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Self-sampling to increase participation in cervical cancer screening: an RCT comparing home mailing, distribution in pharmacies, and recall letter

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Background: We performed a multicentre randomised controlled trial to evaluate the effect on participation in organised screening programmes of a self-sampling device mailed home or picked up at a pharmacy compared with the standard recall letter.

Methods: Women aged 30–64 non-responding to screening invitation were eligible. Response rate to first invitation ranged from 30% to 60% between centres. The control was the standard reminder letter to undergo the test used by the programme (Pap test in three centres and HPV DNA test in three other centres). Home mailing of the self-sampler was preceded by a letter with a leaflet about HPV. The analysis was intention-to-treat.

Results: In all, 14 041 women were randomised and recruited: 5012 in the control arm, 4516 to receive the self-sampler at home, and 4513 to pick up the self-sampler at a pharmacy. Participation was 11.9% in the control, 21.6% (relative participation: 1.75; 95% CI 1.60–1.93) in home, and 12.0% (relative participation: 0.96; 95% CI 0.86–1.07) in the pharmacy arms, respectively. The heterogeneity between centres was high (excess heterogeneity of that expected due to chance, i.e., I^2, 94.9% and 94.1% for home and pharmacy arm, respectively). The estimated impact on the overall coverage was +4.3% for home mail self-sampling compared with +2.2% for standard reminder.

Conclusions: Home mailing of self-sampler proved to be an effective way to increase participation in screening programmes, even in those with HPV as primary testing. Picking up at pharmacies showed effects varying from centre to centre.

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Cervical cancer has become quite rare in most western European countries (<10 cases per 100 000 women per year) (Arbyn *et al*, 2011). Cytological screening, in fact, has dramatically reduced cervical cancer incidence and mortality in most industrialised countries. With few exceptions (Blackwell *et al*, 2008), organised screening programmes have been more effective than spontaneous screening in reducing incidence (Quinn *et al*, 1999; Anttila 2007; Arbyn *et al*, 2009; Giorgi Rossi *et al*, 2014).

The lack of Pap test coverage is the main problem in cervical cancer prevention. Indeed, most tumours occur in women who have not participated in screening programmes or who have not yet been invited (Nieminen *et al*, 1999; Viikki *et al*, 1999; Sung *et al*, 2000; Leyden *et al*, 2005; Morrell *et al*, 2005; Ronco *et al*, 2005; Bos *et al*, 2006; Ingemann-Hansen *et al*, 2008; Lönnberg *et al*, 2010, 2012, 2013; Zucchetto *et al*, 2013). Increasing screening coverage is still a priority in all countries (IARC Working Group on the Evaluation of Cancer Preventive Strategies Cervix Cancer Screening, 2005; WHO, 2006).

The identification of oncogenic human papillomavirus as the necessary cause of cervical cancer opened a new era for cervical cancer screening, introducing HPV DNA detection as a screening test (IARC Working Group on the Evaluation of Cancer Preventive Strategies Cervix Cancer Screening, 2005). This test is more sensitive than conventional Pap test (Arbyn *et al*, 2012) and provides longer protection in negative women (Bulkmans *et al*, 2007; Naucler *et al*, 2007; Dillner *et al*, 2008; Ronco *et al*, 2010, 2014).

In cytology-based screening, the quality of cervical cell sampling is critical; smears must be taken by trained health personnel. Any attempt to simplify the sampling methods or to introduce self-sampling has thus far failed. In fact, cytology on self-collected specimens is not an accurate method to detect precancerous lesions (Garcia *et al*, 2003; Budge *et al*, 2005; Brink *et al*, 2006).

HPV DNA test on self-specimens, instead, is sufficiently accurate: many studies have demonstrated that HPV DNA test on self-samples has the same or better sensitivity but lower specificity than does cytology, albeit worse sensitivity and specificity than on clinically obtained samples (Arbyn *et al*, 2014). According to these premises, many authors have proposed using self-sampling to increase participation in screening programmes and to reduce the number of underscreened women (Snijders *et al*, 2013; Arbyn *et al*, 2014).

In Italy, various studies and pilot programmes using HPV DNA as a primary screening test began in 2007 (Confortini *et al*, 2010; Zorzi *et al*, 2013; Del Mistro *et al*, 2014). Many programmes are now shifting from Pap test every 3 years to HPV DNA test every 5 years (in women over age 30/35).

The aim of this study was to evaluate the effect on test compliance of introducing a self-sampling device either mailed home or picked up at a pharmacy as compared with a standard recall letter.

MATERIALS AND METHODS

Setting. The study was performed within organised screening programmes in six Italian Local Health Authorities: Bologna (Emilia-Romagna, Northern Italy), Roma G (including the eastern outskirts of Rome), Teramo (in Abruzzo Region, Southern Italy), Molise (a region in Southern Italy), Este-Monselice, and Pieve di Soligo (in Veneto region, Northern Italy). Recruitment (invitations) took place from September 2011 to February 2012. Recruitment in each centre lasted for a maximum of 6 working weeks. The public organised screening programmes in three of these areas (Bologna, Pieve di Soligo and Molise) actively invite all the resident female population aged 25–64 for a Pap test every 3 years. Pap tests are interpreted in the local pathology unit of each programme. In the others (Teramo, Roma G, Este-Monselice), HPV-based pilot projects are active. The target age at the time of the study was 25–64 years. The routine HPV tests for these programmes are performed in the reference laboratory of each programme: Istituto Oncologico Veneto in Padua for Este-Monselice, L'Aquila University for Teramo, Tivoli Hospital for Roma G. The protocol includes HPV as a primary test followed by cytology triage for those who are HPV positive. HPV-negative women, instead, are invited to re-screening after 3 years (the recommendation to increase interval to 5 years was published in 2012 and acknowledged by the Ministry of Health in 2013). HPV-positive women with ASC-US or more severe cytology are referred to immediate colposcopy; HPV-positive cytology-negative women are referred to repeat HPV after 1 year. Women with persistent HPV positivity are referred to colposcopy: negatives are rescreened after 3 years.

Participation to first invitation was about 23% in Molise, 25% in Roma G, 33% in Bologna, 44% in Este, 46% in Teramo, and 58% in Pieve di Soligo.

Study population. Women aged 30–64 years who had been invited by the screening programme in the previous months and had failed to respond were eligible for mail recall. Each programme has a different timing for sending recall letters: in Bologna, recalls are sent to all non-responding women once invitations for a whole district have been completed, that is, between 1 and 5 months after the first invitation. In Molise, there usually are no reminders; for the trial, however, recall letters were scheduled for non-responders as per the Bologna scheduling. In all the other centres, recalls are automatically mailed to non-responders 3 months after the first invitation.

All screening tests, ascertainment, and treatment are performed within the screening programme and are completely free of charge.

Study design. Random samples of eligible women were randomly assigned to one of the following arms:

Control:

- Standard invitation letter to perform either a Pap test or an HPV test at the clinic according to that centre's routine screening.

Two intervention arms:

- One group received the self-sampler by mail directly at home, preceded by an explanatory letter 1 week before.
- The other group was offered the opportunity to pick the self-sampling device up at an area pharmacy.

See Table A1 in the appendix for details regarding participating pharmacies and clinics.

For centres adopting Pap test in routine screening, it was initially decided to have a second control arm with HPV test with standard sampling at the clinic to detect any effect of the invitation for a new test and the effect of sampling modalities. Unfortunately, due to organisational problems, it was impossible to perform HPV test on samples collected at the clinics in Molise and in Pieve di Soligo; this arm was randomised only in Bologna (Figure 1).

The lists of eligible women were provided by the centres. Random sampling and arm assignment were performed centrally by the coordinating centre (Teramo) using STATA 8.2 (StataCorp, College Station, TX, USA) with the seed for random number generator being the first number drawn by the most recent National Lottery: three (four for Bologna) consecutive samples of the predetermined size of independent statistical units were drawn and assigned to the corresponding arm. The planned sample size was 500 women per arm per centre. This would allow 80% power to detect, with a 95% confidence interval, a 7% increase

in compliance, in the hypothesis of 15% compliance in the control arm.

Description of the intervention. In the control arm, the intervention was only the recall letter for a Pap smear (Bologna, Pieve di Soligo, Molise) or an HPV test (Bologna, Roma G, Este-Monselice, Teramo) at the clinic on a scheduled date. In the arm with the home mailing of the self-sampler, a letter was sent beforehand explaining that the local Public Screening Programme would provide participants with a box containing a self-sampler completely free of charge. After 1 week, a box containing the following items was sent:

- a presentation letter;
- a leaflet about HPV test and cervical cancer prevention;
- the informed consent form to perform the test and to be contacted by phone in the event of positivity;
- the self-sampler, a second-generation lavage system, Delphi Screener, by Delphi Bioscience, Scherpenzeel, The Netherlands by Delphy (Brink *et al*, 2006);
- the instructions for use;
- a test tube and a pre-paid envelope to mail the sample;
- a short questionnaire.

In third arm, a letter was sent offering the women the opportunity to pick the self-sampler up at a designated pharmacy in the area. Table A1 in the appendix reports the number of the pharmacies and of the clinics for control arm sampling in study areas. The letter was accompanied by the leaflet about HPV test and cervical cancer prevention.

Questionnaires included questions on: the date of last Pap test, reason for non-compliance with the screening programme, questions about the self-sampling performance (pain, embarrassment, feasibility), what was most appreciated about self-sampling (doing it by oneself, privacy, absence of a doctor, absence of speculum), which kind of sampling was preferred (i.e., self-performed or carried out at the clinic).

Management of HPV-positive women. All women who were HPV positive were contacted by phone and letter to propose counselling on HPV and cervical cancer risk. Three centres (Teramo, Roma G, and Molise) proposed cytology triage, followed by colposcopy for women ASC-US or more severe and 1-year HPV check up for those with normal cytology. The other three centres (Este-Monselice, Pieve di Soligo, and Bologna) proposed immediate colposcopy and cytology. The protocol following colposcopy referral was the same as that for the HPV-based pilot programmes: colposcopy-guided biopsies are performed on all abnormal colposcopies, with only CIN2 or more severe lesions referred to treatment. Follow-up after colposcopies negative for CIN2+ (i.e., no biopsy, or negative/CIN1 biopsy result) depended on cytology results: 1-year HPV/cytology check up for negative, borderline, or low grade, and 3/6-month colposcopy for high-grade cytology. Cytologies collected during colposcopies were always on liquid-based samples.

In the control arm of those centres using HPV as routine screening, cytology triage was always performed. Cytology was collected before HPV sampling for all women and stained only if the HPV was positive in Roma G and Este. In Teramo, both HPV and cytology were performed on a liquid-based cytology.

In the control arm of those centres using Pap test as routine screening, women were referred to colposcopy if ASC-US or more severe. All the centres adopted conventional cytology. Colposcopy and post-colposcopy follow-up was the same as for HPV-based screening.

Outcomes. The main outcome of the study was women's participation in screening. All women who accepted to perform a test within 3 months from the recruitment were considered as a success. The date of recruitment was the mailing of the recall letter for control arms and pharmacy arm, and the mailing of the explanatory letter for the at-home arm. Only tests performed in the screening programme were considered.

The secondary outcomes, computed only within the experimental arm, were HPV positivity rate, referral rate, and compliance

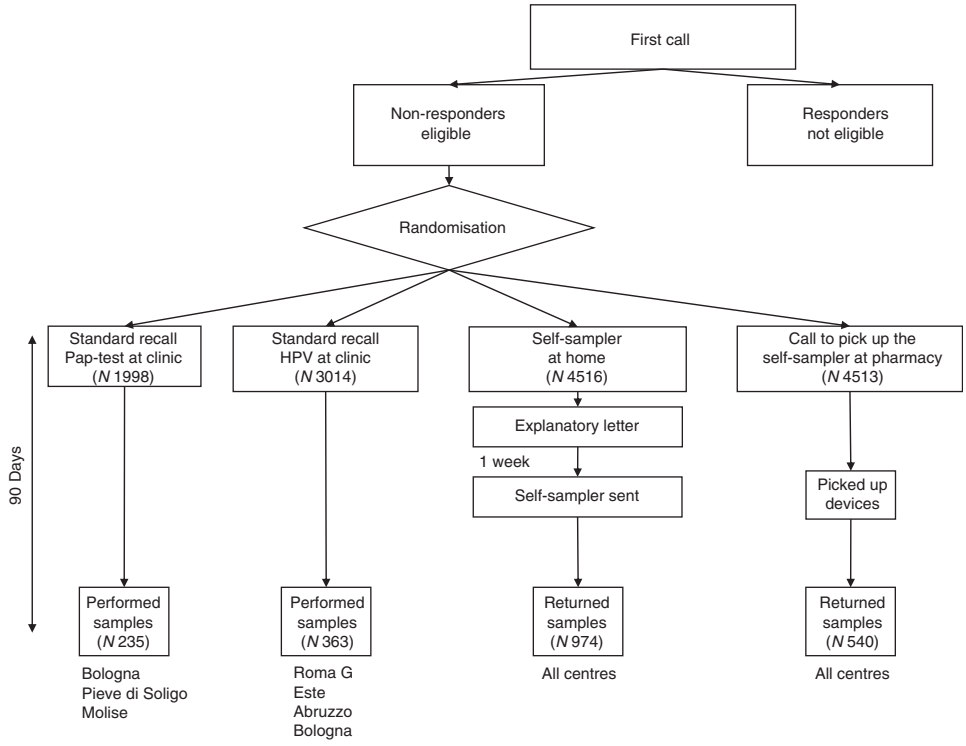

Figure 1. Study flowchart.

to cytology triage and colposcopy (immediate and after 1-year follow-up). Women were considered as lost to follow-up if they did not undergo at least a satisfactory colposcopy and an HPV-negative test was not obtained. All women were followed up for 15 months after the mailing of invitation.

The trial results were used, together with questionnaire answers on last Pap test, to compare the impact of the different strategies on total test coverage in terms of proportion of never or underscreened women (last test performed more than 3 years earlier) who were finally screened.

Laboratory methods. Samples pre-treatment: when self-collected samples arrived at the laboratory, the content was visually examined and empty samples were considered as inadequate. Those containing sampling medium were centrifuged at 500 *g* for 10 min. Supernatants were discarded and pellets suspended in 1 ml of STM (Specimen Transport Medium; Qiagen, Hilden, Germany). Before performing HPV test, 200 μl aliquots were stored at $-20\,^{\circ}$C. High-risk (HR) HPV was performed by HC2 (Qiagen), using only the B probe mix, which is specific for 12 HR HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59) and one probably carcinogenic HPV type (68) (Bouvard *et al*, 2009). According to the manufacturer's instructions, 400 μl of denaturation reagent was added to the remaining 800 μl of STM. The recommended positivity threshold of 1 pg ml^{-1} (equivalent to 5000 viral copies per test well) was used as a cutoff control value, and all samples with an RLU/Control ratio of $\geqslant 1.00$ were considered as HR-HPV positive. The HPV tests on the self-sampled specimens were performed in the following laboratories: Istituto Oncologico Veneto in Padua for Este-Monselice and Pieve di Soligo, L'Aquila University for Teramo and Molise, Tivoli Hospital for Roma G, Pathology Department of S. Orsola Hospital in Bologna for Bologna.

Analysis. For the primary end point, that is, participation, we adopted an intention-to-treat analysis: women providing any kind of sample (Pap smear, HPV at the clinic, or self-collected liquid sample) in any setting (home or screening clinic) were considered as a successful result of the strategy to which they had been randomised.

We report the relative participation (RP) (i.e., the relative risk) of having a test, comparing each intervention arm with the controls, with relative confidence intervals. Relative participation is also reported stratified by 10-year age groups. A linear trend of the interaction between intervention and age was tested using logistic model introducing the interaction component. We decided that, should there be no difference between the two control arms in Bologna ($P>0.2$), they would be pooled. We decided not to account for randomisation of couples living in the same household as a single statistical unit in the analysis owing to the extremely low number of these couples. Participating centres' samples were pooled if there was no heterogeneity. We used the information collected from the questionnaires to calculate the impact on population coverage of each strategy according to the following formula:

((underscreened respondents)/(total randomised sample)) $\times$ (proportion of non-responders at first invitation) $\times$ 100.

The result is the additional coverage, expressed as percentage points, that can be obtained by self-sampling or by standard letter. It should be added to the total coverage as estimated by the routine survey on health status and health service utilisation (PASSI).

Ethics. The study was approved by all the local Ethical Committees.

RESULTS

A total of 14 041 women were recruited and randomised: 5012 in the control arm inviting women to the clinic (1998 for a Pap and 3014 for HPV); 4516 to receive the self-sampler at home; 4513 to pick up the sampler at the pharmacy (Table 1 and, for details, see Appendix Tables A2, A3, and A4). All randomised women are included in the primary outcome measure, that is, participation.

One centre had both cytology and HPV clinic control; we tested for heterogeneity in this centre and found no difference in the participation rate ($P=0.9$). According to the planned analyses, we present all the comparisons for participation as comparison between the control (any invitation to undergo a test at the clinic regardless of the kind of test (Pap or HPV test)) and one of the two interventions, self-sampling mailed at home or picked up at the pharmacy.

The overall participation rate was higher when the sampler was mailed, compared with control (RP 2.01, 95% CI 1.3–3.1): out of 974 responders in this arm, 90 (9.2%) actually went to the clinic and did not use the self-sampler. The proposal to pick the self-sampler up at the pharmacy had an overall participation similar to that of the control (RP 1.01, 95%CI 0.62–1.66): in this arm, 65 out of 540 (12.0%) presented at the clinic and did not pick the sampler up at the pharmacy. The response rate in the control arm was stable with age (Table 2), while for both intervention arms the response was higher in younger women (χ^2 for linear trend of the RP, $P=0.014$ and $P=0.24$ for self-sampling at home and pick up at pharmacies, respectively).

The compliance in the control arm varied from 3.5% to 22.9% among the centres. The efficacy of self-sampler in increasing participation also varied among centres. The heterogeneity was high for both the interventions, but in the case of the mailed self-sampler, five out of six centres achieved a significantly higher participation and only one observed no effect (Figure 2A). In the pharmacy arm, three centres obtained lower participation in the

Table 1. Results of participation, by arm, centre, and mode of participation

	Pap test at clinic			HPV at clinic			Self-sampling at home				Self-sampling pharmacy			
	Invited	Participants		Invited	Participants		Invited	Participants			Invited	Participants		
								Self-sampling	Clinic			Self-sampling	Clinic	
	N	*N*	%	*N*	*N*	%	*N*	*N*	*N*	%	*N*	*N*	*N*	%
Abruzzo				1000	220	22.0	1000	139	76	21.5	1000	106	52	15.8
Roma G				1015	36	3.5	1015	178	0	17.5	1016	135	0	13.3
Este				499	64	12.8	500	164	4	33.6	500	79	0	15.8
Pieve di Soligo	498	114	22.9				501	154	10	32.7	497	57	13	14.1
Molise	1000	77	7.7				1000	176	0	17.6	1000	75	0	7.5
Bologna	500	44	8.8	500	43	8.6	500	73	0	14.6	500	23	0	4.6
Total	1998	235	11.8	3014	363	12.0	4516	884	90	21.6	4513	475	65	12.0

Table 2. Results of participation, by arm and age group

	Test at clinic			Self-sampling at home			Self-sampling pharmacy						
	Invited	Participants		Invited	Participants		Invited	Participants		Self-sampling at home		Self-sampling pharmacy	
	N	*N*	%	*N*	*N*	%	*N*	*N*	%	RR	CI (95%)	RR	CI (95%)
<39	1112	134	12.1	1029	271	26.3	964	129	13.4	2.19	1.77–2.71	1.11	0.87–1.42
40–49	1762	222	12.6	1590	345	21.7	1681	221	13.1	1.72	1.45–2.05	1.04	0.86–1.26
50–59	1548	189	12.2	1403	285	20.3	1347	144	10.7	1.66	1.38–2.01	0.88	0.70–1.10
60+	590	53	9.0	494	73	14.8	521	46	8.8	1.64	1.14–2.39	0.98	0.65–1.49
Total	5012	598	11.9	4516	974	21.6	4513	540	12.0	1.82	1.63–2.00	1.01	0.90–1.13

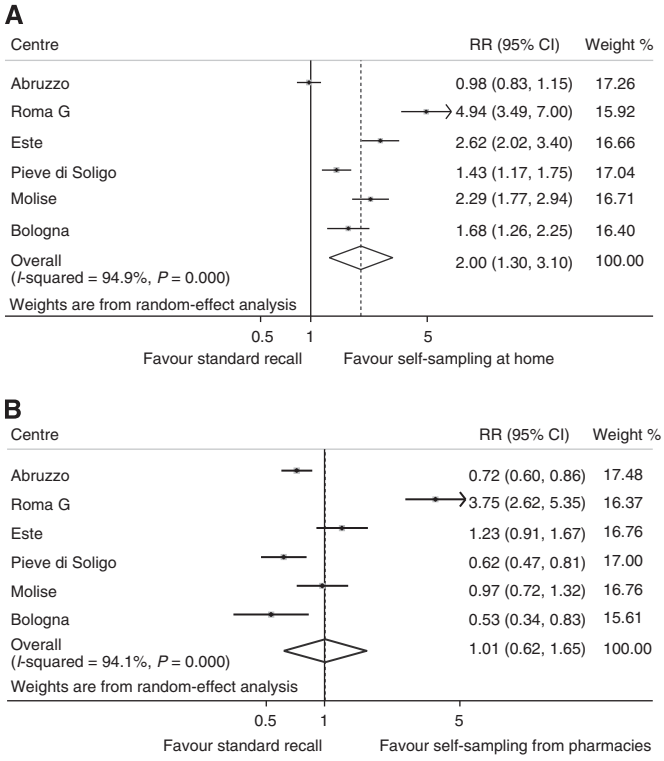

Figure 2. Results: (**A**) self-samplers mailed home; (**B**) self-sampler from pharmacy, random effects.

intervention (all significant), two obtained an increase (one significant), and one observed no effect (Figure 2B).

Impact on coverage. For two centres (Este-Monselice and Roma G), information was available for both the control and experimental arms on when the women had a previous Pap test and whether it had been performed within the screening programme or by a private provider. Thirty-four percent of the women who responded in the control arm and 29% of those in the mailed self-sampler arm had a Pap test more than 4 years before. This figure corresponds to a screening test coverage impact on population of +2.2% (((0.34(proportion under-screened among respondents after recall letter) × 0.10(total responders to recall)) × 0.65(non-responders to first invitation)) × 100) for the standard recall letter and of +4.3% for the self-sampler (((0.29(proportion under-screened among respondents after mailing self-sampler) × 0.23(total responders to recall)) × 0.65 (non-responders to first invitation)) × 100).

Test positivity and compliance to protocols. We obtained a total of 1359 self-collected samples for HPV testing (Table 3), 10 of which were not suitable for testing (the tube had not been correctly closed and the liquid had leaked out). Of the remaining 1349, 168 (12.4%) resulted positive, with no heterogeneity between centres ($P = 0.9$). About one-third (53) of the women had an incomplete follow-up, that is, was HPV and/or cytology positive without a colposcopy within the screening programme. The proportion of women lost to follow-up was 30% in centres offering direct referral to colposcopy and 36% in those adopting cytology triage. The biopsy rate in colposcopies was 34% in HPV-positive women. In the control arm, lost to follow-up was 25% (8 out of 32) and biopsy rate was 53% (8 out of 15).

The overall detection rate was 2 (1 CIN3 and 1 CIN2) out of 1359 self-collected samples, 1 CIN2 out of 363 clinical samples for HPV, and 2 (1 CIN3 and 1 CIN2) out of 235 Pap tests.

DISCUSSION

Our results further confirm the efficacy of offering self-sampling devices in increasing participation in cervical cancer screening, particularly of younger women. Differences between different contexts and countries have been reported in the published literature and have been confirmed in our multicentre study. Nevertheless, the self-sampling device obtained a higher participation than the standard recall letter almost everywhere, when the former was mailed directly to the home of women who did not respond to screening programme invitation (Giorgi Rossi *et al*, 2011b; Szarewski *et al*, 2011; Virtanen *et al*, 2011a, b; Wikström *et al*, 2011; Gök *et al*, 2010, 2012; Piana *et al*, 2011; Sancho-Garnier *et al*, 2013; Darlin *et al*, 2013. For a systematic review, see Camilloni *et al*, 2013 and Racey *et al*, 2013). Some of the previous trials analysed the response rate by age, finding no relevant differences (Gök *et al*, 2010, 2012; Szarewski *et al*, 2011; Virtanen *et al*, 2011a,b; Wikström *et al*, 2011). Only Sancho-Garnier *et al* (2013) described age as an effect modifier of the self-sampler on participation: the participation rate in the arm randomised to undergo Pap test at the clinic increased with age compared to essentially stable participation in the self-sampling arm. It is worth noting that the only centre where we did not find any advantage was Teramo (Abruzzo), the same centre that had a negative result in the first Italian Trial (Giorgi Rossi *et al*, 2011b). The heterogeneity among centres in our trial is of the same magnitude as that observed between studies in different countries, suggesting that there are strong effect modifiers not only at the cultural and social levels, since some of the centres in our studies have very similar sociocultural background, but also at other levels, probably linked to the logistic and organisation of clinics.

Our study is the first trial to test the use of pharmacies as sampler providers. This strategy has been adopted previously for FOBT (faecal occult blood test) in colorectal cancer screening programmes (Pippa *et al*, 2009; Giorgi Rossi *et al*, 2011a), but very few studies have formally tested its effectiveness in terms of participation. This strategy has the advantage that devices mailed

Table 3. Cytology and histology results in the experimental and control arm, by centre and type of test

			Cytology			Colposcopy			
Centre	Samples[a]	HPV positive	Present	ASC-US +	Unsatisfactory	Present	Biopsy	CIN2 +	Incomplete follow-up
Experimental arms (only self sampled)									
Abruzzo	245	35	29	8	4	27	9	1	12
Roma G	313	37	34	7	2	30	4	0	7
Este	243	26	18	2	0	12	3	0	8
Pieve di Soligo	211	34	30	8	2	16	13	1	13
Molise	251	26	24	10	1	9	2	0	10
Bologna	96	10	7	0	1	7	3	0	3
Total	1359	168	142	35	10	101	34	2	53
Control arm									
HPV									
Bologna	43	5	5	3	0	5	2	0	3
Este	64	8	8	2	0	1	1	0	1
Roma G	36	0	0	0	0	0	0	0	0
Abruzzo	220	14	14	7	1	7	3	1	2
Total	363	27	27	12	1	13	6	1	6
Pap-test									
Bologna	44		44	1	0	0	0	0	1
Pieve di Soligo	114		114	3	7	2	2	2	0
Molise	77		77	1	12	0	0	0	1
Total	235		235	5	19	2	2	2	2

[a]10 samples were unsuitable for HPV testing.

to women who will not respond are not wasted. In the case of self-sampling for HPV testing, this is a critical point since the devices are still quite expensive. Overall, the strategy did not work well and participation was similar to that obtained with standard recall letter. In women below 39 years of age, we observed a modest, non-significant increase in participation, counterbalanced by lower participation compared with standard recall letter in older women. We also observed a wide heterogeneity between centres for this intervention. Indeed, the difference is more relevant than the heterogeneity observed for home-mailed self-sampler. In fact, we observed that in many centres, pharmacy supply did not work at all, while in two centres, it had a positive effect. The differences are probably logistical in nature, in particular in terms of how the participating pharmacies were distributed throughout the territory and how the sampling clinics were organised. In particular, Roma G uses mobile clinics for sampling. These campers stay in a village or small town for a certain period of time and then move on to another. Women not responding to the first invitation are often recalled when the mobile clinic is no longer in the village and thus have to go to the district hospital to do the Pap test. Such a strategy obviously obtains very low participation to standard recall and increases the advantage of experimental strategies.

The HPV positivity rate in the self-sampling responders was 12%, about two times the prevalence observed with clinical samples in respondent women in the same age group, that is, 6% (Confortini *et al*, 2010; Ronco *et al*, 2010; Giorgi Rossi *et al*, 2012; Zorzi *et al*, 2013). In previous studies a higher prevalence in non-responders was also observed (Gök *et al*, 2010, 2012). On the other hand, a lower specificity of self-sampling compared with clinic sampling has been observed, particularly for HCII and for lavage self-sampling systems (Arbyn *et al*, 2014). In the Italian pilot projects, the specificity of HCII for CIN2 + was $\geqslant$94% (Confortini *et al*, 2010; Zorzi *et al*, 2013). The relative specificity of self-sampling to clinician sampling estimated by a large meta-analysis was 0.96 (Arbyn *et al*, 2014). Applying this estimate to the observed prevalence in the Italian pilot projects, the expected positivity rate with self-sampling in the Italian population was 10%.

The main limit in the effectiveness of self-sampling that we found in this study was the low compliance to follow-up: about one-third of the women had an incomplete follow-up and the proportion was only slightly lower when a direct referral to colposcopy was adopted. In the previous Italian trial, which had a smaller target population, we observed high compliance to colposcopy. Perhaps the larger sample, reproducing a routine-like situation, accounts for this difference. In the literature, compliance to follow-up ranged from 97% in the most recent Dutch trial (Bosgraaf *et al*, 2015), conducted in an organised screening programme with a strong central management of the ascertainments, to 41% in the French trial, conducted in a programme where follow-up was not directly managed by the screening coordinating centre but was in charge of the woman's referring physician (Piana *et al*, 2011; Sancho-Garnier *et al*, 2013).

Closely linked to the low compliance to follow-up procedures was the low CIN2 + detection rate in women tested with self-sampling, less than 2/1000, which should be compared with the 3/1000 observed in the same centres when HPV was used as a primary screening (Confortini *et al*, 2010; Zorzi *et al*, 2013). Furthermore, we also observed a low positive predictive value of colposcopy referral, both in the centres with direct referral to colposcopy and in those with cytology triage, together with a low biopsy rate in women referred to colposcopy for HPV positivity only. Our sample size does not permit a comparison of the risk of CIN2 + in non-responders with that in responders, but the low detection rate, even taking into account the low compliance to colposcopy, suggests that non-responders are not at a higher risk than are responders. This finding is not consistent with many previous studies (Gök *et al*, 2010, 2012) that found higher prevalence of high-grade lesions in non-responders, when self-sampling was offered, but is consistent with the only previous Italian study, where no CIN2 + was found out of 139 self-sampling tested and 28 HPV-positive women (26 with colposcopy) (Giorgi Rossi *et al*, 2011b).

Finally, we evaluated the impact on Pap test coverage. The majority of women responding to self-sampling were already covered and only 30% of them were underscreened or never-screened. This proportion is similar to that observed in women who responded to the standard recall letter. This finding further suggests that ours is not a population with a markedly higher risk than that of responders. Applying the proportion of never- or underscreened women among those responding during the trial to the whole population of the non-responders, we can estimate an

impact on the overall coverage of +4.3% for self-sampling compared with +2.2% for standard recall letter. According to the routine survey on screening coverage (Bertozzi *et al*, 2013), the estimates for self-sampling impact correspond to an increase from 85% to about 90% in Este, and from 75% to 80% in Roma G.

CONCLUSIONS

Self-sampling proved to be an effective way to increase participation in cervical cancer screening and screening coverage when mailed directly to the homes of women who did not respond to screening invitation, in both Pap test- and HPV-based programmes. The effect is stronger for younger women.

As for using pharmacies as self-sampler providers, a strategy that could be more efficient in terms of the number of devices needed to screen never- or underscreened women, only one centre achieved success.

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REFERENCES

Anttila A (2007) Cervical cancer screening is effective - the Finnish experience. *Entre Nous (WHO Regional Office, Copenhagen)* **64**: 26–28.

Arbyn M, Castellsagué X, de Sanjosé S, Bruni L, Saraiya M, Bray F, Ferlay J (2011) Worldwide burden of cervical cancer in 2008. *Ann Oncol* **22**: 2675–2686.

Arbyn M, Rebolj M, de Kok IM, Becker N, O'Reilly M, Andrae B (2009) The challenges for organising cervical screening programmes in the 15 old member states of the European Union. *Eur J Cancer* **45**: 2671–2678.

Arbyn M, Ronco G, Anttila A, CJLM Meijer, Poljak M, Ogilvie G, Koliopoulos G, Naucler P, Sankaranarayanan R, Peto J (2012) Evidence regarding HPV testing in secondary prevention of cervical cancer. *Vaccine* **30**(Suppl 5): F88–F99.

Arbyn M, Verdoodt F, Snijders PJ, Verhoef VM, Suonio E, Dillner L, Minozzi S, Bellisario C, Banzi R, Zhao FH, Hillemanns P, Anttila A (2014) Accuracy of human papillomavirus testing on self-collected versus clinician-collected samples: a meta-analysis. *Lancet Oncol* **15**: 172–183.

Bertozzi N, Carrozzi G, Sampaolo L, Bolognesi L, Finarelli AC, Angelini P, Mignai R, Sacchi AR, Nieddu A, Bulla C, Ferrari AM, Pandolfi P, Perlangeli V, Collina N, De Lisio S, Blundo G, Stefanelli I, De Togni A, Silvi G, Raineri C, Mingozzi O, Sardonini L, Vitali P, Morri M (2013) I dati della sorveglianza PASSI sulla diagnosi precoce dei tumori del collo dell'utero: confronto fra Emilia-Romagna e Italia (2010-11). *In I programmi di screening oncologici. Regione Emilia-Romagna Collana Contributi* **74**: 84–89.

Blackwell DL, Martinez ME, Gentleman JF (2008) Women's Compliance with Public Health Guidelines for Mammograms and Pap tests in Canada and the United States: an analysis of data from the Joint Canada/United States Survey of Health. *Women's Health Issues* **18**: 85–99.

Bos AB, Rebolj M, Habbema JD, van Ballegooijen M (2006) Nonattendance is still the main limitation for the effectiveness of screening for cervical cancer in the Netherlands. *Int J Cancer* **119**: 2372–2375.

Bosgraaf RP, Verhoef VM, Massuger LF, Siebers AG, Bulten J, de Kuyper-de Ridder GM, Meijer CJ, Snijders PJ, Heideman DA, IntHout J, van Kemenade FJ, Melchers WJ, Bekkers RL (2015) Comparative performance of novel self-sampling methods in detecting high-risk human papillomavirus in 30,130 women not attending cervical screening. *Int J Cancer* **136**: 646–655.

Bouvard V, Baan R, Straif K, El Ghissassi F, Benbrahim-Tallaa L, Guha N, Freeman C, Galichet L, Gogliano V. on behalf of the WHO IARC in Cancer Monograph working group (2009) A review of human carcinogens—part B: biological agents. *Lancet Oncol* **10**: 321–322.

Brink AA, Meijer CJ, Wiegerinck MA, Nieboer TE, Kruitwagen RF, van Kemenade F, Frasen Daalmeijer N, Hesselink AT, Berkhof J, Snijders PJ (2006) High concordance of results of testing for human papillomavirus in cervicovaginal samples collected by two methods, with comparison of a novel selfsampling device to a conventional endocervical brush. *J Clin Microbiol* **44**: 2518–2523.

Budge M, Halford J, Haran M, Mein J, Wright G (2005) Comparison of a self-administered tampon ThinPrep test with conventional pap smears for cervical cytology. *Aust N Z J Obstet Gynaecol* **45**: 215–219.

Bulkmans NW, Berkhof J, Rozendaal L, van Kemenade FJ, Boeke AJ, Bulk S, Voorhorst FJ, Verheijen RH, van Groningen K, Boon ME, Ruitinga W, van Ballegooijen M, Snijders PJ, Meijer CJ (2007) Human papillomavirus DNA testing for the detection of cervical intraepithelial neoplasia grade 3 and cancer: 5-year follow-up of a randomised controlled implementation trial. *Lancet* **370**: 1764–1772.

Camilloni L, Ferroni E, Cendales BJ, Pezzarossi A, Furnari G, Borgia P, Guasticchi G, Giorgi Rossi P. Methods to increase participation Working Group (2013) Methods to increase participation in organised screening programs: a systematic review. *BMC Public Health* **13**: 464.

Confortini M, Giorgi Rossi P, Barbarino P, Passarelli AM, Orzella L, Tufi MC (2010) Screening for cervical cancer with the human papillomavirus test in an area of central Italy with no previous active cytological screening programme. *J Med Screen* **17**: 79–86.

Darlin L, Borgfeldt C, Forslund O, Hénic E, Hortlund M, Dillner J, Kannisto P (2013) Comparison of use of vaginalHPVself-sampling and offering flexible appointments as strategies to reach long-term non-attending women in organized cervical screening. *J Clin Virol* **58**(1): 155–160.

Del Mistro A, Frayle H, Ferro A, Callegaro S, Del Sole A, Stomeo A, Cirillo E, Fedato C, Pagni S, Barzon L, Zorzi M. Veneto HPV-screening Working Group (2014) Cervical cancer screening by high risk HPV testing in routine practice: results at one year recall of high risk HPV-positive and cytology-negative women. *J Med Screen* **21**: 30–37.

Dillner J, Rebolj M, Birembaut P, Petry KU, Szarewski A, Munk C, de Sanjose S, Naucler P, Lloveras B, Kjaer S, Cuzick J, van Ballegooijen M, Clavel C, Iftner T. Joint European Cohort Study (2008) Long term predictive values of cytology and human papillomavirus testing in cervical cancer screening: joint European cohort study. *BMJ* **13**(337): a1754.

Garcia F, Barker B, Santos C, Brown EM, Nuño T, Giuliano A, Davis J (2003) Cross-sectional study of patient- and physician-collected cervical cytology and human papillomavirus. *Obstet Gynecol* **102**: 266–272.

Giorgi Rossi P, Caroli S, Mancini S, Sassoli De' Bianchi P, Finarelli AC, Naldoni C, Bucchi L, Falcini F. the Emilia-Romagna cervical cancer screening and pathology registry group (2014) Screening history of cervical cancers in Emilia-Romagna, Italy: defining priorities to improve cervical cancer screening. *Eur J Cancer Prev*. published online on 2014 April 30. PubMed PMID: 24787379.

Giorgi Rossi P, Chini F, Borgia P, Guasticchi G, Carozzi FM, Confortini M, Angeloni C, Buzzoni C, Buonauguro FM; Gruppo di lavoro HPV Prevalenza (2012) Human Papilloma Virus (HPV), cervical cancer incidence and screening uptake: differences among Northern, Central and Southern Italy. *Epidemiol Prev* **36**(2): 108–119.

Giorgi Rossi P, Grazzini G, Anti M, Baiocchi D, Barca A, Bellardini P, Brezzi S, Camilloni L, Falini P, Maccallini V, Mantellini P, Romeo D, Rubeca T, Venditti MA (2011a) Direct mailing of faecal occult blood tests for colorectal cancer screening: a randomized population study from Central Italy. *J Med Screen* **18**: 121–127.

Giorgi Rossi P, Marsili LM, Camilloni L, Iossa A, Lattanzi A, Sani C, Di Pierro C, Grazzini G, Angeloni C, Capparucci P, Pellegrini A, Schiboni ML, Sperati A, Confortini M, Bellanova C, D'Addetta A, Mania E, Visioli CB, Sereno E, Carozzi F. Self-Sampling Study Working Group (2011b) The effect of self-sampled HPV testing on participation to cervical cancer screening in Italy: a randomised controlled trial (ISRCTN96071600). *Br J Cancer* **104**: 248–254.

Gök M, Heideman DA, van Kemenade FJ, Berkhof J, Rozendaal L, Spruyt JW, Voorhorst F, Beliën JA, Babovic M, Snijders PJ, Meijer CJ (2010) HPV testing on self collected cervicovaginal lavage specimens as screening method for women who do not attend cervical screening: cohort study. *BMJ* **340**: c1040.

Gök M, Heideman DA, van Kemenade FJ, de Vries AL, Berkhof J, Rozendaal L, Beliën JA, Overbeek L, Babović M, Snijders PJ, Meijer CJ (2012) Offering self-sampling for human papillomavirus testing to non-attendees of the cervical screening programme: characteristics of the responders. *Eur J Cancer* **48**: 1799–1808.

IARC Working Group on the Evaluation of Cancer Preventive Strategies Cervix Cancer Screening (2005) *IARC Handbooks of Cancer Prevention No. 10.* Lyon: IARC.

Ingemann-Hansen O, Lidang M, Niemann I, Dinesen J, Baandrup U, Svanholm H, Petersen L (2008) Screening history of women with cervical cancer: a 6-year study in Aarhus, Denmark. *Br J Cancer* **98**: 1292–1294.
Leyden WA, Manos MM, Geiger AM, Weinmann S, Mouchawar J, Bischoff K, Yood MU, Gilbert J, Taplin SH (2005) Cervical cancer in women with comprehensive health care access: attributable factors in the screening process. *J Natl Cancer Inst* **97**: 675–683.
Lönnberg S, Anttila A, Kotaniemi-Talonen L, Kujari H, Melkko J, Granroth G, Vornanen M, Pietiläinen T, Sankila A, Arola J, Luostarinen T, Nieminen P (2010) Low proportion of false-negative smears in the Finnish program for cervical cancer screening. *Cancer Epidemiol Biomarkers Prev* **19**: 381–387.
Lönnberg S, Anttila A, Luostarinen T, Nieminen P (2012) Age-specific effectiveness of the Finnish cervical cancer screening programme. *Cancer Epidemiol Biomarkers Prev* **21**: 1354–1361.
Lönnberg S, Nieminen P, Luostarinen T, Anttila A (2013) Mortality audit of the Finnish cervical cancer screening program. *Int J Cancer* **132**: 2134–2140.
Morrell S, Taylor R, Wain G (2005) A study of Pap test history and histologically determined cervical cancer in NSW women, 1997–2003. *J Med Screen* **12**: 190–196.
Naucler P, Ryd W, Törnberg S, Strand A, Wadell G, Elfgren K, Rådberg T, Strander B, Johansson B, Forslund O, Hansson BG, Rylander E, Dillner J (2007) Human papillomavirus and Papanicolaou tests to screen for cervical cancer. *N Engl J Med* **357**: 1589–1597.
Nieminen P, Kallio M, Anttila A, Hakama M (1999) Organised vs. spontaneous Pap-smear screening for cervical cancer: a case-control study. *Int J Cancer* **83**: 55–58.
Piana L, Leandri FX, Le Retraite L, Heid P, Tamalet C, Sancho-Garnier H (2011) [HPV-Hr detection by home self sampling in women not compliant with pap test for cervical cancer screening. Results of a pilot programme in Bouches-du-Rhône]. *Bull Cancer* **98**: 723–731.
Pippa G, Ferrara M, Valle S, Diego B, Alessandra B, Apuzzo M, Bazuro ME, Tammaro G, Federici A (2009) [Feasibility of colorectal cancer screening with fecal occult blood test distributed by public pharmacies]. *Recenti Prog Med* **100**: 348–351.
Quinn M, Babb P, Jones J, Allen E (1999) Effect of screening on incidence and mortality from cancer of cervix in England: evaluation based on routinely collected statistics. *BMJ* **318**: 904–908.
Racey CS, Withrow DR, Gesink D (2013) Self-collected HPV testing improves participation in cervical cancer screening: a systematic review and meta-analysis. *Can J Public Health* **104**: e159–e166.
Ronco G, Dillner J, Elfström KM, Tunesi S, Snijders PJF, Arbyn M, Kitchener H, Segnan N, Gilham C, Giorgi-Rossi P, Berkhof J, Peto J, CJLM Meijer. the International HPV Screening Working Group (2014) Efficacy of HPV-based screening for preventing invasive cervical cancer: follow-up of European randomised controlled trials. *Lancet* **383**: 524–532.
Ronco G, Giorgi Rossi P, Carozzi F, Confortini M, Dalla Palma P, Del Mistro A, Ghiringhello B, Girlando S, Gillio-Tos A, De Marco L, Naldoni C, Pierotti P, Rizzolo R, Schincaglia P, Zorzi M, Zappa M, Segnan N, Cuzick J (2010) Efficacy of Human Papillomavirus testing on the subsequent detection of cervical invasive and intraepithelial neoplasia: results from a randomised controlled trial. *Lancet Oncol* **11**: 249–257.
Ronco G, Pilutti S, Patriarca S, Montanari G, Ghiringhello B, Volante R, Giordano L, Zanetti R, Mancini E, Segnan N. Turin Cervical Screening Working Group (2005) Impact of the introduction of organised screening for cervical cancer in Turin, Italy: cancer incidence by screening history 1992-98. *Br J Cancer* **93**: 376–378.
Sancho-Garnier H, Tamalet C, Halfon P, Leandri F, Le Retraite L, Djoufelkit K, Heid P, Davies P, Piana L (2013) HPV self-sampling or the pap-smear: a randomized study among cervical screening non-attenders from lower socio-economic groups in France. *Int J Cancer* **133**: 2681–2687.
Snijders PJ, Verhoef VM, Arbyn M, Ogilvie G, Minozzi S, Banzi R, van Kemenade FJ, Heideman DA, Meijer CJ (2013) High-risk HPV testing on self-sampled versus clinician-collected specimens: a review on the clinical accuracy and impact on population attendance in cervical cancer screening. *Int J Cancer* **132**: 2223–2236.
Sung HY, Kearney KA, Miller M, Kinney W, Sawaya GF, Hiatt RA (2000) Papanicolaou smear history and diagnosis of invasive cervical carcinoma among members of a large prepaid health plan. *Cancer* **88**: 2283–2289.
Szarewski A, Cadman L, Mesher D, Austin J, Ashdown-Barr L, Edwards R, Lyons D, Walker J, Christison J, Frater A, Waller J (2011) HPV self-sampling as an alternative strategy in non-attenders for cervical screening - a randomised controlled trial. *Br J Cancer* **104**: 915–920.
Viikki M, Pukkala E, Hakama M (1999) Risk of cervical cancer after a negative Pap smear. *J Med Screen* **6**: 103–107.
Virtanen A, Anttila A, Luostarinen T, Nieminen P (2011a) Self-sampling versus reminder letter: effects on cervical cancer screening attendance and coverage in Finland. *Int J Cancer* **128**: 2681–2687.
Virtanen A, Nieminen P, Luostarinen T, Anttila A (2011b) Self-sample HPV tests as an intervention for nonattendees of cervical cancer screening in Finland: a randomized trial. *Cancer Epidemiol Biomarkers Prev* **20**: 1960–1969.
WHO (2006) Comprehensive Cervical Cancer Control. A guide to essential practice. WHO: Geneva.
Wikström I, Lindell M, Sanner K, Wilander E (2011) Self-sampling and HPV testing or ordinary Pap-smear in women not regularly attending screening: a randomised study. *Br J Cancer* **105**: 337–339.
Zorzi M, Del Mistro A, Farruggio A, de' Bartolomeis L, Frayle Salamanca H, Baboci L, Bertazzo A, Cocco P, Fedato C, Gennaro M, Marchi N, Penon MG, Cogo C, Ferro A (2013) Use of high-risk Human Papillomavirus DNA test as primary test in a cervical cancer screening programme: a population-based cohort study. *BJOG* **120**: 1260–1267.
Zucchetto A, Ronco G, Giorgi Rossi P, Zappa M, Ferretti S, Franzo A, Falcini F, Visioli CB, Zanetti R, Biavati P, La Rosa F, Baracco S, Federico M, Campari C, De Togni A, Piffer S, Pannozzo F, Fusco M, Michiara M, Castaing M, Seghini P, Tisano F, Serraino D. IMPATTO CERVICE Working Group (2013) Screening patterns within organized programs and survival of Italian women with invasive cervical cancer. *Prev Med* **57**: 220–226.

APPENDIX

The following are members of the HPV Self-sampling Italian Working Group

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Table A1. Characteristics of the catchment areas: surface, number of municipalities, inhabitants, pharmacies, and clinics involved in the trial for self-sampling distribution and cervical sampling

	Municipalities in catchment area	Catchment area km^2	Inhabitants	Type of neighbourhood	Number of pharmacies	Number of clinics	Notes
Bologna	1	141	384 202	Urban	3	1	
Roma G	2	102	17 000	Rural	2	1	The clinic was 30 km from the catchment area
Abruzzo	3	182	51 226	Rural-small cities	6	1	
Pieve Soligo	12	270	112 109	Rural	2	3	
Este	15	300	79 959	Rural-small cities	21	4	
Molise	14	466	80 049	Rural and 1 city	1	1	

Table A2. Results of randomisation: distribution of women by age group and arm (Bologna excluded)

	Test at clinic		Self-sampling at home		Self-sampling at pharmacy		Total	
Age group	*N*	%	*N*	%	*N*	%	*N*	%
<39	982	24.5	972	24.2	903	22.5	2856	23.7
40–49	1406	35.0	1397	34.8	1499	37.4	4302	35.7
50–59	1200	29.9	1220	30.4	1165	29.0	3585	29.8
60+	424	10.6	427	10.6	446	11.1	1297	10.8
Total	4012		4016		4013		12 041	

	HPV test at clinic		Self-sampling at home		Self-sampling pharmacy	
	Y	95% CI	Y	95% CI	Y	95% CI
Mean age	47.57	47.29–47.85	47.63	47.35–47.91	47.63	47.35–47.91

Pearson $\chi^2(6) = 10.29$, *P*-value = 0.113.

Table A3. Results of randomisation in Bologna: distribution of women by age group and arm

	HPV test at clinic		Self-sampling at home		Self-sampling pharmacy		Pap test at clinic		Total	
Age group	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%
<39	62	12.4	57	11.4	61	12.2	68	13.6	248	12.4
40–49	191	38.2	193	38.6	182	36.4	165	33.0	731	36.6
50–59	169	33.8	183	36.6	182	36.4	179	35.8	713	35.7
60+	78	15.6	67	13.4	75	15.0	88	17.6	308	15.4
Total	500	100	500	100	500	100	500	100	2000	100

	HPV test at clinic		Self-sampling at home		Self-sampling pharmacy		Pap test at clinic	
	Y	95% CI	Y	95% CI	Y	95% CI	Y	95% CI
mean age	50.23	49.51–50.95	50.32	49.63–51.03	50.66	49.99–51.38	50.71	49.98–51.44

Pearson $\chi^2(9) = 7.30$. *P*-value = 0.606.

Table A4. Results of randomisation: distribution of women by arm and municipality of residence, classified according to the number of inhabitants (Bologna excluded)

	Test at clinic		Self-sampling at home		Self-sampling pharmacy		
	N	%	*N*	%	*N*	%	Total
<10 000	886	22.1	874	21.8	855	21.3	2615
10 000–24 999	1454	36.2	1491	37.1	1518	37.8	4463
⩾25 000	1672	41.7	1651	41.1	1640	40.9	4963
	4012	100.0	4016	100.0	4013	100.0	12 041

Pearson $\chi^2(4) = 2.27$. *P*-value = 0.687. All randomised women in Bologna centre are resident in the municipality of Bologna (384 000 inhabitants).