Detecting cervical precancer and reaching underscreened women by using HPV testing on self samples: updated meta-analyses

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ABSTRACT

OBJECTIVE

To evaluate the diagnostic accuracy of high-risk human papillomavirus (hrHPV) assays on self samples and the efficacy of self sampling strategies to reach underscreened women.

DESIGN

Updated meta-analysis.

DATA SOURCES

Medline (PubMed), Embase, and CENTRAL from 1 January 2013 to 15 April 2018 (accuracy review), and 1 January 2014 to 15 April 2018 (participation review).

REVIEW METHODS

Accuracy review: hrHPV assay on a vaginal self sample and a clinician sample; and verification of the presence of cervical intraepithelial neoplasia grade 2 or worse (CIN2+) by colposcopy and biopsy in all enrolled women or in women with positive tests. Participation review: study population included women who were irregularly or never screened; women in the self sampling arm (intervention arm) were invited to collect a self sample for hrHPV testing; women in the control arm were invited or reminded to undergo a screening test on a clinician sample; participation in both arms was documented; and a population minimum of 400 women.

RESULTS

56 accuracy studies and 25 participation trials were included. hrHPV assays based on polymerase chain reaction were as sensitive on self samples as on clinician samples to detect CIN2+ or CIN3+ (pooled ratio 0.99, 95% confidence interval 0.97 to 1.02). However, hrHPV assays based on signal amplification were less sensitive on self samples (pooled ratio 0.85, 95% confidence interval 0.80 to 0.89). The specificity to exclude CIN2+ was 2% or 4% lower on self samples than on clinician samples, for hrHPV assays based on polymerase chain reaction or signal amplification, respectively. Mailing self sample kits to the woman's home address generated higher response rates to have a sample taken by a clinician than invitation or reminder letters (pooled relative participation in intention-to-treat-analysis of 2.33, 95% confidence interval 1.86 to 2.91). Opt-in strategies where women had to request a self sampling kit were generally not more effective than invitation letters (relative participation of 1.22, 95% confidence interval 0.93 to 1.61). Direct offer of self sampling devices to women in communities that were underscreened generated high participation rates (>75%). Substantial interstudy heterogeneity was noted (I^2>95%).

CONCLUSIONS

When used with hrHPV assays based on polymerase chain reaction, testing on self samples was similarly accurate as on clinician samples. Offering self sampling kits generally is more effective in reaching underscreened women than sending invitations. However, since response rates are highly variable among settings, pilots should be set up before regional or national roll out of self sampling strategies.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Tests performed on self samples are less sensitive and less specific than tests performed on clinician samples when using a high-risk human papillomavirus (hrHPV) assay based on signal amplification

Response rates for hrHPV testing are higher for self sampling kits than for conventional invitations

WHAT THIS STUDY ADDS

Tests performed on self samples are similarly sensitive and slightly less specific than tests performed on clinician samples when using a hrHPV assay based on polymerase chain reaction

Response rates for hrHPV testing continue to be higher for self sampling kits than for conventional invitations

Introduction

Cervical cancer rates in western Europe, North America, Australia, and New Zealand are relatively low compared with rates in less developed countries.[1] However, demographic and social disparities in the burden of disease exist. In the United States, incidence is higher among Hispanic (8.9 per 100 000 women years in 2011-15, age adjusted using the 2000 US population as reference) and black (8.4) populations, versus the white population (7.4).[2] The contrasts can be explained by differences in access to screening. In western and northern Europe, both cervical cancer incidence and mortality have decreased after widespread screening.[3] In eastern Europe, where the coverage or quality, or both, of screening often is low to moderate, incidence has not dropped to the same extent and in some countries trends are even rising.[4-6] To be noted, 85% of cases of cervical cancers occur in less developed countries, with incidence rates reaching 35 per 100 000 women years in eastern Africa.[1]

Most cervical cancer cases occur in women who have never been screened for cervical cancer, or do not participate in routine screening.[7] However, recent trend analyses reveal an increasing burden of

cervical cancer, even in countries with well organized screening programs based on cytology and good coverage.[8-12] These observations can be reasonably explained by three arguments. First, the prevalence of exposure to the main etiologic factor, high-risk human papillomavirus (hrHPV) infection, has increased over time.[13 14] Second, certain groups of the target population do not attend screening.[15-17] Third, a proportion of screened women with cervical precancer and cancer show false negative Pap tests.[18 19] We now have high level evidence that screening by hrHPV testing is more effective than screening by cytology for protecting against future cervical precancer and cancer.[18 20] hrHPV testing provides another advantage: it can be done on vaginal samples collected by the patient (self samples), whereas cytology on self samples shows poor accuracy.[21]

hrHPV testing on self samples could be one way to increase access to cervical cancer screening for women not participating in routine screening. hrHPV testing also removes the need for a pelvic exam. In order to assess whether vaginal self sampling could improve cervical cancer prevention among underscreened populations, we updated two meta-analyses: one on the accuracy of self samples tested for hrHPV to detect cervical precancer; and one on the potential of strategies to reach women who were not screened or underscreened by offering them self sampling devices.[22 23]

The previous accuracy meta-analysis concluded that hrHPV testing was less sensitive on self samples than on clinician samples, but also found that the reason for lower sensitivity was the use of assays based on signal amplification.[22] In this review, we separately pooled the accuracy of hrHPV assays based on signal amplification from hrHPV assays based on polymerase chain reaction. We also included subgroup meta-analyses and multivariable analyses assessing the variation in hrHPV testing accuracy on self samples by assay, self sampling device, and storage medium.

Two previous participation meta-analyses showed that sending self sampling kits to a woman's home address generated greater response rates than invitation or reminder letters.[23 24]

New assays, self sampling devices, storage media, and participation strategies have entered the market since the publication of these two meta-analyses; and more accuracy and participation studies have been conducted. Moreover, countries such as Australia and the Netherlands have introduced self sampling to national screening guidelines. Other countries, such as the US, Canada, and some European countries, have called for rigorous comparative accuracy and participation studies.[25-27]

Methods

Study designs

Two different aspects of hrHPV testing on self samples were addressed (accuracy to detect cervical precancer and the participation of women who were underscreened) through two joint reviews. The reviews comprised of previous meta-analyses that were updated with new references published up to 15 April 2018.[22 23]

The first meta-analysis included diagnostic test accuracy studies that answered the following questions: what is the relative accuracy a hrHPV assay on a self sample compared with a clinician sample; and does the relative accuracy vary by clinical setting (screening population, high-risk population, follow-up for previous abnormalities, and monitoring after treatment), assay, self sampling device, and storage medium? We distinguished hrHPV assays based on a principle of signal amplification from hrHPV assays based on polymerase chain reaction and included only assays that were clinically validated for cervical cancer screening on clinician samples.[28] However, we also performed more comprehensive analyses that included non-clinically validated assays (supplementary materials). The targeted disease was cervical intraepithelial neoplasia grade 2 or worse (CIN2+) and CIN3+.

The second meta-analysis included randomized clinical trials and aimed to answer whether offering self sampling kits to women who were underscreened generated higher response rates than sending invitation or reminder letters. Secondary outcomes were test positivity rates, adherence to follow-up in women who were screened, and detection of CIN2+.

Criteria for study selection

Diagnostic studies for the accuracy review were eligible if the following criteria were met: a vaginal sample was collected by a woman herself (self sample) followed by a cervical sample collected by a clinician (clinician sample); the same hrHPV assay was performed on both samples; and the presence or absence of CIN2+ was verified by colposcopy and biopsy in all enrolled women, or in women with one or more positive tests. Studies with cytological follow-up for women with negative colposcopy results at baseline assessment were accepted as well, but were indexed for sensitivity analyses.

Randomized clinical trials for the participation review were eligible if the following criteria were met: the study population involved women who were irregularly screened, never screened, or did not respond to invitation or reminder letters for conventional screening for cervical cancer; women in the intervention group (self sampling arm) were invited to collect a self sample for hrHPV testing; women in the control arm were invited or reminded to undergo conventional cytology screening or hrHPV testing, or both, on a sample taken by a clinician; participation in the self sampling arm and the control arm was documented; and a minimum of 400 women were included in the study.

Study selection, data extraction, and checking

Search strategies are explained in the supplementary materials. To ensure that there were at least 12 months

of overlap with the previous meta-analyses, the search period was 1 January 2013 to 15 April 2018 for the accuracy review and 1 January 2014 to 15 April 2018 for the participation review.[22 23] Newly retrieved studies from each search were added to those already included in the corresponding review. We restricted the retrieval of references to published literature that had been peer reviewed. MA and one other author (SBS, ST, FS, or a Collaboration on Self-Sampling and HPV Testing group member) independently performed the study selection and data extraction. PC judged any unresolvable discordances. We assessed the quality of the diagnostic studies for the accuracy review by using the QUADAS-2 check list.[29] We assessed the quality of the randomized clinical trials for the participation review by using the Cochrane Collaboration's tool for risk of bias in randomized trials.[30]

Statistical methods

The meta-analyses followed PRISMA guidelines for reporting of meta-analyses, and recommendations established by the Cochrane Collaboration for diagnostic test accuracy and intervention trials.[31 32] We used the bivariate normal model for the logit transforms of sensitivity and specificity taking the intrinsic correlation between true and false rates of positivity and the variability between studies into account for the pooling of accuracy data.[33 34] We estimated relative accuracy of tests on self samples versus clinician samples by incorporating assay category as a covariate in the model.[32 35] The same type of analysis was performed to assess the variation of the accuracy according to clinical setting (screening population, high-risk population, follow-up for previous abnormalities, and monitoring after treatment), assay, self sampling device, and storage medium. We assessed publication bias by using Deeks' and Harbord's regression tests for the pooled absolute and relative accuracy estimates, respectively.[36 37]

In the per protocol analyses of randomized clinical trials, only women who took a self sample in the experimental arm were counted. In the intention-to-treat analyses, which reflected the overall public health effect in a real world situation, we additionally included women in the experimental arm who had been offered self sampling but choose to have a clinician sample taken instead. We included the following invitation scenarios: mail-to-all, opt-in, community campaign, and door-to-door. In mail-to-all studies, self sampling kits were mailed directly to a woman's home address for her to return by mail or in person to a local clinic. In opt-in studies, women had to request a self sampling kit. Community campaigns included community supported actions and outreach supported by mass media. In door-to-door interventions, community health workers delivered self sampling kits to women's homes or workplaces. Given the intrinsic strategic differences, participation rates were pooled separately by invitational scenario.

We ran a random effects model using Metaprop, a statistical procedure for meta-analysis of binomial data, to pool proportions.[38] We assessed statistical heterogeneity by using the I^2 statistic, which measures the variation across studies that is due to interstudy heterogeneity.[39] Relative participation rates (self/control) and absolute participation differences (self–control) were assessed by applying random effects models for ratios of proportions.[40 41] We used meta-regression to assess the influence of study characteristics on study outcomes.[42]

Statistical significance was defined as $P<0.05$. We used STATA/SE 14 (STATA Corp, College Station, TX) for statistical analyses, except for the bivariate normal model, which was run in SAS 9.3 (SAS Institute Inc, Cary, NC).

Patient and public involvement

Since the meta-analyses only included published reports, no patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. No patients were asked to advise on interpretation or writing up of results. There are no plans to disseminate the results of the research to study participants or the relevant patient community. It was not evaluated whether the studies included in the review had any patient involvement.

Results

This update contains 19 new reports containing 22 diagnostic studies and nine new randomized participation trials, [26 43-69] which were added to the 34 accuracy studies and to the 16 participation trials already included in the previous meta-analyses.[70-117] The updated meta-analyses finally comprised 56 diagnostic test accuracy studies and 25 randomized trials. The PRISMA flowcharts and study characteristics are available in the supplementary materials.

Quality of diagnostic studies in the accuracy review

The risk of bias for enrolment of women was considered low in 59%, moderate in 39%, and high in 2% of the 56 diagnostic studies (supplementary materials). Reporting and execution of tests (description of cut-off, blinding of the index test toward comparator and reference test) was adequate in 73% and unclear in 27%, but the risk of bias was never assessed as high. The quality of verification with a reference standard (acceptable validity, blinding toward tests, and avoidance of incorporating test results in final conclusion of disease outcome) was good in 84%, moderate in 13%, and problematic in 4% of the studies. The delay between self sampling, clinician sampling, and verification with the reference standard was short in 61%, unreported in 38%, and long in 2% of the studies. Partial verification was avoided in 70% but clearly present in 25%, whereas differential verification was absent in 89% but unclear or present in 11% of the studies. Withdrawal of patients was explained appropriately in 70%, but not in 18%,

and unclear in 12% of the studies. In most papers, uninterpretable results were poorly reported for the evaluated tests and for the reference standard (39% and 45%, respectively).

Quality of randomized clinical trials in the participation review

Three (12%) of the 25 trials met the criteria for low risk of bias in all categories.[114 115 117] In eight trials (32%) allocation was random and concealed,[26 63-65 104 114 115 117] in 14 trials (56%) allocation was unclear,[66 67 102 103 105-113 116] and in three trials (12%) allocation was problematic.[62 68 69] All trials had complete data for the participation outcome and were therefore at low risk of attrition bias. The quality of reporting was adequate in 12 trials (48%),[26 67 102-104 107-109 114-118] incomplete in one trial,[106] and intermediate in the other trials.

Accuracy of hrHPV assay

The pooled absolute sensitivity and specificity for outcomes CIN2+ and CIN3+, varied substantially by clinical setting and, therefore, accuracy measures were pooled separately by setting. Figure 1 shows that in screening studies, the pooled absolute sensitivity of hrHPV assays for CIN2+ based on signal amplification was substantially lower in self samples (77%, 95% confidence interval 69% to 82%) than in clinician samples (93%, 89% to 96%). The pooled absolute specificity to exclude CIN2+ was 84% (95% confidence interval 77% to 88%) in self samples and 86% (81% to 90%) in clinician samples. The pooled absolute sensitivity of hrHPV assays for CIN2+ based on polymerase chain reactions was 96% for both self samples and clinician samples. The specificity to exclude CIN2+ was similar for both self samples and clinician samples (79%).

Supplementary table 10 shows the pooled absolute accuracy values for all clinical settings (screening population, high-risk population, follow-up for previous abnormalities, and monitoring after treatment). The absolute specificity of all hrHPV assays on self samples and clinician samples was substantially lower in the other clinical settings than with screening.

The relative accuracy of hrHPV assays on self samples versus clinician samples did not vary substantially by clinical setting and therefore we could estimate overall relative sensitivity and specificity under the condition to separate hrHPV assays based on signal amplification from hrHPV assays based on validated polymerase chain reaction.

Table 1 shows that hrHPV assays based on signal amplification were less sensitive (ratio 0.85, 95% confidence interval 0.80 to 0.89 for CIN2+; 0.86, 0.76 to 0.98 for CIN3+) and less specific (0.96, 0.93 to 0.98 to exclude CIN2+) on self samples versus clinician samples. The test positivity rate was, on average, 14% higher and the positive predictive value was significantly lower for both CIN2+ and CIN3+ for self samples (positive predictive value< 1).

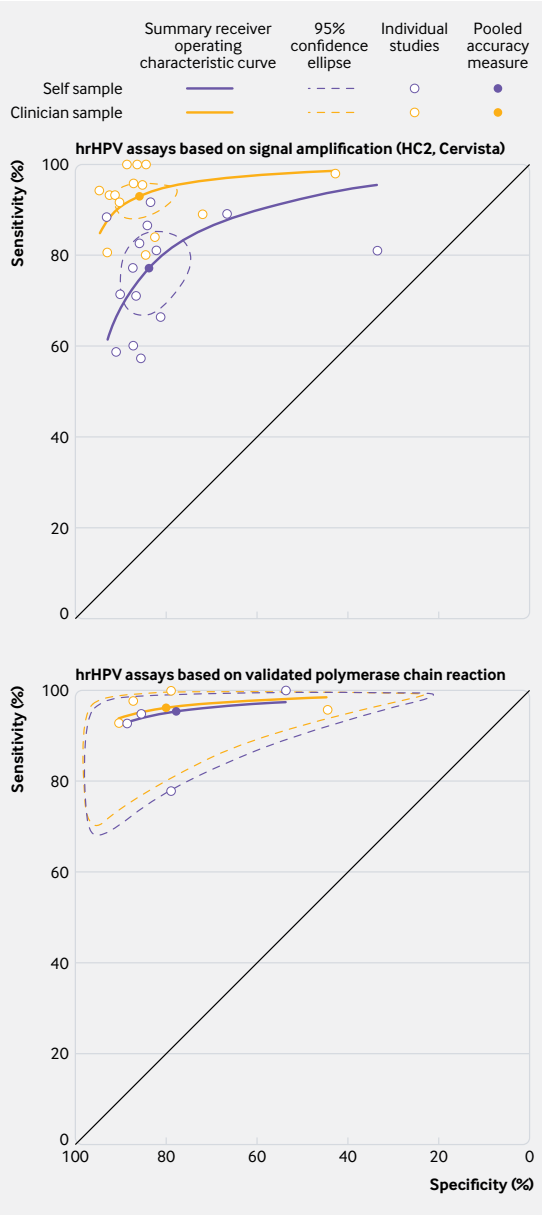

Fig 1 | Meta-analysis of the accuracy, for hrHPV assays for CIN2+ based on signal amplification and polymerase chain reaction for self samples and clinician samples in primary cervical cancer screening. Estimates are derived from a bivariate model for pooling of diagnostic data

hrHPV assays based on polymerase chain reaction were equally sensitive (ratio 0.99, 95% confidence interval 0.97 to 1.02 for CIN2+; 0.99, 0.96 to 1.02 for CIN3+) and slightly less specific (0.98, 0.97 to 0.99 to exclude CIN2+) on self samples versus clinician samples (table 1 and supplementary figs 3-6). The test positivity rate was similar in self samples versus clinician samples. Table 1 shows that the positive predictive values for CIN2+ or CIN3+ were not significantly lower for self samples.

Supplementary table 11 shows the pooled relative sensitivity and specificity for individual hrHPV assays for CIN2+ on self samples versus clinician samples. Each hrHPV assay based on signal amplification

Table 1 | Pooled relative sensitivity and specificity of high-risk human papillomavirus (hrHPV) assays based on signal amplification (SA) and polymerase chain reaction (PCR) on self samples versus clinician samples

			Ratio (95% CI)			
Assay	Outcome	No of studies	Sensitivity	Specificity	Test positivity	PPV
SA	CIN2+	23	0.85 (0.80 to 0.89)*	0.96 (0.93 to 0.98)*	1.14 (1.05 to 1.24)	0.71 (0.62 to 0.82)
	CIN3+	9	0.86 (0.76 to 0.98)*	0.97 (0.95 to 0.99)*		0.65 (0.57 to 0.78)
PCR	CIN2+	17	0.99 (0.97 to 1.02)	0.98 (0.97 to 0.99)*	1.00 (0.94 to 1.06)	0.97 (0.90 to 1.04)
	CIN3+	8	0.99 (0.96 to 1.02)	0.98 (0.97 to 0.99)*		0.90 (0.78 to 1.05)

PPV=positive predictive value; CIN2+=cervical intraepithelial neoplasia of grade 2 or worse; CIN3+=cervical intraepithelial neoplasia of grade 3 or worse.
*Statistically significantly different from unity.

(HC2, careHPV, and Cervista) as well as the hrHPV E6/E7 mRNA test with APTIMA were at least 15% less sensitive for CIN2+ on self samples versus clinician samples. Each hrHPV assay based on polymerase chain reaction was equally sensitive for CIN2+ and for CIN3+ on self samples versus clinician samples.

Table 2 shows that the pooled sensitivity of hrHPV assays based on signal amplification was 10% to 16% lower on a self sample versus a clinician sample for all self sampling device and storage medium categories.

Table 2 shows that the pooled sensitivity of hrHPV assays based on polymerase chain reaction on a self sample was similar (the 95% confidence interval for the ratio included unity) to a clinician sample for all of the self sampling devices and storage media. In general, hrHPV assays were less specific on self samples except for the HC2 assay on a tampon self sample (n=1) or an assay based on polymerase chain reaction on a vaginal lavage self sample (2). All hrHPV assays were less specific on self samples stored in cell preserving media (9) or virological media (18). Pooled relative accuracy data for each self sampling device and storage medium can be found in supplementary tables 12 and 13.

No important patterns in the relation between the accuracy and QUADAS items or small study effects could be discerned (supplementary materials). However, in screening studies, where partial verification bias was avoided, the specificity of the hrHPV assay based on signal amplification on self samples was significantly lower (83%) than in studies where verification was not avoided or unclear (87%; P=0.03).

Efficacy of invitation scenarios

Participation in the self sampling arm

Table 3 and supplementary figure 9 show that the percentage of women in the self sampling arm that had a hrHPV test done on a self sample, when the self sampling kit was mailed to a woman's home (mail-to-all), varied in the per protocol analysis between 6.4% and 34.0%, with a pooled average of 19.2% (95% confidence interval 15.7% to 23.0%).

Table 2 | Variation in relative sensitivity and specificity of high-risk human papillomavirus (hrHPV) assays on self samples versus clinician samples, by self sampling device and storage medium

Covariate	No of studies	Relative sensitivity (95% CI)	Relative specificity (95% CI)
Self sampling device			
hrHPV assay based on signal amplification			
Brush	13	0.84 (0.78 to 0.90)*	0.93 (0.91 to 0.96)*
Swab	7	0.85 (0.78 to 0.91)*	0.93 (0.90 to 0.95)*
Lavage†	2	0.84 (0.69 to 1.04)	0.74 (0.55 to 0.98)*
Tampon	1	0.86 (0.78 to 0.96)*	1.02 (1.00 to 1.03)
hrHPV assay based on polymerase chain reaction			
Brush	12	0.98 (0.95 to 1.02)	0.95 (0.91 to 0.99)*
Swab	4	0.98 (0.93 to 1.03)	0.93 (0.89 to 0.98)*
Lavage†	4	0.95 (0.87 to 1.04)	1.09 (0.91 to 1.30)
Tampon	0	NA	NA
Storage medium			
hrHPV assay based on signal amplification			
Cell preserving†	3	0.84 (0.78 to 0.90)*	0.93 (0.91 to 0.96)*
Virological†	15	0.86 (0.81 to 0.91)*	0.95 (0.92 to 0.98)*
Dry samples	0	NA	NA
Other	1	0.90 (0.71 to 1.13)	0.92 (0.71 to 1.21)
hrHPV assay based on polymerase chain reaction			
Cell preserving	6	1.00 (0.96 to 1.04)	0.92 (0.88 to 0.97)*
Virological†	3	0.97 (0.91 to 1.04)	0.94 (0.89 to 0.99)*
Dry samples†	7	0.96 (0.90 to 1.02)	1.01 (0.94 to 1.10)
Other	1	0.95 (0.80 to 1.13)	1.05 (0.69 to 1.58)

Relative values were computed by using a bivariate normal model, separating studies using a hrHPV assay based on signal amplification or a hrHPV assay based on polymerase chain reaction. Pooling was performed using a bivariate normal model.
NA=not available.
*Relative accuracy statistically significantly different from unity.
†When the bivariate model containing covariates did not fit or when the number of studies <4, a separate pooling of the relative sensitivity and relative specificity using a model for ratios of proportions was run.

Table 3 | Absolute participation in self sampling arm and control arm, participation difference and relative participation in self sampling versus control arm, by invitation scenario

Invitation scenario	No of studies	Absolute participation		Participation difference % (95% CI)	Relative participation (95% CI)
		Self sampling % (95% CI)	Control % (95% CI)		
Per protocol					
Mail-to-all	19/21*	19.2 (15.7 to 23.0)	11.5 (8.3 to 15.1)	7.3 (4.1 to 10.6)	1.87 (1.43 to 2.44)
Opt-in	6/8*	7.8 (5.2 to 10.9)	13.4 (10.2 to 16.9)	−5.1 (−10.0 to −0.2)	0.73 (0.51 to 1.04)
Community campaign	1	15.6 (12.4 to 19.5)	6.0 (4.2 to 8.7)	9.5 (5.4 to 13.7)	2.58 (1.67 to 3.99)
Door-to-door	4	94.2 (80.2 to 100.0)	53.3 (10.5 to 93.2)	39.7 (4.0 to 75.4)	1.99 (0.68 to 5.85)
Intention-to-treat†					
Mail-to-all	19/21*	24.8 (21.6 to 28.1)	11.5 (8.3 to 15.1)	12.8 (10.4 to 15.1)	2.33 (1.86 to 2.91)
Opt-in	6/8*	17.7 (12.3 to 23.9)	13.4 (10.2 to 16.9)	3.3 (−0.7 to 7.3)	1.22 (0.93 to 1.61)
Community campaign	1	15.6 (12.4 to 19.5)	6.0 (4.2 to 8.7)	9.5 (5.4 to 13.7)	2.58 (1.67 to 3.99)
Door-to-door	4	94.6 (83.0 to 99.9)	53.3 (10.5 to 93.2)	40.5 (3.0 to 78.0)	2.01 (0.66 to 6.15)

*Giorgi-Rossi, 2011 and Giorgi-Rossi, 2015 had two control groups (one in which a Pap smear was taken by a clinician and another in which a sample for hrHPV testing was taken by a clinician). Kellen et al, 2018 also had two control arms (one with and one without recall letters).
†Certain studies reported that some women, allocated to the self sampling, had a Pap smear taken by a clinician. The sum of the number of self samples taken and Pap smears taken, were counted in the intention-to-treat analyses. In studies, where no such cases were reported, the number of events in the per protocol and intention-to-treat analyses analyses were considered as equal.

The pooled participation rate was 7.8% (95% confidence interval 5.2% to 10.9%) when women had to request a self sampling kit (opt-in), 15.6% (12.4% to 19.5%) in one trial where women were invited through community campaigns, and 94.2% (80.2% to 100.0%) when community health workers delivered self sample kits directly to women's homes or workplaces (door-to-door). In the trials in which additional Pap tests were reported in the mail-to-all group (intention-to-treat analysis), the overall participation rate was slightly or substantially higher, ranging from 10.2% to 39.0%, with an average rate of 24.8% (21.6% to 28.1%). The pooled percentage of participating women, in the intention-to-treat analysis of the self sampling arm, was 17.7% (12.3% to 23.9%) in the opt-in scenario and 94.6% (83.0 to 99.9%) in the door-to-door scenario.

Participation in the control arm

Table 3 and supplementary figure 10 show that the average percentage of women who participated in the control arm was 11.5% (95% confidence interval 8.3% to 15.1%) in the mail-to-all scenario, 13.4% (10.2% to 16.9%) in the opt-in scenario, 6.0% (4.2% to 8.7%) in the community campaigns scenario, and 53.3% (10.5% to 93.2%) in the door-to-door scenario. By default, the participation rates in the control arm were the same in the intention-to-treat analysis. In two Italian studies,[104 117] there were groups of women who were offered hrHPV testing on clinician samples in the control arm. The participation was not significantly different when hrHPV testing was performed versus when cytology was performed (P=0.60 *v* P=0.76).[104 117] In the Belgian randomized clinical trial,[69] two control arms were included: one where the usual reminder letter was sent to non-responders and another one where no letter was sent to non-responders. In the first control arm (reminder letter) the response rate was 10.5% (95% confidence interval 9.9% to 11.2%), whereas in the second control arm (no letter), the response rate was slightly lower (8.0%, 95% confidence interval 7.5% to 8.6%).

Participation differences between self sampling and control arms

Table 3 and figure 2 show that in the per protocol analysis of the mail-to-all scenario, the pooled participation difference was 7.3% (95% confidence interval 4.1% to 10.6%, I^2=99%). The participation difference was nearly always positive except for two studies where the difference was significantly lower than zero. In the opt-in scenario, the pooled difference tended to be negative in several studies and was also lower than zero when trials were pooled (participation difference −5.1%, 95% confidence interval −10.0% to −0.2%). In the community campaign, the participation difference was 9.5% (95% confidence interval 5.4% to 13.7%), whereas in the door-to-door scenario the pooled difference was 39.7% (95% confidence interval 4.0% to 75.4%, range 11% to 64%, I^2=99.9%).

In the intention-to-treat analysis of the mail-to-all scenario, the pooled participation difference was 12.8% (95% confidence interval 10.4% to 15.1%, range 5% to 30%, I^2=97%), whereas in the opt-in scenario the difference was not significantly different from zero (participation difference 3.3%, 95% confidence interval −0.7% to 7.3%). For the other scenarios, the intention-to-treat analyses showed similar participation differences as in the per protocol analyses.

Relative participation in self sampling versus control arms

Table 3 and supplementary figure 11 show that, on average, the relative participation rate was 1.87 times (95% confidence interval 1.43 to 2.44) and 2.33 times (1.86 to 2.91) higher in the self sampling arm versus the control arm of the trials with a mail-to-all scenario, in the per protocol and intention-to-treat analyses, respectively. In the per protocol analysis of the trials with opt-in scenarios, the average relative participation was lower in the self sampling versus the control arm, although not significantly (0.73, 95% confidence interval 0.51 to 1.04), whereas on average in the intention-to-treat analysis, the pooled relative

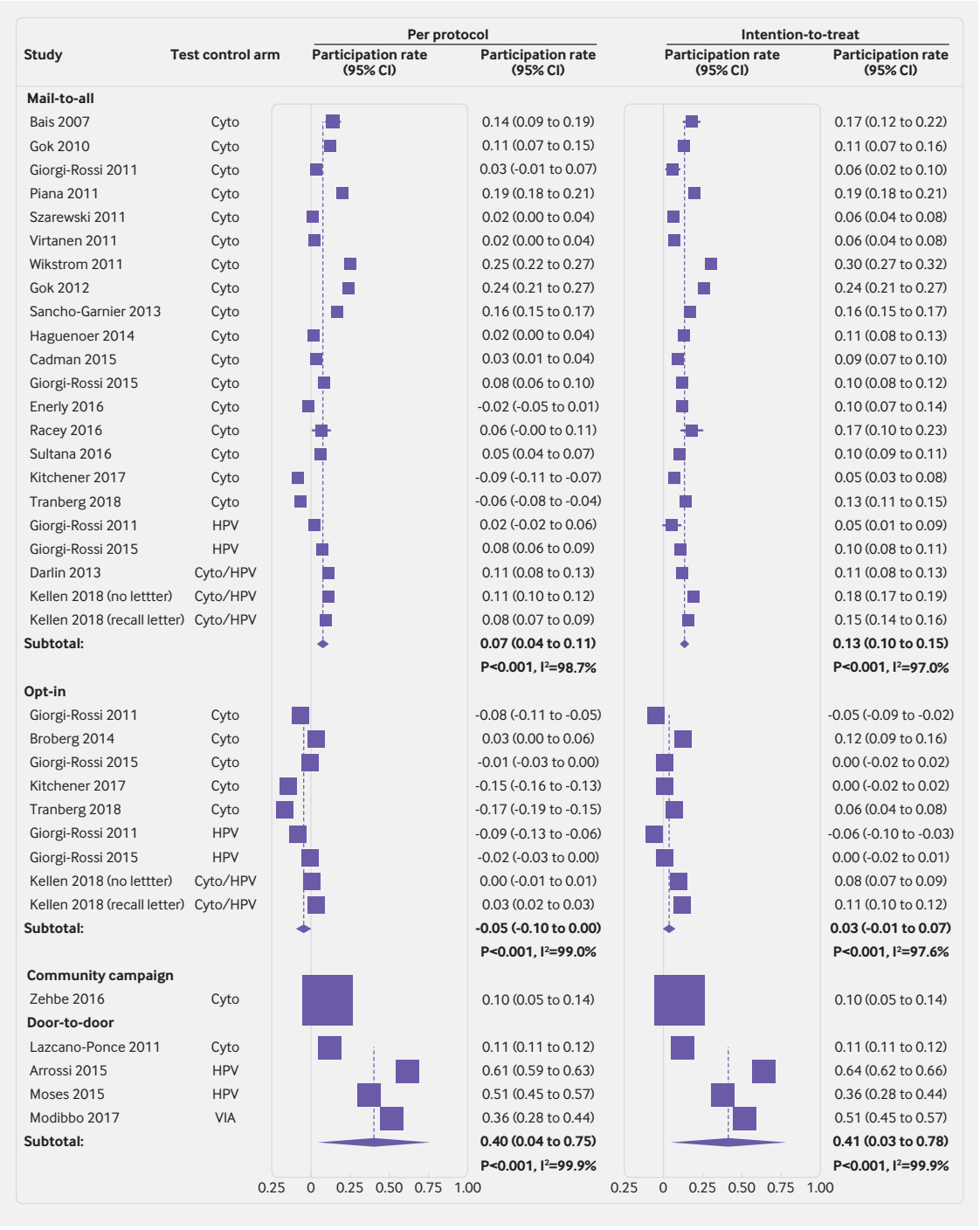

Fig 2 | Difference in participation rate between the self sampling and the control arms of randomized trials. Cyto=cytology; HPV=human papillomavirus; VIA=visual inspection after application of acetic acid

participation exceeded unity, although not significantly (1.22, 0.93 to 1.61). The relative participation was on average twice as high in the self sampling versus the control arms in the community campaign and door-to-door scenarios.

We found five studies that provided response rates in both trial arms stratified by categories defined on the screening history status.[26 65 103 113 114] Since the categorization was different throughout studies, subgroup meta-analysis or meta-regressions were not possible and, therefore, we analyzed participation rates and relative participation separately for the trials with stratified data (supplementary table 16).

We observed that participation rates decreased generally with length of time since last screening in both trial arms. The lowest rates were in women with no screening records except for one study.[65] However, the relative participation tended to increase with time since last screening, not taking the women with no screening records into account.

Table 4 | Absolute proportion in self sampling arm and contrasts between self sampling and control arms

Parameter	No of studies*	Absolute proportion self sampling % (95% CI)	No of studies†	Relative proportion (95% CI)	Proportion difference % (95% CI)
Unsatisfactory sample	16	0.7 (0.4 to 1.0)	NA	NA	NA
Test positivity‡	22	11.1 (9.8 to 12.4)	NA	NA	NA
Adherence to follow-up	20	80.6 (67.0 to 91.5)	10	0.91 (0.80 to 1.04)	−4.8 (−13.1 to 3.5)
CIN2+ detection per thousand invited §¶	18	2.6 (1.4 to 4.1)	14	2.28 (1.44 to 3.61)	1.6 (0.1 to 3.1)
CIN2+ detection per thousand screened**¶	18	9.8 (7.1 to 13.0)	14	1.13 (0.63 to 2.04)	2.9 (−1.7 to 7.5)

NA=Not available; CIN2+=cervical intraepithelial neoplasia grade 2 or worse.
*Reporting the parameter in both the self sampling and control arms.
†Reporting the parameter in the self sampling arm.
‡Of high-risk human papillomavirus (hrHPV) assay in the self sampling arm (per protocol).
§Depends on participation, adherence to follow-up, prevalence of disease among participants, and sensitivity of tests (screening and follow-up).
¶Restricted to data where a Pap smear was taken in the control arm.
**Depends on adherence to follow-up, prevalence of disease among participants and sensitivity of tests (screening and follow-up).

We did not find evidence of publication bias in the mail-to-all or opt-in scenarios for relative participation (supplementary table 17).

Sample adequacy, test positivity rate, adherence to follow-up, detection of CIN2+

Sixteen of the trials reported on the adequacy of self collected samples. Table 4 and supplementary figure 12 show that, on average, 0.7% of self samples (95% confidence interval 0.4% to 1.0%, range 0.0% to 2.7%, I^2=77.5%) were unsatisfactory for hrHPV testing.

The hrHPV test positivity varied between 6.0% and 29.4%. The hrHPV positivity rate, pooled from 22 trials, was 11.1% (95% confidence interval 9.8% to 12.4%, I^2=92.2%) (table 4 and supplementary fig 14).

In 20 trials in which adherence to follow-up among women with self samples that tested positive for hrHPV was reported, on average, 80.6% (95% confidence interval 67.0% to 91.5%, range 41% to 100%, I^2=98.7%) had a follow-up examination. The rate of adherence to follow-up varied by applied triage policy, with higher adherence in studies with direct referral compared with studies with a triage policy (supplementary fig 14). The adherence to follow-up was lower in women who tested positive for hrHPV in the self sampling arm versus women in the control arm, but the difference was not significant in 10 trials in which the follow-up adherence was reported in both arms (relative proportion of 0.91, 95% confidence interval 0.80 to 1.04; proportion difference of −4.8%, 95% confidence interval −13.1% to 3.5%).

The CIN2+ detection rate in the self sampling arm varied between 0 to 11 per 1000 invited women (supplementary fig 15). On average, the detection rate was 2.28 times (95% confidence interval 1.44 to 3.61, I^2=41.4%) higher in the self sampling arm versus the control arm. The detection rate ratio varied by triage policy, with a greater detection rate ratio (P=0.031) when women with a self sample that tested positive for hrHPV were directly referred to colposcopy (relative detection for the self sampling *v* control arm of 3.03 *v* 1.79; supplementary fig 16). The detection rate per 1000 screened women varied between 0 and 35. On average, the detection of CIN2+ per number of screened women was similar in the two trial arms (relative proportion 1.13, 95% confidence interval 0.63 to 2.04, range 0.05-4.31, I^2=64.8%; table 4 and supplementary fig 17). No detection rate heterogeneity by self sample triage strategy was observed.

Discussion

Our first meta-analysis, on test accuracy, showed that hrHPV testing with an hrHPV assay based on polymerase chain reaction is as sensitive for detection of CIN2+ and CIN3+ and slightly less specific on self samples compared with clinician samples. On the other hand, Hybrid Capture II and Cervista, two hrHPV assays based on signal amplification, have lower sensitivity to detect CIN2+ and CIN3+ and are less specific to exclude CIN2+ when applied to self samples. mRNA testing with APTIMA and hrHPV DNA testing with careHPV were less sensitive but as specific on self samples compared with clinician samples. No strong effects of self sampling devices or storage media could be shown. However, most studies compared accuracy of self samples with clinician samples using certain sampling devices or storage media. Differences could be assessed by subgroup meta-analyses. More comparative diagnostic studies are needed, comparing combinations of assays, sampling devices, and storage media to generate more robust data in order to develop more precise guidelines.[119]

Our first meta-analysis also confirmed that the estimates of the relative accuracy of hrHPV testing of self samples compared with clinician samples is a robust outcome that does not vary substantially across clinical setting. This finding justifies the choice of a colposcopy clinic as an appropriate research setting in which combinations of hrHPV tests, self sampling devices (including instruments to collect urine), and storage media can be evaluated.[119]

Comparison with other studies

Recent randomized trials have shown that cytology triage after hrHPV screening results in lower incidence of cancer.[18 20] Since reflex cytology triage is not recommended on self samples because of its poor accuracy,[21] an additional visit is needed to collect a cervical sample for cytological assessment. If follow-up to the cytology visit is poor, the overall gain in screening coverage could be partly compromised.

Therefore, we consider that finding a molecular test that permits reflex testing of samples that test positive for hrHPV should be a priority for future research. Hyper-methylation of certain viral or human genes involved in carcinogenesis has shown promising accuracy profiles and could be applied to self samples, but needs to be validated.[120 121] Recent studies have revealed that hrHPV testing is also feasible on urine.[122] Collection of urine could be easier for women who dislike vaginal collection. However, most studies document only virological outcomes.[123] Studies assessing the clinical accuracy of hrHPV testing on urine are urgently needed.[124]

The relative participation, the main effect size of participation trials, is determined by the response rate in the control arm. An absolute gain in participation (participation difference) will yield a larger relative effect when the participation in the control intervention is low. For instance, relative participation tended to be highest among women who were never screened or who were last screened five or more years ago (supplementary table 16).[103 113 114]

Mailing self sampling kits to women's home address is more effective in reaching populations that are underscreened compared with sending invitation or reminder letters for clinician sampling. The size of effect is highly variable among the included trials. Therefore, we recommend the set up of local trials to assess feasibility, effectiveness, and cost effectiveness before rolling out programs that include self sampling at regional or national levels.

The opt-in scenario, in which women request a self sampling kit, looks interesting from an economic and ecological point of view, but is not significantly more efficacious in generating responses in women who do not attend the regular screening program than routine invitations. Also, the results were very heterogeneous (P<0.001) for the opt-in scenario, warning against generalization. In two observational studies conducted in Sweden and Denmark, women who were underscreened had the option to request a self sampling kit. In the Swedish study, 63% of the invited women, who did not have a screening record in the previous six years, requested a kit and 39% took a self sample and sent it to the laboratory.[125] In the Copenhagen cohort, 32% of women, not screened in the previous four to six years, requested self sampling kits and 20% took a self sample and sent it to the laboratory.[126] These response rates correspond with the better rates observed in the mail-to-all randomized clinical trials. All randomized clinical trials conducted in less developed countries included home visits in the self sampling arm and noted excellent participation rates (>80%, fig 2). However, high participation was also noted in demonstration studies when women had to contact health centers to obtain or return the self sampling kit, as observed in rural Bhutan (average participation of 71%, with a negative trend by distance).[127]

The proportion of hrHPV tests applied on inadequate self samples in participation studies was low, showing that this sampling method is suitable for hrHPV testing. The adherence to follow-up among women with a self sample that tested positive for hrHPV was remarkably high (81% on average), probably owing to measures foreseen in the randomized clinical trials. It remains to be elucidated whether these high adherence rates observed in trials could be reproduced in routine screening programmes, in which resources to maximize follow-up are more limited.

Study limitations

A limitation, inherent among meta-analyses based on aggregated results extracted from published reports, is the lack of detailed data equally stratified according to potentially influencing factors related to the target population. A meta-regression, including only eight studies, did not reveal age effects. An Italian study showed a greater participation difference (self sampling arm minus the control arm of 11% to 12%) in urban than in rural areas (participation difference of 3%, with zero included in the confidence interval).[104] Certain studies observed a lower response to the offer of a self sampling kit in more socially deprived groups,[128] whereas others did not observe a social gradient.[65 114] Several trials reported lower response rates in the self sampling arm in women who were never screened than in women who had been screened,[26 114 126] whereas others observed an opposite trend.[65] Subgroup analyses and meta-regressions were not possible in the current systematic review because covariates were categorized differently. In order to evaluate the impact of influential factors more efficiently, we propose pooling individual patient data from the best trials.

Future research

Future research could explore whether primary care providers could contribute to raising screening coverage. Primary care providers could verify the screening status of their patients belonging to the target screening population and offer self sampling kits to those who have not been screened recently.[129 130] Primary care providers could be an effective alternative in settings where mailing sampling kits as part of an organized screening program is not feasible and door-to-door invitation is too costly. Self sampling could also become the new paradigm for primary cervical cancer screening in the general population as an alternative for the collection of a clinician sample.[131] This idea is currently being explored in the IMPROVE trial in the Netherlands.[132] A more detailed list of study proposals on self sampling is included in the research agenda in the supplementary materials.

Policy implications

For the first time, test accuracy of hrHPV screening and participation in programmes offering self sampling kits have been assessed in two joint reviews. This enabled simulating program sensitivity, determined as program participation multiplied by test sensitivity, as well as other parameters needed for cost effectiveness modeling. When adequate resources and infrastructure

are available, a hrHPV assay based on polymerase chain reaction test should be used to achieve optimal program sensitivity. When funds are limited, using a less expensive hrHPV assay based on signal amplification could still provide an overall gain in program sensitivity despite the loss in test sensitivity.

The highest participation rates in our systematic review were observed in studies that included door-to-door invitation scenarios conducted in Latin America or Africa. However, the direct offer of a self sampling kit by a health professional might also be an effective strategy to reach non-responders in countries with established screening programmes. Point-of-care hrHPV testing on self samples could also be appropriate in a context of providing preventive care to medically underserved communities.

Conclusions

hrHPV testing with an appropriate assay offers a promising new strategy that could increase population coverage substantially. Whereas accuracy of new combinations of assays and self sampling devices can be evaluated in a diagnostic setting, acceptance and participation should be shown locally in a screening setting before general roll out.

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Contributors: MA designed the study concept and protocol. MA and PC formulated the clinical questions and the definition of PICOS components. MA elaborated data extraction forms for the review update. MA, SBS, ST, and FS extracted data. MA conducted the statistical analysis. MA, SS, and PC wrote the manuscript. SBS, ST, FS, and PC conducted a critical revision of the manuscript. MA, SBS, and PC revised and approved the manuscript before submission. Members of the Collaboration on Self sampling and HPV Testing (MS, VS, DC, AW, JG, NW, CMZ, JJ, FARG, WKH, JSS, TCR, MHE, KMS, RAS, and MAG) provided feedback on the study protocol, performed and verified the initial part of study selection, and reviewed the manuscript. All authors had full access to the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis. MA is the guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Supplementary materials: Supplementary materials and supplementary figures 1-17 and tables 1-18