Point-of-care HPV DNA testing of self-collected specimens and same-day thermal ablation for the early detection and treatment of cervical pre-cancer in women in Papua New Guinea: a prospective, single-arm intervention trial (HPV-STAT)

Andrew J B Vallely, Marion Saville, Steven G Badman, Josephine Gabuzzi, John Bolnga, Glen D L Mola, Joseph Kuk, Malts Wai, Gloria Munnull, Suzanne M Garland, Julia M L Brotherton, Angela Kelly-Hanku, Christopher Morgan, Pamela J Toliman, Zore Kombati, Grace Kariwiga, Delly Babona, Grace Tan, Kate T Simms, Alyssa M Cornell, Sepehr N Tabrizi, Handan Wand, Rebecca Guy, Karen Canfell, John M Kaldor

Summary

Background WHO recommends human papillomavirus (HPV) testing and same-day treatment for cervical screening in low-income and middle-income countries (LMICs); however, few published data exist on the validity of the strategy. We aimed to evaluate the clinical performance, treatment completion rates, adverse events profile, and acceptability of a fully integrated strategy, comprising point-of-care HPV DNA testing of self-collected specimens and same-day thermal ablation, for screening of cervical cancer in women in Papua New Guinea.

Methods HPV-STAT was a large-scale, prospective, single-arm intervention trial conducted at two clinical sites in Papua New Guinea. Cervical screening clinics with an on-site consultant gynaecologist were selected in consultation with national and provincial health authorities, church health services, and local stakeholders. Eligible participants were women aged 30–59 years attending cervical screening services at the two clinics, who were willing to comply with study procedures and able to provide written informed consent. Women self-collected vaginal specimens for point-of-care GeneXpert testing (Cepheid, Sunnyvale, CA, USA) for oncogenic HPV types. Women testing positive for HPV underwent pelvic examination followed by same-day thermal ablation or referral for gynaecology review. All HPV-positive women and a 15% random sample of HPV-negative women provided a clinician-collected cervical specimen for liquid-based cytology. The primary outcome was clinical performance (ie, sensitivity, specificity, positive predictive value [PPV], and negative predictive value [NPV]) of the strategy for the detection of high-grade squamous intraepithelial lesion (HSIL) or worse. This trial is registered with ISRCTN, ISRCTN13476702.

Findings Between June 5, 2018, and Jan 6, 2020, we recruited 4285 women, 3638 (84·9%) of whom tested negative for HPV and 647 (15·1%) tested positive for one or more oncogenic HPV type. Sensitivity of the algorithm to detect HSIL or worse was 85·4% (95% CI 81·0–89·6), with specificity 89·6% (88·6–90·6), PPV 35·2% (31·6–39·0), and NPV 98·9% (98·6–99·2). Among HPV-positive women, 602 (93·0%) received same-day thermal ablation and HSIL or worse was 85·4% (95% CI 81·0–89·6), with specificity 89·6% (88·6–90·6), PPV 35·2% (31·6–39·0), and NPV 98·9% (98·6–99·2). Among HPV-positive women, 602 (93·0%) received same-day thermal ablation and HSIL or worse was 85·4% (95% CI 81·0–89·6), with specificity 89·6% (88·6–90·6), PPV 35·2% (31·6–39·0), and NPV 98·9% (98·6–99·2). Among HPV-positive women, 602 (93·0%) received same-day thermal ablation and HSIL or worse was 85·4% (95% CI 81·0–89·6), with specificity 89·6% (88·6–90·6), PPV 35·2% (31·6–39·0), and NPV 98·9% (98·6–99·2). Among HPV-positive women, 602 (93·0%) received same-day thermal ablation and HSIL or worse was 85·4% (95% CI 81·0–89·6), with specificity 89·6% (88·6–90·6), PPV 35·2% (31·6–39·0), and NPV 98·9% (98·6–99·2). Among HPV-positive women, 602 (93·0%) received same-day thermal ablation and HSIL or worse was 85·4% (95% CI 81·0–89·6), with specificity 89·6% (88·6–90·6), PPV 35·2% (31·6–39·0), and NPV 98·9% (98·6–99·2). Among HPV-positive women, 602 (93·0%) received same-day thermal ablation and HSIL or worse was 85·4% (95% CI 81·0–89·6), with specificity 89·6% (88·6–90·6), PPV 35·2% (31·6–39·0), and NPV 98·9% (98·6–99·2). Among HPV-positive women, 602 (93·0%) received same-day thermal ablation and HSIL or worse was 85·4% (95% CI 81·0–89·6), with specificity 89·6% (88·6–90·6), PPV 35·2% (31·6–39·0), and NPV 98·9% (98·6–99·2).

Interpretation We conducted the first real-world evaluation of a fully integrated point-of-care HPV self-collect, test, and treat strategy for same-day cervical screening in a LMIC and found it to be effective, acceptable, and safe when implemented at scale in primary health-care facilities in Papua New Guinea. Our findings support the introduction and scale-up of HPV screening and treatment for the control and elimination of cervical cancer in LMICs, as recommended by WHO.

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Diseases Research, Royal Women's Hospital, Melbourne, VIC, Australia (Prof S M Garland MD, A M Conall PhD); Infectious and Immunity, Murdoch Children's Research Institute, Parkville, VIC, Australia (Prof S M Garland); Department of Obstetrics and Gynaecology, Women's Hospital, Melbourne, VIC, Australia (Prof S N Tabrizi PhD); Department of Obstetrics and Gynaecology, Daffodil Centre, The University of Melbourne, VIC, Australia (Prof K Canfell, NSW, Australia); Department of Obstetrics and Gynaecology, Burnet Institute for Medical Research and Public Health, Melbourne, VIC, Australia (C Morgan PhD); Department of Obstetrics and Gynaecology, Alotau Provincial Hospital, Alotau, Papua New Guinea (G Kaimega MBBS); Department of Obstetrics and Gynaecology, St Mary's Vunapope Rural Hospital, Kokopo, Papua New Guinea (D Babona MMed); Daffodil Centre, The University of Sydney–Cancer Council New South Wales, Sydney, NSW, Australia (Prof K Cantil, KT Simms PhD); Correspondence to: Prof Andrew J B Vallely, Papua New Guinea Institute of Medical Research, Gokora EHP 641, Papua New Guinea avallely@kirby.unsw.edu.au

Research in context

Evidence before this study
HPV DNA testing has been shown in earlier clinical research, meta-analyses, and modelling studies to be the most effective primary screening strategy for the early detection and treatment of cervical pre-cancer lesions to reduce incidence of and mortality from cervical cancer in low-income and middle-income countries (LMICs). WHO has recommended same-day HPV screening and treatment strategies in LMICs and that primary HPV DNA screening is scaled up as part of the global strategy for the elimination of cervical cancer, launched in 2020. We searched PubMed for original research articles published in English between Jan 1, 1990, and Oct 1, 2021, using the following search terms (separately and in combination): “HPV”, “point of care”, “cervical screening”, “cervical pre-cancer treatment”, and “low middle income country”. We also did a manual search based on bibliographies of relevant papers. Studies in Cameroon, Papua New Guinea, and South Africa have evaluated HPV DNA testing, followed by clinical triage with colposcopy and biopsy or visual inspection methods (eg, with acetic acid or Lugol's iodine). Treatment was by cervical cryotherapy or thermal ablation. However, no previous study has reported on primary HPV DNA screening and treatment strategies, as recommended by WHO. A paucity of robust real-world evidence of the effectiveness, acceptability, and safety of fully integrated same-day HPV screening and treatment strategies represents a major barrier to progressing the global elimination agenda.

Added value of this study
We conducted the first real-world evaluation of a novel, fully integrated strategy comprising point-of-care HPV DNA testing of self-collected specimens, followed by same-day thermal ablation. We found this strategy to be effective, acceptable, and safe for the early detection and treatment of cervical pre-cancer in women, when implemented at scale in routine health-care facilities in the LMIC setting of Papua New Guinea.

Implications of all the available evidence
Our findings support the introduction and scale-up of integrated HPV DNA screening and treatment strategies for the control and elimination of cervical cancer as a public health problem in LMICs, as recommended by WHO.

In May, 2018, the director-general of WHO announced a global call to action towards achieving the elimination of cervical cancer as a public health problem. The call was endorsed by the World Health Assembly in August, 2020, and the WHO global elimination strategy launched on Nov 17, 2020. The strategy put forward three coverage targets to be met globally by 2030, the so-called 90–70–90 targets: 90% of girls fully vaccinated with the HPV vaccine by age 15 years; 70% of women screened with a HPV DNA test or other high-precision test by age 35 years, and again by age 45 years; 90% of women with cervical pre-cancer treated; and 90% of women with invasive cancer managed. Achieving the triple intervention targets in the next decade would facilitate countries in achieving elimination of cervical cancer in 2100, reducing mortality from this type of cancer by 99% and saving more than 62 million lives over the next 100 years.1 Supporting this agenda, WHO has released new guidance to increase access to cervical screening and treatment services in LMICs.45 The new recommendations include a framework shift from primary screening with visual inspection methods, such as with acetic acid or Lugol's iodine (as endorsed in earlier recommendations by WHO), to detection of HPV DNA as the primary screening test in all settings, as well as the endorsement of self-collected vaginal specimens for primary HPV-based screening. Additionally, WHO has recommended thermal ablation over cryotherapy for the treatment of cervical pre-cancer lesions due to higher treatment rates, a more favourable profile of adverse events, and fewer logistical requirements.56 Modelling has shown that HPV-based screen and treat algorithms are the most effective primary screening method for reducing long-term risk of cervical cancer in populations from LMICs;7 however, there is a paucity of real-world data showing the performance of these algorithms across LMICs.

Papua New Guinea has the highest incidence of and mortality from cervical cancer in the Asia-Pacific region. Compared with Australia, the age-standardised incidence of cervical cancer in Papua New Guinea is five times higher (29.4 cases per 100 000 people vs 6.0 cases per 100 000 people) and the mortality rate is 12 times higher (19.8 cases per 100 000 people vs 1.7 cases per 100 000 people).1 In a field evaluation among 1005 women in Papua New Guinea, point-of-care GeneXpert HPV DNA testing (Cepheid, Sunnyvale, CA, USA) of self-collected vaginal specimens was found to have similar sensitivity and specificity to cervical specimens collected by clinicians for the detection of oncogenic HPV infection and underlying cervical pre-cancer (high-grade squamous intraepithelial lesion [HSIL] or worse).8 In the same cohort, visual inspection of the cervix with acetic acid showed poor performance for the detection of cervical pre-cancer, either alone (sensitivity 52%) or in combination with HPV testing (sensitivity 46%), compared with HPV testing alone (sensitivity 92%), rendering this method inappropriate for primary screening and clinical triage of HPV-positive women in this setting.9 Furthermore, it was shown that suitable training and support, point-of-care HPV testing, and treatment by cervical cryotheraphy could be provided routinely in primary care facilities across LMICs.10

Building on this previous research, we aimed to evaluate the clinical performance, treatment completion
rates, adverse events profile, and acceptability of a novel, fully integrated strategy, comprising point-of-care HPV DNA testing of self-collected specimens followed by same-day thermal ablation, for screening of cervical cancer in women in Papua New Guinea.\textsuperscript{10,13}

**Methods**

**Study design and participants**

HPV-STAT was a large-scale, prospective, single-arm intervention trial conducted at two clinical sites in Papua New Guinea: Modilon Hospital (Madang, Madang province) and Mt Hagen General Hospital (Mount Hagen, Western Highlands province), which serve provincial populations of 49,216 people and 36,206 people, respectively.\textsuperscript{11}

Sites were selected in consultation with national and provincial health authorities, church health services, and local stakeholders (including health facility staff) in each province. Criteria for site selection were having an experienced consultant gynaecologist working on site and who was available to support the research, including review of referral cases; a clinic dedicated to cervical screening operating for at least 3 days per week and currently providing screening based on conventional cytology (ie, the Papanicolaou test) or visual inspection with acetic acid; suitable clinic space available for the setup of new equipment, conduct of clinical interviews, and other study activities; a clinical workload of at least 200 women screened per month; and previous participation in collaborative research or studies on cervical screening involving use of GeneXpert point-of-care tests.

Women aged 30–59 years attending cervical screening services at the two clinical sites, willing to comply with study procedures, and able to provide written informed consent were eligible to participate. Women who were pregnant or who had given birth in the past 6 weeks, or women had a history of cervical cancer or hysterectomy, were excluded. Women who were menstruating at the time of the clinical visit were advised to return for screening 1–2 weeks later.

A randomised design was not ethically feasible in this interventional trial due to the absence of an appropriate comparator group, following the demonstration in our earlier research that the current standard of care for screening, based on visual inspection with acetic acid, had poor performance.\textsuperscript{10,14} The study protocol was approved by human research ethics committees in Papua New Guinea (IRB 1712, MRAC 17.36) and Australia (HC17631).

**Procedures**

Women attending the clinics for screening were provided with general information about the study on arrival through a 5–10 min group talk (referred to as a tok save in Papua New Guinea Pidgin), given by a member of the clinical research team. A pictorial flipchart was used to explain key procedures, such as the collection of specimens and treatment options. Examples of unused vaginal swabs and specimen collection kits were made available for women to look at and handle. At the end of the talk, women were given an opportunity to ask questions and were provided with a copy of the study participant information sheet. Those women interested in participating in the study then completed a short eligibility assessment and provided written informed consent.

We used a pictorial guide developed in an earlier study\textsuperscript{10} to advise women how to collect a mid-cavity vaginal specimen using a Just for Me cytobrush (Preventative Oncology International, Cleveland Heights, OH, USA). Immediately after collection, each self-collected vaginal specimen was tested for oncogenic HPV types at the point of care by a trained research nurse in each clinic. Following agitation of the sample in 20 mL of ThinPrep PreservCyt solution (Hologic, Marlborough, MA, USA), 1 mL of PreservCyt fluid was then tested with the rapid fully automated GeneXpert platform (Cepheid, Sunnyvale, CA, USA), as per the manufacturer’s instructions.\textsuperscript{16,17} Disposable cartridges held the reagents, primers, and probes for the simultaneous detection of 14 oncogenic HPV types responsible for over 95% of cervical cancers (ie, HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68), a human reference gene to assess adequacy of the sample, and an internal control to verify reagent integrity and adequacy of processes.\textsuperscript{17} The system monitored the presence of inhibitors in the real-time PCR assay to signal a potentially false negative result. Test results were available in 60 mins and were displayed on the accompanying laptop, typically as three outputs: HPV16, HPV18 or HPV45, and other HPV (a summary of test results for HPV31, 33, 35, 39, 51, 52, 56, 58, 59, 66, and 68). Test results were provided to women before midday on each clinic day to allow sufficient time for same-day counselling, pelvic examination, and treatment or referral as indicated.

Women with a positive HPV DNA test were counselled about their test result and offered a pelvic examination to assess their eligibility for thermal ablation on the same day. Women with a healthy cervix on naked eye examination after application of acetic acid, and who had a transformation zone visible in its entirety, were offered same-day ablation, in which the entire transformation zone was treated using one to five applications of the thermal ablation probe as required. If an abnormality was seen on examination, such as a suspected cervical cancer or a cervical polyp, or the transformation zone was not visible in its entirety, the woman was advised that referral for specialist review was necessary, and an appointment was made for her to attend a gynaecology outpatient clinic. Pelvic examination, eligibility assessment, and same-day thermal ablation or gynaecology referral were all carried out by a trained nurse at each primary screening clinic and conducted in accordance with study-specific standard operating procedures.
All HPV-positive women who agreed to have a pelvic examination were asked to provide a cervical specimen collected by a clinician, before application of acetic acid, for assessment of the study primary outcome. Cervical specimens were collected using a Cervex-Brush Combi (Rovers Medical Devices, Oss, Netherlands), which enabled simultaneous collection of cells of the ectocervix, endocervix, and transformation zone in a single sample. Following collection, specimens were immediately placed in 20 mL of PreservCyt and stored onsite at 4°C before shipment to VCS Foundation (Melbourne, VIC, Australia), a laboratory accredited by the National Association of Testing Authorities–Royal College of Pathologists Australia. At VCS Foundation, liquid-based cytology (LBC) was carried out in accordance with established laboratory procedures. All specimens were independently read by two separate teams consisting of scientists and pathologists at VCS (including GT, overseen by MS), who were masked to HPV DNA test results and the other team's assessment results. When both teams agreed on a diagnosis of HSIL or worse, no further investigation was instituted, and a final diagnosis was recorded. If the assessment differed and one team assessed the case to be possible HSIL or worse, p16/Ki-67 dual stain cytology (CINTec PLUS Cytology, Roche Diagnostics, Rotkreuz, Switzerland) was carried out and the result was used to make a final diagnosis.

A random systematic sample of 600 (15·0%) HPV-negative women was also asked to provide a cervical specimen collected by a clinician for LBC. Selection was based on study numbers allocated sequentially at enrolment from a preprinted study register. Before the start of the study, one (15%) in six study numbers in the register were systematically marked to indicate which women should be invited to provide a specimen. If a woman allocated a marked study number from the register was found to test positive for HPV, clinic staff were instructed to ask the next HPV-negative woman to provide a specimen. All women with a negative HPV test (including those in the 15·0% sample) were counselled regarding their test result and advised to return to the clinic for HPV-based screening in 5 years. HPV-negative women were not routinely offered a pelvic examination, unless indicated for clinical reasons.

During the enrolment visit, a short face-to-face interview in English or Papua New Guinea Pidgin (as appropriate for the participant) was conducted by a member of the clinical research team to collect sociodemographic, behavioural, and clinical information; views on visit experience and acceptability of the screening algorithm; and HPV test results. These data were collected in study case record forms. Following quality checks by the study coordinator at each site (JG or GM), data were entered into a dedicated study REDCap database by use of electronic tablets.

All participants were advised that they could return to the clinic at any time if they had any concerns or additional questions, or if they had any unexpected adverse symptoms following thermal ablation (eg, discomfort, vaginal discharge, or bleeding). HPV-positive women treated by thermal ablation and the 15·0% sample of HPV-negative women who provided a clinician-collected specimen were asked to return for a follow-up visit at 3 months after enrolment to receive their LBC test results. Management and outpatient follow-up of HPV-positive women referred for gynaecology review was done by the gynaecology team. Women with a positive HPV test at first visit were also asked to return at 12 months after enrolment for a repeat HPV test and were advised that if they tested positive again, they would be offered repeat pelvic examination, thermal ablation, or gynaecology referral. Women who did not reattend the clinic for scheduled follow-up were contacted by mobile phone, visited in the community by a member of the clinical research team or by a local community volunteer, or both. In addition, all women with a cytological diagnosis of high-grade disease suggestive of squamous cell carcinoma or adenocarcinoma were contacted by the study team and were provided counselling and support to attend gynaecology review, if they had not already done so.

Outcomes

The primary outcome of the trial was the clinical performance (ie, sensitivity, specificity, positive predictive value [PPV], and negative predictive value [NPV]) of a point-of-care HPV self-collect, test, and treat strategy for the detection and treatment of underlying cervical pre-cancer. We used HSIL as our reference threshold for disease. We calculated the clinical performance (with 95% CIs) of the algorithm to detect high-grade disease (ie, HSIL or worse) and to examine the proportion of women with high-grade disease who received appropriate treatment (ie, same-day thermal ablation or gynaecology referral).

As in our earlier evaluation, and consistent with studies in other LMICs, we used LBC as the reference standard, against which to evaluate our screening algorithm, for two main reasons. First, although colposcopy-guided biopsy for a histological diagnosis is the preferred standard in high-income settings, currently this approach cannot be implemented on a large scale in routine health-care settings across LMICs, including Papua New Guinea. Second, outside of pure research settings, biopsy cannot be used ethically to assess women who test negative for HPV on primary screening tests; therefore, histology cannot be used as the reference standard in measurement of the specificity of real-world screening algorithms.

Secondary outcomes were the cost-effectiveness, requirements for health system implementation, and acceptability of the screening algorithm. These outcomes were measured using a combination of quantitative and
qualitative research methods\textsuperscript{4,13} and will be presented separately, except for data on acceptability collected by clinic staff as part of the clinical visit using a short semi-structured questionnaire, which are presented in this Article.

Statistical analysis
Based on findings from our earlier research,\textsuperscript{4,10} we estimated that the prevalence of oncogenic HPV infection among age-eligible women in this current study would be 14–18%, and that 8–10% of women would have HSIL or worse. HPV DNA testing alone has been shown to have a sensitivity of 88–96.0% for the detection of histologically confirmed cervical intra-epithelial lesions grade 2 (CIN2) or worse.\textsuperscript{17,23–27} In our earlier study among histologically confirmed cervical intra-epithelial lesions in performance characteristics between alternative HPV test result scenarios (eg, HPV16 alone vs HPV16, HPV18, or HPV45 alone) performed less favourably than did an algorithm based on all HPV infections combined. Therefore, we estimated that, in a sample size of 4000 women, around 600 (15.0%) would test positive for HPV and that around 320 (8.0%) would have HSIL or worse. Subsequently, a systematic random selection of 600 (15.0%) HPV-negative women would provide approximately the same number of LBC specimens as HPV-positive women. With data on primary and secondary outcomes available for approximately 1200 women, we could estimate the clinical performance characteristics of the algorithm separately, except for data on acceptability collected by clinic staff as part of the clinical visit using a short semi-structured questionnaire, which are presented in this Article.

Role of the funding source
The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results
Between June 5, 2018, and Jan 6, 2020, a total of 4285 women were recruited. All women attending for screening in the study period were invited to participate and 100% were enrolled. Overall, at enrolment, 3638 (84.9%) women tested negative for HPV and 647 (15.1%) women tested positive for oncogenic HPV types (table 1, figure 1). HPV16 was prevalent in 180 (4.2%) women, HPV18 or HPV45 in 84 (2.0%) women, and other HPV types in 450 (10.5%) women. Compared with HPV-negative women, women with a positive HPV test at study entry were younger (p<0.0001), less likely to be married (p=0.032), more likely to have completed high school (p=0.0001) and to be in paid employment (p=0.0001), and more likely to report ever having a sexually transmitted or genital infection (p=0.011; table 1). The prevalence of HPV infection

### Table 1: Selected baseline sociodemographic, behavioural, and clinical characteristics of study participants by HPV status (n=4285)

| Characteristic                                      | HPV-positive (n=647) | HPV-negative (n=3638) | p value |
|-----------------------------------------------------|----------------------|-----------------------|---------|
| Age, years                                          | 38 (34–45)           | 40 (35–46)            | <0.0001 |
| Age group, years                                    |                      |                       |         |
| <35                                                 | 188 (29.1%)          | 793 (21.8%)           | <0.0001 |
| 35–39                                               | 168 (26.0%)          | 848 (23.3%)           |         |
| 40–44                                               | 125 (19.3%)          | 718 (19.7%)           |         |
| ≥45                                                 | 165 (25.5%)          | 1265 (34.8%)          |         |
| Data missing                                        | 1 (0.2%)             | 14 (0.4%)             |         |
| Marital status                                      |                      |                       |         |
| Married                                             | 522 (80.7%)          | 3073 (84.5%)          | 0.032   |
| Single, divorced, or widowed                        | 125 (19.3%)          | 561 (15.4%)           |         |
| Data missing                                        | 0                    | 4 (0.1%)              |         |
| Highest level of attained education                 |                      |                       |         |
| Never attended school                               | 516 (79.8%)          | 2822 (77.6%)          |         |
| Primary school (aged 6–12 years)                    | 514 (79.4%)          | 2821 (77.3%)          |         |
| High school (aged 13–18 years)                      | 245 (37.9%)          | 1100 (30.2%)          | 0.0001  |
| Tertiary (eg, higher education)                     | 144 (22.3%)          | 654 (18.0%)           | 0.035   |
| Type of current work or employment                  |                      |                       |         |
| Household duties                                    | 528 (81.6%)          | 2926 (80.4%)          |         |
| Subsistence farming                                 | 321 (49.4%)          | 1995 (54.9%)          | 0.014   |
| Selling goods at market                             | 273 (42.7%)          | 1737 (47.7%)          | 0.0092  |
| Paid formal employment                              | 139 (21.5%)          | 552 (15.2%)           | 0.0001  |
| Self-employed business                              | 27 (4.2%)            | 165 (4.5%)            |         |
| Age of sexual debut, years                          | 20 (18–21)           | 19 (17–20)            |         |
| Age group of sexual debut, years                    |                      |                       |         |
| <18                                                 | 149 (23.0%)          | 910 (25.0%)           |         |
| 18–19                                               | 174 (26.9%)          | 1016 (27.9%)          |         |
| 20–24                                               | 245 (37.9%)          | 1555 (37.2%)          |         |
| ≥25                                                 | 79 (12.2%)           | 1555 (37.2%)          |         |
| Number of sexual partners                           | 1 (1–2)              | 1 (1–2)               |         |
| Lifetime number of sexual partners                  |                      |                       |         |
| <2                                                  | 332 (51.3%)          | 2208 (60.7%)          | <0.0001 |
| 2                                                   | 155 (24.0%)          | 822 (22.6%)           |         |
| ≥3                                                  | 160 (24.7%)          | 608 (16.7%)           |         |
| Current genital symptoms                            |                      |                       |         |
| Vaginal discharge                                   | 217 (33.5%)          | 991 (27.2%)           | 0.0011  |
| Abdominal pain                                       | 281 (43.4%)          | 1519 (41.8%)          |         |
| Pain on passing urine                               | 83 (12.8%)           | 384 (10.6%)           | 0.087   |
| Itching                                             | 116 (17.9%)          | 615 (16.9%)           | 0.52    |
| Sores                                               | 9 (1.4%)             | 47 (1.3%)             | 0.84    |
| Any of the above                                    | 372 (57.5%)          | 1980 (54.4%)          | 0.15    |
| Sexual and reproductive history                     |                      |                       |         |
| History of STI or genital infection                 | 268 (41.4%)          | 1320 (36.3%)          | 0.011   |
| History of pregnancy                                | 558 (86.2%)          | 3222 (88.6%)          |         |
| History of cervical screening                       | 155 (24.0%)          | 966 (26.6%)           |         |
| HPV vaccination                                     | 2 (0.3%)             | 12 (0.3%)             |         |
| Condom use during last sex                          | 80 (12.4%)           | 421 (11.6%)           |         |

Data are median (IQR) or n (%). HPV=human papillomavirus. STI=sexually transmitted infection.
decreased with age, from 19·0% among women aged 30–34 years to 12·0% among women aged 45 years or older (appendix p 1). Of a total of 1182 specimens collected at enrolment, 174 (14·7%) specimens were considered to be unsatisfactory for LBC due to blood staining or low cellularity, with similar proportions among HPV-positive women (86 [13·6%] of 631) and HPV-negative women (88 [16·0%] of 551; p=0·27). Accordingly, a total of 1008 (85·3%) specimens were examined per protocol, 545 specimens from HPV-positive women and 463 specimens from HPV-negative women (table 2). Sociodemographic data and reported symptoms among the 463 HPV-negative women with a satisfactory specimen for LBC were similar to those among all 3638 women who tested negative for HPV (data not shown).

Among the 545 HPV-positive women with a satisfactory specimen for LBC, 155 (28·4%) tested positive for HPV16; 67 (12·3%) tested positive for HPV18, HPV45, or both; and 384 (70·5%) tested positive for other HPV types. The prevalence of HSIL or worse was higher among women with HPV16 (89 [57·4%] of 155) than among those with HPV18 or HPV45, or other HPV types (103 [26·4%] of 390; p<0·0001). Age-specific prevalence of HSIL or worse was highest among HPV-positive women aged 40–44 years, 41% of whom had high-grade disease compared with 26% of HPV-positive women aged 30–34 years (appendix p 1).

The 155 women with HPV16 had a significantly higher risk of HSIL or worse than did the 390 women with HPV18 or HPV45, or other HPV types (odds ratio [OR] 2·61 [95% CI 1·78–3·81]). The association between HPV16 and high-grade disease increased with disease severity. Compared with women with HPV18 or HPV45, or other HPV types, the odds of women with HPV16 having HSIL was around 2·4 times higher (2·42 [1·62–3·61]) and having cytologically predicted squamous cell carcinoma was nearly 6·0 times higher (5·58 [2·77–11·22]). 25 (65·8%) of 38 cases of squamous cell carcinoma were among women with HPV16.

Among 463 HPV-negative women randomly selected to provide a LBC specimen, five (1·1%) had high-grade disease (three HSIL cases and two adenocarcinoma cases). The prevalence of underlying adenocarcinoma was similar between HPV-positive women and HPV-negative women (one [0·2%] of 545 vs two [0·4%] of 463;
Estimates of high-grade disease among the total 1008 HPV-positive women and HPV-negative women who provided a satisfactory specimen for LBC were used to estimate the overall prevalence of high-grade disease in the full study cohort of 4285 women and to calculate clinical performance characteristics (table 3).

The point-of-care self-collect, test, and treat strategy detected underlying HSIL or worse with an estimated 85.4% sensitivity (95% CI 81.0–89.6), 89.6% specificity (88.6–90.6), 35.2% PPV (31.6–39.0), and 98.9% NPV (98.6–99.2). These estimates were similar to those reported in our earlier trial among 1005 women in this same setting (figure 2). Clinical algorithms based on HPV16 alone or on HPV16, HPV18, or HPV45 alone had lower sensitivity (72.9% and 76.7%) but greater specificity (96.7% and 97.9%) than did an algorithm based on detection of any HPV type (data not shown).

Among 647 HPV-positive women at enrolment, 602 (93.0%) received thermal ablation on the same day; 42 (6.5%) were referred for gynaecology review, 602 (93.0%) received thermal ablation on the same day and six (4.0%) had been reassessed at 3 months. Overall, 37 (88.1%) of 42 women referred for gynaecology review attended the clinical follow-up visit at 3 months, 51 (15.5%) women reported that they had experienced adverse symptoms within 1–7 days of thermal ablation (ie, vaginal discharge in 15 women, lower abdominal pain in 14, vaginal bleeding in 13, and backache in ten), including 23 (45.1%) who had reattended the clinic between enrolment and follow-up at 3 months due to concerns about these symptoms (data not shown). All adverse symptoms reported were considered to be mild and had resolved in all cases by the time of the follow-up visit at 3 months. No serious adverse events were reported.

Acceptability of the screening service and clinical procedures was high among both HPV-positive women and HPV-negative women at enrolment (appendix p 2). Overall, 4279 (99.9%) of 4285 women reported high

| LBC findings by HPV status (n=1008) | | | | |
|---|---|---|---|---|
| HPV status | Negative for HPV | Positive for HPV (any type) | Positive for HPV16 or HPV45 | Positive for HPV18 or other type of HPV |
| All | 436 | 282 | 55 | 35 | 217 |
| Negative for abnormality | 22 | 71 | 11 | 7 | 59 |
| ASCUS or LSIL | 5 | 192 | 89 | 25 | 108 |
| HSIL or worse | 463 | 545 | 155 | 67 | 384 |
| HSIL | 31 | 149 | 63 | 19 | 93 |
| Adenocarcinoma in situ | 0 | 4 | 0 | 2 | 2 |
| Squamous cell carcinoma | 0 | 38 | 25 | 4 | 13 |
| Adenocarcinoma | 21 | 1 | 1 | 0 | 0 |
| Total | 5 | 192 | 89 | 25 | 108 |

LBC=liquid-based cytology. HPV=human papillomavirus. ASCUS=atypical squamous cells of undetermined significance. LSIL=low-grade squamous intraepithelial lesion. HSIL=high-grade squamous intraepithelial lesion. *A total of 157 HSIL or worse cases were identified, of which 63 (32.0%) were confirmed by p16/Ki-67 dual immunostaining due to a difference in assessment made by two independent teams of scientists and pathologists. †All cases were positive for p16/Ki-67 dual stain; one woman who was asymptomatic and two women who reported vaginal discharge for more than 4 weeks at baseline. ‡Considered to be HPV-negative adenocarcinomas; both women reported vaginal discharge for more than 4 weeks at baseline.

Table 2: Performance of point-of-care HPV testing of self-collected vaginal specimens for detection of HSIL or worse

| HPV status | Positive for HSIL or worse | Negative for HSIL or worse | Total |
|---|---|---|---|
| Raw data (n=1008)* | 192 | 353 | 545 |
| Positive for HPV | 5 | 458 | 463 |
| Negative for HPV | 228 | 419 | 647 |
| Estimated performance (n=4285)† | 228 | 3599 | 3627 |

Sensitivity, % (95% CI) ·· ·· 85.4% (81.0–89.6)
Specificity, % (95% CI) ·· ·· 89.6% (88.6–90.6)
Positive predictive value, % (95% CI) ·· ·· 35.2% (31.6–39.0)
Negative predictive value, % (95% CI) ·· ·· 98.9% (98.6–99.2)

All specimens underwent HPV DNA testing with GeneXpert (Cepheid, Sunnyvale, CA, USA). HPV=human papillomavirus. HSIL=high-grade squamous intraepithelial lesion. LBC=liquid-based cytology. HPV=positive predictive value. HPV-negative predictive value. *Based on satisfactory LBC specimens provided by 545 HPV-positive women and 463 HPV-negative women at baseline. †Calculated after fitting estimates of high-grade disease (ie, HSIL or worse) among HPV-positive and HPV-negative women observed in raw data to the entire cohort of 4285 women and a HPV prevalence of 15.1% (647 of 4285 women).

Table 3: Performance of point-of-care HPV testing of self-collected vaginal specimens for detection of HSIL or worse on LBC
Study 1 refers to a field evaluation of 1005 women by Toliman and colleagues and study 2 refers to this current interventional trial of 3638 women. Error bars represent 95% CI. p<0.5 for study 1 versus study 2 across all performance characteristics. HPV=human papillomavirus. HSIL=high-grade squamous intraepithelial lesion. PPV=positive predictive value. NPV=negative predictive value.

The clinical performance (ie, sensitivity, specificity, PPV, and NPV) of our HPV-based screening model was consistent with a pilot study in Papua New Guinea and with earlier field evaluations. However, compared with these earlier studies, in this HPV-STAT trial, we were able to conduct HPV DNA testing at the point of care and to provide same-day test results to all women attending screening, as well as same-day treatment or referral to all women who tested positive for oncogenic HPV types. Same-day thermal ablation was provided to 602 (93.0%) of all 647 women testing positive for HPV, including 164 (85.4%) women with underlying HSIL or worse and 143 (96.0%) women with HSIL. Of the 42 (6.5%) HPV-positive women referred for gynaecology review, around half (22 [52.4%]) had underlying squamous cell carcinoma, and 37 (88.1%) attended for assessment and treatment. No squamous cell carcinoma was detected among HPV-negative women who provided a specimen for LBC. Acceptability of the screening service and clinical procedures was excellent among both HPV-positive and HPV-negative women, with adverse events among women treated by thermal ablation being short-lived and similar in frequency and clinical features to those reported in earlier research.

Studies in Papua New Guinea, Cameroon, and South Africa have evaluated individual components of the model used in this HPV-STAT trial; however, no previous study has reported on the use of all components in combination for primary HPV screening and treatment, as recommended by WHO. In an earlier study of 1005 women in Papua New Guinea, we evaluated point-of-care GeneXpert HPV DNA testing of self-collected specimens, followed by visual inspection of the cervix with acetic acid for clinical triage, and same-day cryotherapy. In Cameroon, a test, triage, and treat approach was evaluated, comprising self-collection and GeneXpert HPV DNA testing at the point of care, followed by clinical triage based on visual inspection methods (ie, with acetic acid or Lugol’s iodine) and thermal ablation if indicated. A study in South Africa evaluated the performance of GeneXpert HPV DNA testing with self-collected and clinician-collected specimens, followed by colposcopy and biopsy among HPV-positive and HPV-negative women. Compared

Table 4: Treatment completion and clinical follow-up among HPV-positive women

![Figure 2: Clinical performance of point-of-care HPV testing for detection of HSIL or worse in two trials in Papua New Guinea](https://www.thelancet.com/lancetgh)
with the findings of this HPV-STAT trial, the study\(^3\) found similar sensitivity (87·7\% vs 85·4\%) but lower specificity (77·5\% vs 89·6\%) and PPV (15·1\% vs 35·2\%) for the detection of underlying cervical pre-cancer among HIV-negative women. In this HPV-STAT trial, visual inspection with acetic acid was used to assess eligibility for same-day thermal ablation and not as an additional diagnostic or clinical triage step to identify and treat so-called acetowhite lesions that can appear on the cervix following application of acetic acid. Although acetowhite staining was previously thought to have high predictive value for pre-cancer lesions, further research has found this occurrence to be a highly subjective finding with substantial observer variability and low sensitivity for the detection of cervical pre-cancer, even in combination with HPV DNA testing.\(^3\)

Therefore, in the current study, we used visual inspection with acetic acid for visualisation of the transformation zone only. If visible in its entirety, the entire transformation zone was treated regardless of whether or not any acetowhite lesions were seen, rather than providing focal ablation to acetowhite lesions only, or deferring ablation among women without any such staining. This same assessment and treatment strategy has now been endorsed in the updated WHO screening guidelines for women in the general population across LMICs.\(^4\)

A key feature of our design was the use of LBC as the diagnostic reference standard with HSIL as the pre-defined disease threshold, rather than histology with a disease threshold of CIN2, which is the preferred diagnostic reference or gold standard for cervical pre-cancer in high-resource settings. There were five reasons underlying this decision. First, it is not currently feasible from a staffing and logistical perspective to provide colposcopy or to collect four quadrant cervical biopsies for histological examination in real-world health facility settings in Papua New Guinea. Researchers in other LMICs have used HSIL as their preferred disease threshold for the same reason.\(^20–22\)

Second, a key advantage of our chosen reference standard was that it allowed us to include HPV-negative women in the measurement of our primary outcome, a group in whom it would have been neither feasible nor ethical to take four quadrant cervical biopsies for histological examination. Three studies in Malawi\(^21\) and Cameroon\(^22\) used CIN2 as a disease threshold, but obtained biopsies from HPV-positive women only; therefore, they could estimate PPV but not broader clinical performance characteristics (ie, sensitivity, specificity, and NPV). Two studies in El Salvador\(^23\) (n=1824) and South Africa\(^24\) (n=1107) were the only ones from LMICs to have included colposcopy and biopsy in a subset of HPV-negative women, but both were conducted at established tertiary centres of excellence and neither were designed as large-scale pragmatic intervention trials. Third, we believe that earlier research supporting the excellent performance of GeneXpert HPV testing for the detection of underlying CIN2 or cervical intra-epithelial lesions grade 3 (CIN3)\(^25\) made it acceptable to use LBC results of HSIL or worse as a proxy for high-grade disease. Fourth, in the Australian setting, we found that over 80% of HSIL diagnoses based on LBC were confirmed histologically to be CIN2 or worse, with around 54% of cases diagnosed as CIN3 or worse.\(^26\)

In the current trial, use of two independent teams of expert readers masked to each other’s assessment and to field-based HPV test results, in addition to the use of p16/Ki-67 immunostaining if necessary, ensured optimal predictive value of HSIL or worse for cervical pre-cancer. Finally, a further advantage of our chosen reference standard and sampling strategy was that it allowed us to collect robust primary outcome data without adversely impacting our assessment of real-world acceptability, health system, and economic outcomes.

Our study had several possible limitations. Our decision to estimate clinical performance by use of data from all HPV-positive women and a subpopulation of HPV-negative women might have resulted in underestimation or overestimation of the true clinical performance of our screening algorithm in this setting. There is a theoretical possibility that our systematic random sampling strategy among HPV-negative women might not have been fully adhered to in practice and could have led to selection bias. For example, HPV-negative women with symptoms suggestive of cervical pre-cancer or cancer (eg, vaginal discharge or intermenstrual bleeding) might have been more likely to be selected for specimen collection for LBC than were asymptomatic women. Nevertheless, we believe this risk of bias to be extremely low because socio-demographic characteristics and self-reported symptoms among HPV-negative women who provided an LBC specimen were similar to those among all HPV-negative women. Furthermore, although four (80·0\%) of five HPV-negative women diagnosed with HSIL (three women) or adenocarcinoma (two women) on LBC reported vaginal discharge at baseline, all individuals were confirmed to have been allocated study numbers selected a priori in our sampling strategy—ie, HPV-negative women were selected for LBC as per protocol and not due to self-reported symptoms.

Our decision to offer thermal ablation to all eligible women who tested positive for HPV is consistent with new WHO guidelines,\(^7\) but might raise concerns about overtreatment given that the estimated PPV of our screening model was 35·2\% (95\% CI 31·6–39·0). Our PPV estimates were consistent with baseline screening round estimates for primary HPV-based screening reported in both LMICs and high-income settings.\(^8–11\)

Of note, baseline HPV infection is a predictor of both current and future disease; therefore, it is anticipated that PPV will increase during ongoing follow-up of HPV-positive women.\(^28–30\)

We were unable to make a definitive diagnosis among women with cytologically confirmed HSIL or worse, or
squamous cell carcinoma. Although the predictive value of LBC for CIN2 or worse is high, the cytological distinction between HSIL and invasive disease is not as strong, and can only be made with confidence histologically. It is probable that a high proportion of women with cytologically confirmed squamous cell carcinoma and a healthy cervix on examination, who were treated by same-day thermal ablation, could be found to have CIN2 or worse rather than squamous cell carcinoma on histology, but this cannot be known for certain. Newly available and emerging technologies, such as visualisation of cervix by digital colposcopy or deep-learning-based automated visual evaluation, and disease biomarkers (eg, host DNA methylation), could have roles in augmenting future algorithms for HPV-based screening in women from LMICs and in identifying women at greatest risk of invasive disease.

Despite community-based tracing and follow-up, retention at 3 months was suboptimal in this trial. This situation might have led to an overestimation or underestimation of the proportion of women experiencing an adverse event following thermal ablation. It is probable that reattendance was higher among women with symptoms than among those without, given that 45% of women who experienced an adverse event attended both an early unscheduled visit and a scheduled visit at 3 months. Our follow-up data underlie the importance of same-day screening and treatment strategies in LMICs, including Papua New Guinea, to ensure that care is not compromised by poor retention.

This HPV-STAT trial showed that a comprehensive screen and treat algorithm was effective, safe, and acceptable when implemented in routine clinical settings in Papua New Guinea and achieved WHO’s 2030 coverage target of 90% treatment completion among women with underlying cervical pre-cancer. This strategy has now been adopted for introduction and scale-up in Papua New Guinea and Vanuatu within a new regional partnership for the elimination of cervical cancer in the western Pacific.

Contributors
AJBV, MS, SGB, JB, GDLM, SMG, JMLB, PJT, SNT, RG, KC, and JMK conceived the study and initiated the study design. AK-H, CM, and KTS led the qualitative, health systems, and health economics considerations. HW provided statistical expertise in trial design and conducted the primary statistical analysis. All contributors contributed to the refinement of the study protocol and approved the final manuscript. All authors had full access to all the data in the study and had full responsibility for the decision to submit for publication.

Declaration of interests
The Papua New Guinea Institute of Medical Research (AJBV, AK-H, JG, JB, GM, and PJT) and the Kirby Institute, UNSW Sydney (AJBV, SGB, AK-H, HW, RG, and JMK) have received subsidised test kits for research from Cepheid. VCS Foundation (MS, JMLB, and GT) has received donated test kits for research from Roche, Abbott, Seegene, Cepheid, AusDiagnostics, and Becton Dickinson. AJBV, MS, and KC jointly lead the Elimination of Cervical Cancer in the Western Pacific programme with philanthropic funding support from the Minderoo Foundation and the Frazer Family Foundation; and equipment, tests, and consumables donated by Cepheid for HPV-based cervical screening in Papua New Guinea and Vanuatu. SMG is a member of the Merck HPV Global Advisory Board and has led investigator-initiated grants from Merck on HPV in young women. All other authors declare no competing interests. All authors declare that neither they or their institutions have received direct funding from industry for this or any other research project.

Data sharing
The data are not publicly available due to confidentiality and ethical considerations. Deidentified data are available from the authors upon reasonable request and subject to approval by the ethics committees overseeing the study.

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