women’s Hospital, Department of Microbiology and Infectious Diseases for HPV testing. Ethical approval was received for the study from the relevant ethics committee at the 34 sites and the Research and Ethics Committees at the Royal Women’s Hospital, Melbourne.

3.2 HPV testing

DNA was prepared from PreservCyt-stored specimens by MagNA Pure LC extraction \(^{(19, 20)}\) and tested as described previously \(^{(18)}\). Briefly, 10μl of DNA was screened by HPV AMPLICOR (AMP) for the detection of HR-HPV (16,18,31,33,35,39,45,51,52,56,58,59,68); with this result used for clinical reporting. All extracts negative for HR-HPV by AMP were also analyzed by an “in-house” PGMY09/11-based HPV consensus PCR/ELISA (20μl of DNA) detecting mucosal HPV types, as previously described \(^{(21)}\). Ultimately, DNA testing positive by AMP or the in-house PCR were genotyped (50μl of DNA) using the HPV Linear Array® Genotyping Test (Roche) according to the manufacturer’s instructions, with minor modifications as previously
reported\(^{19, 22, 23}\). We considered types 26,53,66,73 and 82 as possible high-risk types and other types were designated low risk.

### 3.3 Statistical analysis

Cytology results were grouped into normal cytology, low-grade abnormalities (LGA) (possible or definite low grade squamous intraepithelial abnormality) and high-grade abnormalities (HGA) (possible or definite high-grade squamous intraepithelial abnormality). No endocervical abnormalities were detected on Pap testing in this cohort of women. Statistical analyses were performed in SPSS version 22.0, with two-sided \(P\)-values calculated using either the Fisher's exact test or chi squared as appropriate. Tests for trend used the linear by linear association measure in SPSS. \(P\) values in the summary tables are presented in three groups as \(p<0.001\); \(p>0.001 < 0.01\); and \(p>0.01 <0.05\). \(P\) values in the latter group should be interpreted with caution given the multiple comparisons made between each HPV type prevalence by group, with \(p<0.01\) less likely to be a chance finding.
4. Results

4.1 Study Participants

Overall, 2620 women presenting for Pap tests with adequate samples collected for HPV detection were recruited. There were 1933 (73.8%) Non-Indigenous and 684 (26.1%) Indigenous women, with 3 (0.1%) of unknown ethnicity. The mean age was 32 years (median 30; SD 9.9; range 15-66). A Pap test result was available for 2589 women, including 32 women with an unsatisfactory smear. Of the 2557 women with a result, 239 (9.3%) had a possible or definite low-grade abnormality/ low grade (LGA) and 47 (1.8%) had a possible or definite high-grade abnormality (HGA), including one squamous cell cancer predicted at Pap testing (Table 1).

4.2 Overall HPV detection

Of the 2620 participants, 694 (26.5%) tested positive for HR-HPV by the AMP test; of these, 668 were positive by the LA test for one or more of the 37 detectable genotypes, including 648 with a HR genotype, while the other 26 women were negative. For the 1926 women who were negative by the AMP test, 382 tested positive for HPV by the in-house consensus assay of which 345 tested positive by the LA test including 43 with a HR genotype. In total, 1013 HPV DNA positive samples were genotyped, including 691 (68.2%) with a HR genotype. The prevalence of infection with any HPV was 38.7% (1013/2620) and with a HR-HPV was 26.4% (691/2620).

4.3 Type-specific HPV prevalence

The most commonly detected genotypes were HPV 16 (8.3%), 51 (5.1%), 53 (4.7%), 62 (4.3%), 89 (3.9%) and 52 (3.8%). For the vaccine-targeted genotypes, 334 women (12.7%) had one or
more of genotypes 6, 11, 16 and/or 18 detected, with 283 women (10.8%) detected with
genotypes 16 and/or 18.

Infection with a single HPV genotype was detected in 17.2% of women. Multiple HPV
infections were detected in 21.6% of all women tested and in 55.6% of those HPV-positive. HPV
16 was the most common genotype detected in women with either a single (13.1%) or multiple
(28.3%) type infection, with genotypes 51, 53 and 62 among the next four most common
genotypes for both single and multiple infections. As with HPV 16, HPV 18 infections were less
common among single (2.9%) than multiple (14.1%) HPV infections (p<0.001).

4.4 Age-stratified HPV prevalence
Reflecting the overall decline in prevalence of HPV detection with age, the prevalence of HR,
possible HR and LR genotypes all decreased with increasing age (p<0.001 for trend) (Figure
1A). Similarly the prevalence of vaccine-preventable HPV genotypes decreased significantly
with increasing age ($\chi^2(5)=220.4;p<0.001;p<0.001$ for trend) (Figure 1B). The rate of decline was
greater and more consistent for multiple types than for single types and, in women over 40 years
old, single type infections were more common than multiple types (p<0.001 for trend) (Figure
1C). When entered into a binary logistic regression model, the odds ratio for presence of multiple
type infection with every year increase in age was 0.913 (95%CI 0.901-0.925), whereas the odds
ratio was 0.973(95%CI 0.962-0.984) with every year increase for single type infections.

4.5 HPV prevalence versus cytological result
HPV16 positivity increased by lesion grade amongst HPV positive specimens, with HPV16 detected in 17.5% (131/749) of HPV positive normal cytology specimens, 29.2% (58/198) of HPV positive low grade and 52.2% (24/46) of HPV positive high grade.

Of the 239 women with a LGA Pap result, 33% had a vaccine-preventable (VP) HPV genotype (Table 1), with 5.9% having two VP genotypes, and 5.0% having only VP genotypes. When stratified by Indigenous status, the only high risk genotype that differed in prevalence (with borderline significance) between non-Indigenous women (n=168) and Indigenous women (n=70) with an LGA result was HPV56, which was more common amongst Non Indigenous women (10.1 vs 1.4%; p=0.03). Of the 47 women with HGA Pap results, 62% had a VP genotype. HPV 16 was found in 51%, two VP genotypes in 11%, and only VP genotypes in 19%. There were no detectable difference in the prevalence of any high risk HPV types between non-Indigenous (n=21) and Indigenous women (n=26) who had HGA on their concurrent Pap, with only the probably high risk type HPV66 differing in prevalence with borderline significance (19% amongst non-Indigenous vs 0%; p=0.03).

For women with either a normal or a LGA Pap result, the prevalence of any HPV infection was higher for younger (aged 25 years or less) than older (aged over 25 years) women (normal Pap: 50.1% and 26.6% respectively p <0.001; LGA Pap: 89.1% and 74.5% p =0.003), as was the prevalence of most individual genotypes. For many individual genotypes this difference was statistically significant, particularly for women with normal Pap test results, possibly because the sample size was much larger (Table 2). For women with a LGA Pap result, younger women had
a significantly higher prevalence of multiple types (p<0.001), HR types (p=0.002) and vaccine-preventable types (6/11/16/18) (p=0.003).

For women with a HGA Pap result, all except one had one or more HPV genotypes detected. Within our limited sample size no difference in the prevalence of most individual HPV genotypes were noted between the age groups, although younger women had higher prevalence of a vaccine-preventable genotype (p=0.02) and were more likely to have only a vaccine preventable type detected (p=0.003).
5. Discussion

This is the largest group of cervical specimens collected from sexually active Australian women prior to vaccination for HPV genotyping. We found a high rate of HPV detection (39%) and large diversity of types present. Use of highly sensitive and multiple assay types allowed us to be confident in the detection and identification of these types. International meta-analyses of data from a range of other countries have shown that detection of HPV is highly correlated with younger age \(^{(24, 25)}\). Importantly our data add an Australian contribution to the international knowledge about HPV types detected in abnormal Pap tests prior to introduction of the vaccine, data that has been conspicuously absent until now \(^{(26, 27)}\). Among women in our sample with a low-grade abnormality detected on cytology, one third had a vaccine preventable type detected, but it is noteworthy that 95% of these LGAs also had a non-vaccine type detected. Half of the women with a high grade abnormality on cytology had HPV16 detected, in line with emerging international evidence \(^{(28, 29)}\) showing the enrichment of the more virulent HPV 16 causing high-grade lesions faster. In general, younger women were much more likely to have vaccine preventable types detected and only a vaccine preventable type as a single type detected than older women. We did not find any significant differences in vaccine preventable HPV prevalence between Indigenous and non-Indigenous women with cytological abnormalities, although the study was relatively underpowered to do so. Our findings that HPV56 was more common in low grade lesions and that HPV66 was more common in high grade lesions from Non-Indigenous women need to be interpreted with caution due to multiple comparisons, the relatively small sample size and weak statistical association (p=0.03).
The high prevalence of HPV detected in this group of specimens probably reflects a combination of the population tested and the high sensitivity of the methods for HPV detection used (19). Our population included a large number of young women, including teenagers, who have very high rates of HPV infection; did not exclude women with previous or current Pap abnormalities amongst whom HPV infection is more frequent; and enrolled women attending clinics whose services are free, which may increase the proportion of women of lower socioeconomic status, a risk factor for under screening and cervical cancer (30).

In addition to the study population criteria, the method of HPV detection is crucial when comparing inter-laboratory HPV genotype prevalence studies, particularly due to the extensive variation in available tests. The HPV-LA genotyping test used in this study uses 5 times more DNA than the AMP assay, which would be expected to increase the detection rate. Moreover, LA detects 37 HPV types compared with 13 for the AMP (19). Recent studies that have used the LA test on screening populations have shown similar HR-HPV rates of 22% among Italian women (31), mean age 34y; and 30% among Greek women (2), mean age 28.4y.

The prevalence of any HPV in the current study declined with age, as did the prevalence of HR, multiple and vaccine-preventable HPV types. Women ≤ 25 years had the highest levels of HPV infections. In this group, HPV 16 and/or 18 were common at 21% combined (17% and 7%, individually), while HPV 6 and/or 11 were detected in 6% (5% and 1% respectively). In all, vaccine preventable types were identified in 25% of women ≤ 25 years. Vaccination has already been shown to have a significant impact on HPV infection in this age group, with Australian data showing a decrease in prevalence of vaccine preventable HPV types by 77% among women aged
18-24 years post vaccination\textsuperscript{(32)}. Vaccine-only types were detected in 5% of these women. The prevalence of single, HR HPV-only, and HPV 16/18 all demonstrated a significant increase with cytologically predicted disease in line with other reports. HR-HPV increased from 21% among cytology-normal women to 81% in women with HGA, consistent with consensus findings that such types are the causative agent of cervical cancer\textsuperscript{(7)(8)}. The five most common genotypes among women with HGA cytology were all HR-types, being HPV 16 (51%), 18 (15%), 52 (13%), 31 (11%), and 33 (11%). Interestingly, there were five cases whereby LR HPV types were exclusively detected among women with HGA Pap cytology prediction. Two of these women had a single HPV 69 infection, which has an undetermined risk association (belonging to the same group as HPV 51). However, without histological findings, a definitive diagnosis (rather than a predictive one provided by Pap smear) of these cases could not be made.

Although new data is beginning to emerge internationally\textsuperscript{(33)}, the data reported in this study provide a valuable insight into the HPV genotype distribution among women participating in cervical screening within the Australian population, prior to the implementation of the current HPV vaccines. This information provides important baseline data for assessing HPV vaccine impact on HPV infection rates and type distribution in Australia, which has achieved the most broadly targeted, high coverage HPV vaccine program using quadrivalent HPV vaccine to date\textsuperscript{(12)}. Dramatic declines in vaccine preventable HPV types have already been recorded, using the data presented in detail here\textsuperscript{(32)}. 

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Author Contribution
ST, JB and SG designed the study with assistance from JC, PM and DS. SG coordinated the study, and managed recruitment of participating sites and the study team, including performing study workshops at most sites, and was responsible for overall specimen and laboratory methods. JC coordinated site recruitment in the Northern Territory, and DS coordinated site recruitment in Western Australia. ST managed specimen coordination and HPV DNA typing which was performed by MS. JB analyzed the study data. Data interpretation was led by JB, ST and SG. ST, JB and MS drafted the initial manuscript with critical revisions by all authors. All authors approved the final version.

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Competing interest:
Other than the grant funding received for this study (see below), JC, ST, MS and DS have no competing interests. JB has been an investigator on investigator initiated epidemiological research that has been partially funded by unrestricted grants from CSL/Merck but has received no personal financial benefit. SG has received advisory board fees and grant support from CSL and GlaxoSmithKline, and lecture and consultancy fees from Merck and Co. SG reports having previously owned stock in CSL. SG has received grant support through her institution from Merck and Co and GlaxoSmithKline (GSK) to carry out clinical trials for HPV/cervical cancer vaccines, and she is a member of the Merck global advisory and scientific advisory boards.
Project design, analysis and write up of the study findings was the work of the chief investigators, with no input from those supporting the funding for the study.

Ethical Approval:

Ethical approval was received for the study from the relevant local ethics committee at the 34 sites with overall approval from Research and Ethics Committees at the Royal Women’s Hospital, Melbourne under reference number 04/14.

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References


<table>
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<th></th>
<th>Normal (n = 2271)</th>
<th>LGA (n = 239)</th>
<th>HGA (n = 47)</th>
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<tr>
<td>Any HPV</td>
<td>749 (33.0)</td>
<td>* 198 (82.8)</td>
<td>* 46 (97.9)</td>
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<tr>
<td>Single</td>
<td>366 (16.1)</td>
<td># 55 (22.0)</td>
<td>* 21 (44.7)</td>
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<tr>
<td>Multiple</td>
<td>383 (16.9)</td>
<td>* 144 (60.3)</td>
<td>* 25 (53.2)</td>
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<td>HR-Positive</td>
<td>478 (21.0)</td>
<td>* 164 (68.6)</td>
<td>* 38 (80.9)</td>
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<tr>
<td>HR-only</td>
<td>214 (9.4)</td>
<td>* 63 (26.4)</td>
<td>* 20 (42.6)</td>
</tr>
<tr>
<td>LR-only</td>
<td>196 (8.6)</td>
<td>17 (7.1)</td>
<td>^ 5 (10.6)</td>
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<td>16/18 positive</td>
<td>177 (7.8)</td>
<td>* 72 (30.1)</td>
<td>* 29 (61.7)</td>
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<tr>
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<td>218 (9.6)</td>
<td>* 79 (33.1)</td>
<td>* 29 (61.7)</td>
</tr>
<tr>
<td>16/18 only</td>
<td>51 (2.2)</td>
<td>^ 11 (4.6)</td>
<td>* 9 (19.1)</td>
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<td>6/11/16/18 only</td>
<td>61 (2.7)</td>
<td>^ 12 (5.0)</td>
<td>* 9 (19.1)</td>
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</table>

High risk defined as positive for 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68. Possible high risk defined as positive for types 26, 53, 66, 73 or 82. All other types designated low risk.

Statistically significant with normal cytology as the comparator (P < 0.05): * < 0.001; # > 0.001, < 0.01; ^ > 0.01, < 0.05.

^ Types detected were 2x69, 42, 70, and 84.
Table 2: HPV prevalence by cytological status and age

<table>
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<td>6</td>
<td>* 27 (4.4)</td>
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<td>13 (61.9)</td>
<td>11 (42.3)</td>
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<tr>
<td>18</td>
<td>* 35 (5.7)</td>
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<td>31</td>
<td>* 29 (4.7)</td>
<td>27 (1.6)</td>
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<td>33</td>
<td>* 17 (2.8)</td>
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<td>39</td>
<td>* 31 (5.0)</td>
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<td>40</td>
<td># 10 (1.6)</td>
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<td># 28 (4.5)</td>
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*NIL* | 308 (49.9) | 1214 (73.4) | # 15 (10.9) | 26 (25.5) | 0 (0.0) | 1 (3.8) |

Any HPV | * 309 (50.1) | 440 (26.6) | # 122 (89.1) | 76 (74.5) | 21 (100) | 25 (96.2) |

Single | # 124 (20.1) | 242 (14.6) | 25 (18.2) | 29 (28.4) | 10 (47.6) | 11 (42.3) |

Multiple | * 185 (30.0) | 198 (12.0) | * 97 (70.8) | 47 (46.1) | 11 (52.4) | 14 (53.8) |

HR type | *216 (35.0) | 262 (15.8) | # 105 (76.6) | 59 (57.8) | 19 (90.5) | 19 (73.1) |

VP type only | * 121 (19.6) | 97 (5.9) | # 56 (40.9) | 23 (22.5) | ^ 17 (81.0) | 12 (46.2) |

^25 (4.1) | 36 (2.2) | 7 (5.1) | 5 (4.9) | # 8 (38.1) | 1 (3.8) |

Sixty three samples had unreported cytology findings.
High risk defined as positive for HPV.
Statistically significant within cytology category between the two age groups (P < 0.05): * <0.001; # >0.001; ^ <0.01; V >0.01, <0.05.
Figure 1A: Age-stratified HPV cervical prevalence according to risk association* in 2620 Australian women attending Pap testing

High risk defined as positive for 16,18,31,33,35,39,45,51,52,56,58,59,68. Possible high risk defined as positive for types 26,53,66,73 or 82. All other types designated low risk.
Figure 1B: Age-stratified cervical HPV prevalence of vaccine preventable genotypes in 2620 Australian women attending Pap testing
Figure 1C: Age-stratified cervical HPV prevalence* in 2620 Australian women attending Pap testing according to detection of a single or multiple HPV types.

HPV genotypes in Australia pre-vaccination.
Minerva Access is the Institutional Repository of The University of Melbourne

Author/s:
Tabrizi, SN; Brotherton, JML; Stevens, MP; Condon, JR; McIntyre, P; Smith, D; Garland, SM

Title:
HPV genotype prevalence in Australian women undergoing routine cervical screening by cytology status prior to implementation of an HPV vaccination program

Date:
2014-07-01

Citation:
Tabrizi, SN; Brotherton, JML; Stevens, MP; Condon, JR; McIntyre, P; Smith, D; Garland, SM, HPV genotype prevalence in Australian women undergoing routine cervical screening by cytology status prior to implementation of an HPV vaccination program, JOURNAL OF CLINICAL VIROLOGY, 2014, 60 (3), pp. 250 - 256

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