

# Clinical efficacy of primary human papillomavirus (HPV) screening with partial genotyping for HPV-16 and HPV-18 subtypes in women from 25 years old

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## ABSTRACT

**Introduction:** Cervical screening programmes differ in the age of women recommended for primary human papillomavirus (HPV) testing. This study aims to determine the clinical efficacy and impact of 14-high-risk HPV DNA testing for women from 25 years old.

**Method:** This was a retrospective analysis of data collected prospectively from women 25 years or older who attended hospital-based gynaecology clinics for cervical screening. Women with history of cervical neoplasia or abnormal cytology were excluded. High-risk HPV DNA testing with partial genotyping for HPV-16 and HPV-18 were performed on cobas 4800 System (Roche Diagnostics International AG, Rotkreuz, Switzerland). Women tested positive for the 12 other high-risk HPV subtypes (HPV-12 other) had a reflex cytology test. Positive screening included positive for HPV-16 and/or HPV-18, HPV-12 other with cytology abnormalities equal to or greater than atypical squamous cells of undetermined significance, and repeated positive HPV at 12 months. HPV detection and colposcopy referral rates, and detection of high-grade neoplasia were determined.

**Results:** Of 10,967 women studied, 822 (7.50%) were HPV DNA positive. The overall discharge rate to routine screening according to screening protocol was 93.1%. Colposcopy referral rate was 4.4%. The screening detected 41 cervical intraepithelial neoplasia grade 2+ (CIN2+) (0.37%) and 31 (0.28%) CIN3+. The number of colposcopies needed per case of CIN2+ was 9.5, similar for women below and above 30 years old. The number of colposcopies needed per case of CIN3+ for HPV-16 positivity was 8.5, compared to 17.0 for other categories ( $P=0.040$ ). Colposcopy efficacy was similar for HPV-18 and HPV-12 other positivity with abnormal cytology.

**Conclusion:** Taking CIN2+ detection and colposcopy referral rate as endpoints, HPV testing in Singapore can be extended to include women from 25 years old.

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**Keywords:** Cervical cancer screening, cervical intraepithelial neoplasia, colposcopy, obstetrics and gynaecology, Pap smear

## INTRODUCTION

The World Health Organization has launched a campaign to eliminate cervical cancer on the basis of effective vaccines against oncogenic human papillomavirus (HPV) subtypes, with mass screening and eradication of high-grade pre-malignant lesions, cervical intraepithelial neoplasia grade-2 (CIN2) and grade-3 (CIN3).<sup>1,2</sup> HPV-based screening has been shown to be sensitive in detecting high-grade lesions and is effective and suitable in mass cervical screening.<sup>3-5</sup> More importantly, recent evidence shows that HPV-based screening prevented

development of invasive cervical carcinoma among women who screened negative.<sup>6</sup> HPV DNA testing is cost-effective and has been adopted by many national cervical screening programmes.<sup>7,8</sup>

However, HPV-based screening faces several challenges, including the low specificity of HPV-positivity for high-grade lesions.<sup>9</sup> The problem is exaggerated for young women who experience high prevalence of HPV infection. Some national screening programmes limit HPV-based testing to women beyond 30 years old.<sup>10</sup> Appropriate strategies are needed to improve the

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## CLINICAL IMPACT

### What is New

- Cervical screening in Singapore can be simplified to a single human papillomavirus (HPV)-based modality for all eligible women from 25 years old.

### Clinical Implications

- This study identified areas that could improve the efficacy of the current cervical screening protocol in Singapore.
- Our data provided evidence that HPV-18-positive cases should also undergo cytology triage instead of the current practice of immediate referral to colposcopy.
- The persistent HPV positivity rate was 51.9% at 12-months follow-up. Additional mode of screening such as HPV-self screening should also be explored to overcome the low compliance rate for 12-month follow-up (32.2%).

positive predictive value of HPV testing for high-grade lesions especially in women who are positive for a group of 12 oncogenic HPV subtypes: HPV-31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68—collectively HPV-12 other. When compared to HPV-16 and HPV-18, HPV-12 other are associated with a substantially lower risk of high-grade lesions.<sup>11,12</sup> Among many approaches evaluated, partial genotyping for HPV-16 and HPV-18 and introduction of a cytology triage test for the HPV-12 other positive cases emerged to be the best option today.<sup>3,13</sup>

In 2013, our institution started a cervical screening programme using primary HPV DNA testing with partial genotyping for HPV-16 and HPV-18, and reflex liquid-based cytology on specimens positive for HPV-12 other. Women whose reflex cytology was normal were scheduled for a repeat HPV testing at 12 months. This study was conducted to evaluate the clinical efficacy of HPV testing in this protocol-based screening programme. Data were analysed for HPV DNA detection rate, colposcopy referral rate, prevalence of high-grade lesions and number of colposcopies to detect a high-grade lesion.

## METHOD

Clinical data were collected in a database prospectively from all women 25 years or older who attended hospital-based gynecology clinics in Singapore and had

undertaken a routine cervical screening between November 2013 and December 2021. The data analysis was based on information from this database on primary HPV screening. Women who had previous cervical neoplasia or abnormal cytology were excluded.

One cervical scrape sample was obtained from each woman and kept in 20mL PreservCyst Solution (ThinPrep Hologic, Marlborough, US). The sample was sent to the hospital's molecular laboratory for HPV DNA analysis.

Screening was done with primary high-risk HPV DNA testing with partial genotyping for HPV-16 and HPV-18 (cobas 4800 System, Roche Diagnostics International AG, Rotkreuz, Switzerland). A reflex liquid-based cytology test was performed on the same sample as triage for cases positive for HPV-12 other. All cases positive for HPV-16 or HPV-18, and cases positive for HPV-12 other with reflex cytology showing atypical squamous cells of undetermined significance (ASCUS) or worse by Bethesda classification were considered abnormal. Cases positive for HPV-12 other in which reflex cytology showing changes less than ASCUS were scheduled for a repeat HPV testing 12 months later. These cases were then considered abnormal if repeat testing was positive for HPV DNA.

Women with normal screening results were discharged to routine screening scheduled in 5 years. Women with abnormal results were referred to colposcopy in the same hospital. Colposcopy was performed by a fixed team of trained colposcopists. Cervices with abnormal findings were biopsied for histopathology examination. The final diagnosis of CIN and invasive cancer was based on the histology of cervical biopsies (cervical punch biopsies or loop electrosurgical excision procedure), and hysterectomy specimen where applicable. The results were reviewed by gynaecologic histopathologists.

The outcome measures of the analysis were detection rate for CIN2+ and CIN3+, numbers of abnormal tests, repeat tests at 12 months, and colposcopies for each case of CIN2+ and CIN3+.

Waiver of consent was granted for this retrospective study by the hospital's ethics committee (CIRB: 2016/2385) and carried out in accordance with the 1964 Declaration of Helsinki ethical standards.

Pearson's chi-square analysis was performed using SPSS Statistics software version 21.0 (IBM Corp, Armonk, US). Statistical significance was set at  $P < 0.05$ .

## RESULTS

The database included 10,967 eligible women. Of these, 966 (8.8%) were below 30 years old and 10,001 (91.2%)

were 30 years old or more. Of the latter subgroup, the mean age was 47.8 years (95% confidence interval [CI] 47.58–48.02).

The overall prevalence of high-risk HPV DNA positivity for the entire screening cohort was 7.50% ( $n=822/10,967$ ) (Table 1). The detection rates of the high-risk HPV subtypes were 1.25% for HPV-16, 0.52% for HPV-18, and 6.21% for HPV-12 other (Table 2). Comparing women below 30 years old to older women, the odds ratio of HPV positivity was 2.43 (95% CI 2.012.95) ( $P<0.0001$ ). Generally, the overall prevalence of HPV and its subtypes declined steadily across increasing years of age groupings (Table 2).

Table 1. Overall detection rate of at least one category of high-risk HPV DNA on first screening.

| Age grouping |       | High-risk HPV positive |      |             |
|--------------|-------|------------------------|------|-------------|
| years        | n     | n                      | %    | 95% CI      |
| <30          | 966   | 145                    | 15.0 | 12.67–17.66 |
| 30–39        | 2726  | 265                    | 9.72 | 8.59–10.97  |
| 40–49        | 2988  | 203                    | 6.79 | 5.89–7.80   |
| 50–59        | 2655  | 118                    | 4.44 | 3.68–5.32   |
| ≥60          | 1632  | 91                     | 5.58 | 4.49–6.85   |
| Total        | 10967 | 822                    | 7.50 | 6.99–8.03   |

CI: confidence interval; HPV: human papillomavirus

In all, 685 women tested positive for HPV-12 other. Of these, 629 (92.4%) did not show concurrent positivity with HPV-16 and/or HPV-18. These women had a reflex liquid-based cytology evaluation (Table 3). Overall, 419 women (66.6%) were negative for intraepithelial lesions or malignancy (NILM). The frequency of NILM was similar across the age groupings ( $P=0.145$ ). Mild cytological abnormalities (ASCUS or low-grade squamous intraepithelial lesion (LSIL)) were more often observed among women below 30 years old (35.5%) compared to older women (23.5%). High-grade lesions were seen in 0.9% of women below 30 years old, compared to 3.7% of women aged 30 years or above ( $P=0.135$ ).

Of the 419 women assigned for repeat testing at 12 months, 284 (67.8%) defaulted. The default rate was similar across all age groupings. Of the 135 (32.2%) women who undertook the test, 65 (48.1%) cases were negative, and 70 (51.9%) cases were positive for HPV DNA (Fig. 1). All HPV positive cases had HPV-12 other, with concurrent HPV-16 positivity in 3 cases and HPV-18 positivity in 1 case.

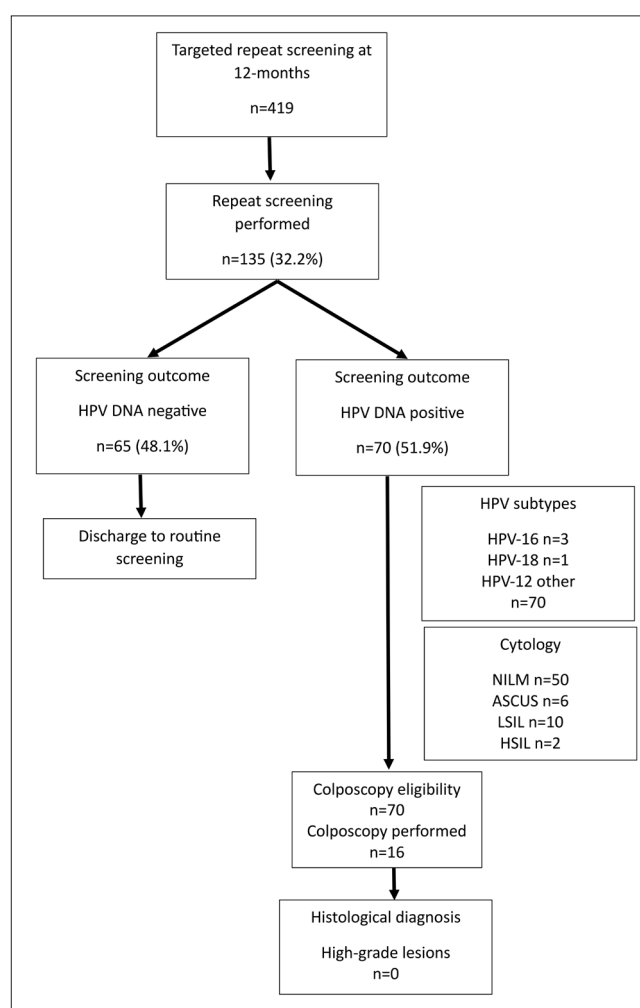


Fig. 1. Outcome of repeat screening at 12-months.

ASCUS: atypical squamous cells of undetermined significance; HPV: human papillomavirus; HSIL: high-grade intraepithelial lesions; LSIL: low-grade intraepithelial lesions; NILM: negative for intraepithelial lesions and malignancy

Of the total screened cohort, 10,210 women tested negative for HPV DNA. These included 10,145 women from the initial screening test and 65 women from repeat testing at 12-months. These women (93.1%) were discharged to routine 5-yearly screening.

The final histological diagnosis confirmed 41 cases of CIN2+ (0.37%) and 31 (0.28%) cases of CIN3+ (Table 4). The detailed breakdown showed 10 CIN2, 25 CIN3 and 6 cases of invasive carcinoma. More than half of all cases of high-grade lesions (51.2% CIN2+ and 51.3% of CIN3+) were related to HPV-16. The frequency of CIN3+ by HPV subtype category was 11.8% for HPV-16, 5.4 % for HPV-18 and 6.6% for HPV-12 other ( $P=0.175$ ).

Excluding 284 women who defaulted repeat testing at 12 months, 4.4% of the women were recommended

Table 2. Distribution of human papillomavirus subtypes by age grouping of subjects at initial screening.

| HPV subtype  | Age Grouping, years |      |             |        |      |           |        |      |           |        |      |           |
|--------------|---------------------|------|-------------|--------|------|-----------|--------|------|-----------|--------|------|-----------|
|              | <30                 |      |             | 30–39  |      |           | 40–49  |      |           | 50–59  |      |           |
|              | n=966               |      |             | n=2726 |      |           | n=2988 |      |           | n=2655 |      |           |
|              | n                   | %    | 95% CI      | n      | %    | 95% CI    | n      | %    | 95% CI    | n      | %    | 95% CI    |
| HPV-16       | 29                  | 3.0  | 2.01–4.31   | 42     | 1.54 | 1.11–2.08 | 36     | 1.20 | 0.84–1.67 | 14     | 0.53 | 0.29–0.88 |
| HPV-18       | 6                   | 0.6  | 0.23–1.35   | 14     | 0.51 | 0.28–0.86 | 19     | 0.64 | 0.38–0.99 | 10     | 0.38 | 0.18–0.69 |
| HPV-12 other | 126                 | 13.0 | 10.87–15.53 | 224    | 8.22 | 7.18–9.37 | 163    | 5.46 | 4.65–6.36 | 99     | 3.73 | 3.03–4.54 |

CI: confidence interval, HPV: human papillomavirus

Table 3. Outcome of reflex cytology examination among women tested positive for HPV-12 other.

| Cytology outcome | Age Grouping, years |      |             |       |      |           |       |      |           |       |      |           |
|------------------|---------------------|------|-------------|-------|------|-----------|-------|------|-----------|-------|------|-----------|
|                  | <30                 |      |             | 30–39 |      |           | 40–49 |      |           | 50–59 |      |           |
|                  | n=629               |      |             | n=209 |      |           | n=148 |      |           | n=94  |      |           |
|                  | n                   | %    | 95% CI      | n     | %    | 95% CI    | n     | %    | 95% CI    | n     | %    | 95% CI    |
| NILM             | 419                 | 66.6 | 60.39–73.31 | 70    | 63.6 | 53.6–73.6 | 104   | 70.3 | 61.2–79.4 | 70    | 74.5 | 66.1–82.9 |
| ASCUS            | 80                  | 12.7 | 10.09–15.38 | 17    | 15.5 | 9.5–21.5  | 18    | 12.2 | 6.2–18.2  | 15    | 16.0 | 9.0–23.0  |
| LSIL             | 107                 | 17.0 | 13.94–20.56 | 22    | 20.0 | 14.0–26.0 | 23    | 15.5 | 9.5–21.5  | 6     | 6.4  | 2.4–10.4  |
| HSIL             | 20                  | 3.2  | 1.94–4.91   | 1     | 0.9  | 0.0–1.8   | 3     | 2.0  | 0.0–4.0   | 2     | 2.1  | 0.1–4.1   |
| Others           | 3                   | 0.5  | 0.10–1.39   | 0     | 0.0  | 0.0–0.0   | 0     | 0.0  | 0.0–0.0   | 1     | 1.1  | 0.0–2.2   |

ASCUS: atypical squamous cells of undetermined significance; HSIL: high-grade intraepithelial lesions; LSIL: low-grade intraepithelial lesions; NILM: negative for intraepithelial lesions and malignancy; Others: included unsatisfactory smears

Table 4. Histological diagnosis of overall screening.

| Histology | Age Grouping (years) | Diagnosis by HPV subtypes |         |                        | Overall |
|-----------|----------------------|---------------------------|---------|------------------------|---------|
|           |                      | HPV-16+                   | HPV-18+ | HPV-12 other+ and LBC+ |         |
| CIN2+     | <30                  | 5                         | 0       | 2                      | 7       |
|           | 30–39                | 6                         | 1       | 8                      | 15      |
|           | 40–49                | 7                         | 1       | 4                      | 12      |
|           | 50–59                | 2                         | 1       | 1                      | 4       |
|           | ≥60                  | 1                         | 0       | 2                      | 3       |
|           | Overall              | 21                        | 3       | 17                     | 41      |
| CIN3+     | <30                  | 1                         | 0       | 1                      | 2       |
|           | 30–39                | 6                         | 1       | 5                      | 12      |
|           | 40–49                | 6                         | 1       | 4                      | 11      |
|           | 50–59                | 2                         | 1       | 1                      | 4       |
|           | ≥60                  | 1                         | 0       | 1                      | 2       |
|           | Overall              | 16                        | 3       | 12                     | 31      |

CIN: cervical intraepithelial neoplasia; HPV: human papillomavirus; LBC: liquid-based cytology

for colposcopy (n=472/10,683) (Table 5). This prevalence amounted to 69.1% of all women tested positive for HPV DNA at the initial screening. Of these, 391 (82.8%) undertook colposcopy examination. Both the eligibility and compliance of colposcopy showed a statistically significant difference across age groupings from less than 30 years old to 60 years old and more. Most notably, 8.3% of women below 30 years old were recommended for colposcopy compared to 4.4% for the entire cohort.

There was no statistically significant difference across age groupings for detecting CIN2+ (Fig. 2). However, to detect a case of CIN3+, the number of colposcopies needed was 38.5 for women below 30 years old, compared to 10.8 for women in the older age groupings ( $P=0.053$ ). Compared to the other categories of HPV subtypes collectively, HPV-16 positive group of women needed a lower number of colposcopies for each case of high-grade lesions: CIN2+ (6.5 versus 12.8,  $P=0.051$ ) and CIN3+ (8.5 versus 17.0,  $P=0.040$ ) (Table 5).

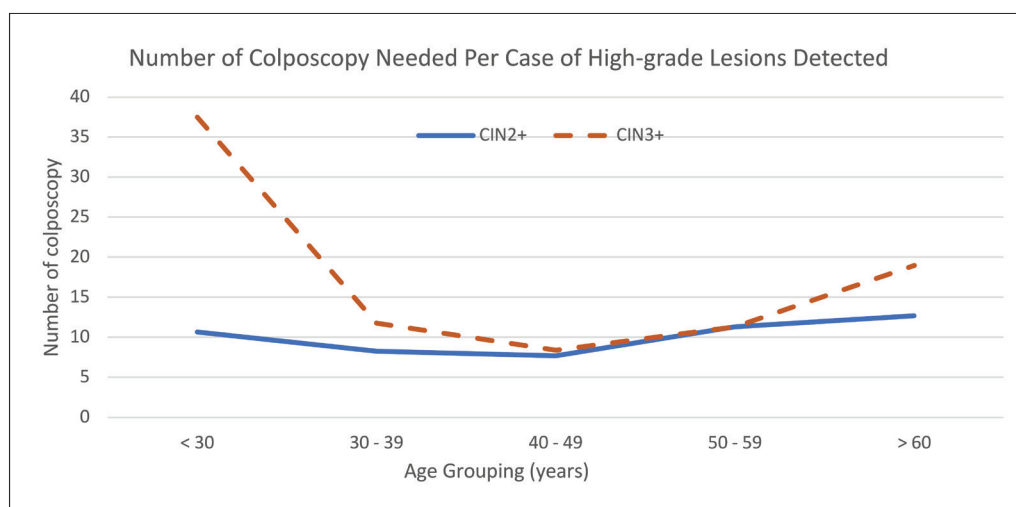


Fig. 2. Number of colposcopy needed per case of CIN2+ and CIN3+. CIN: cervical intraepithelial neoplasia

## DISCUSSION

This report presented a real-world experience of a cervical screening protocol involving primary HPV DNA testing with partial genotyping for HPV-16 and HPV-18, and reflex liquid-based cytology testing on positive HPV-12 other cases. In the cohort, there were 41 cases of CIN2+ (0.37%) and 31 (0.28%) cases of CIN3+, including 6 cases of invasive carcinoma. The detection rate of high-grade lesions reflected the low and steadily declining trend in the incidence rate of cervical cancer in Singapore,<sup>14</sup> and was similar to the rates (0.27–0.87%) reported in other studies.<sup>15,16</sup>

The overall prevalence of high-risk HPV DNA positivity was 7.50%. The detection rate of HPV and its subtypes were within ranges reported globally.<sup>13,17–20</sup> The variation in the reported HPV positivity rate between individual studies largely reflected the age of screening population. As universally observed, the prevalence of HPV infection peaks in women in their 20s and declines steadily after 30 years old. Not surprisingly, comparing women below 30 years old to older women, the odds ratio of HPV positivity in this study was 2.43 ( $P<0.0001$ ).

The rate of returning to routine screening, an important outcome measure of a screening programme, was 93.1% in our study. This high discharge rate dispelled fears that HPV-based screening might increase the burden on clinical services. It underscores the importance of using HPV technology validated for disease endpoints. In fact, the extremely high negative predictive value of HPV testing for high-grade lesions and invasive cancers—over a long interval of 5 years or more—contributes to a favourable cost-effectiveness of the screening programme.<sup>8,21,22</sup>

It has been long recognised that HPV testing has a very high sensitivity and is significantly superior to cytology in detecting high-grade lesions. However, it is important to note that, based on our management protocol of partial genotyping for HPV-16 and HPV-18, and reflex cytology for HPV-12 other, 69.1% of women who had detected HPV DNA at the initial screening were referred to colposcopy. The referral rate for colposcopy and number of colposcopies needed for detecting a case of high-grade lesion are well accepted measures for assessing the performance of a cervical screening programme. In our study, the colposcopy referral rate of 4.4% was consistent with published data of 3–4.1%.<sup>9,18–20</sup> However, detailed analysis of referral rate by age groupings showed a significant trend of higher rates among young women ( $P<0.0001$ ). The referral rate was almost double (8.3%) for women below 30 years old (Table 5). Overall, the attendance rate for colposcopy was 82.8%. A higher

attendance rate in the younger women group was observed ( $P=0.0016$ ).

The number of colposcopies performed for detecting a case of high-grade lesion was 9.5 for CIN2+ and 12.6 for CIN3+ (Table 5). These numbers can be translated to a colposcopy detection rate of 10.5% for CIN2+ and 7.9% for CIN3+. These rates are generally accepted and justified the current referral criteria for colposcopy.<sup>11,23</sup> Despite the high colposcopy referral rate for younger women, the relatively high prevalence of CIN2 lesions among them resulted in an overall comparable colposcopy efficacy between all age groupings.

Our observations carry 3 significant implications on managing HPV-based cervical screening. Firstly, the detection rate for CIN2+ and CIN3+ was most significant for HPV-16 positivity ( $P=0.040$ ) compared to other subtypes of HPV. HPV-16 positivity alone accounted for more than half of all cases of CIN2+ (51.1%) and CIN3+ (51.3%) in this study. HPV-16 genotyping in HPV-based screening is clearly beneficial. However, the number of colposcopies needed for a case of CIN2+ or CIN3+ was similar for women referred by HPV-18 positivity or by HPV-12 other-and-cytology positivity. Similar findings have also been reported.<sup>24</sup> These data support the suggestion that HPV-18 positivity may be managed with a reflex cytology triage test as with HPV-12 other positivity.

Secondly, women younger than 30 years old contributed 17% of all CIN2+ cases in this study. Others have reported that women between 25 and 29 years old contributed a large number of CIN2+ in screening populations.<sup>25</sup> The number of colposcopies needed for a case of CIN2+ in this age grouping was 11, which is similar to the older age groupings ( $P=0.8062$ ). It seems logical that primary HPV-based cervical screening should be extended to women between 25 and 29 years old.

Thirdly, it was important to note that the observed compliance rate of 32% for repeat testing was unacceptably low. This rate was lower than the reported rate of exceeding 80% in some reports.<sup>24</sup> The low rate mirrored the participation rate of women attending recommended regular cytology screening at 3-yearly intervals in the previous national screening programme, a phenomenon that appeared to be obstinately constant in Singapore.<sup>26</sup> The low compliance rate could not be ignored as HPV positivity was found in more than half of the women who attended the repeat testing. In fact, 4 (3%) women acquired additional HPV subtypes: 3 were positive for HPV-16 and one for HPV-18, in addition to being positive for HPV-12 other. The prevalence of HPV-16 among these women was more than doubled that found in the initial screening cohort (1.25%). Although

Table 5. Summary of overall colposcopy outcome: eligibility, compliance and efficacy from cumulative data from round-1 screening and repeat testing on subgroup of women tested positive for HPV-12 other at 12 months.

|                                                                               | Age Grouping, years                      |       |       |       |      | HPV typing                          |        |        |              |       |
|-------------------------------------------------------------------------------|------------------------------------------|-------|-------|-------|------|-------------------------------------|--------|--------|--------------|-------|
|                                                                               | <30                                      | 30-39 | 40-49 | 50-59 | ≥60  | Total                               | HPV-16 | HPV-18 | HPV-12 other | Total |
| Overall (n) <sup>a</sup>                                                      | 913                                      | 2642  | 2918  | 2612  | 1598 | 10683                               | 136    | 56     | 491          | 683   |
| Colposcopy recommended (cumulative number including repeat test at 12 months) |                                          |       |       |       |      |                                     |        |        |              |       |
| No. of cases                                                                  | 80                                       | 156   | 117   | 59    | 60   | 472                                 | 136    | 56     | 280          | 472   |
| %                                                                             | 8.8                                      | 5.9   | 3.0   | 2.3   | 3.8  | 4.4                                 | 100    | 100    | 57.1         | 69.1  |
| Difference between groups                                                     | P<0.00001 <sup>b</sup>                   |       |       |       |      | Not applicable                      |        |        |              |       |
| Colposcopy performed                                                          |                                          |       |       |       |      |                                     |        |        |              |       |
| No. of cases                                                                  | 77                                       | 128   | 95    | 49    | 42   | 391                                 | 136    | 56     | 199          | 391   |
| %                                                                             | 96.3                                     | 82.1  | 81.2  | 83.1  | 70   | 82.8                                | 100    | 100    | 71.1         | 82.8  |
| Difference between groups                                                     | P=0.0016 <sup>b</sup>                    |       |       |       |      | Not applicable                      |        |        |              |       |
| No. of colposcopy per CIN2+ case                                              |                                          |       |       |       |      |                                     |        |        |              |       |
|                                                                               | 11                                       | 18.5  | 7.9   | 12.3  | 14   | 9.5                                 | 6.5    | 18.7   | 11.7         | 9.5   |
| Difference between groups                                                     | P=0.8062 <sup>b</sup>                    |       |       |       |      | P=0.051 <sup>b</sup>                |        |        |              |       |
| No. of colposcopy per CIN3+ case                                              |                                          |       |       |       |      |                                     |        |        |              |       |
|                                                                               | 38.5                                     | 10.7  | 8.6   | 12.3  | 21   | 12.6                                | 8.5    | 18.7   | 16.6         | 12.6  |
| Difference between groups                                                     | P=0.2244 <sup>b</sup>                    |       |       |       |      | P=0.1205 <sup>b</sup>               |        |        |              |       |
| Difference between subgroups                                                  | P=0.053 <sup>b</sup>                     |       |       |       |      | P=0.040 <sup>b</sup>                |        |        |              |       |
|                                                                               | Subgroup: age <30 years versus ≥30 years |       |       |       |      | Subgroup: HPV-16 versus Other HPV's |        |        |              |       |

<sup>a</sup> Overall number excluded 284 women who defaulted repeat HPV DNA testing at 12-months follow-up.<sup>b</sup>  $\chi^2$ -test

no high-grade lesions were detected in this small group of women in the present analysis, the poor compliance rate for a recommended management protocol is worrisome for a large population in a nationwide programme. It is important for national programmes to consider including alternative sampling methods such as self-sampling, which improves participation in screening.<sup>27</sup> Emerging evidence confirmed that the sensitivity of HPV testing between physician-collected samples and women self-collected samples was comparable.<sup>28,29</sup>

It is reasonable to question if the findings of a retrospective institutional study of this nature can be extended to community-based national screening. We overcome this limitation by including only women attending the health service for primary screening. Women on clinical management of abnormal screening tests were actively excluded. The low prevalence of high-grade lesions observed in this analysis was indicative of the primary screening nature of the studied cohort, reflecting similar prevalence as the general population.

We examined the potential impact of low compliance rate of repeat HPV testing at 12 months on detection rate of high-grade lesions among the defaulters. There was no difference in the default rate between age groupings to suggest potential bias between compliant and non-compliant women. Of those who undertook repeat tests, HPV positive rate was 51.9%. However, there were no high-grade lesions detected. The potential contribution of CIN2+ cases from defaulters, if any, to the overall pool of high-grade lesions was likely to be small and would not have altered the overall conclusions.

The strengths of this study include its prospective nature of clinical data collection from a single institution, which ensured the accuracy and completeness of clinical information in the database. In addition, single institutional practice ensured consistency in the execution of screening management protocol, standard of colposcopy, cytopathology and histopathology examination and reporting. These characteristics increased the robustness of the data analysed.

Distinct from HPV DNA technological studies, this report focused on the outcome of a screening protocol. The analysis on 10,967 women carried a large sample size. The inference from the observations was of clinical significance.

## CONCLUSION

Our findings indicated that the current cervical screening protocol was efficacious with a discharge rate of 93.1% of women to routine screening. The overall HPV DNA positive rate was 7.5%. The colposcopy referral rate was

4.4%. The number of colposcopies performed to detect a case of high-grade lesion was 9.5 for CIN2+ and 12.6 for CIN3+. Comparable colposcopy efficacy between different age groupings of women suggests that primary HPV screening should be extended to women between 25 and 29 years old. The impact of introducing cytology triage testing for HPV-18 positive cases, instead of immediate referral to colposcopy, warrants further evaluation to reduce the colposcopy referral rate. Sample collection alternative to routine clinic collection should be explored to increase the compliance rate of follow-up repeat testing.

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