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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12See appendix.

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667
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 (Nieminet 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 groups:

- **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.](image-url)
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 °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 ≥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 participation also varied among centres. The heterogeneity was stable with age (Table 2), while for both intervention arms the participation rate (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 (χ² 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

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

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 14041 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 (χ² for linear trend of the RP, P = 0.014 and P = 0.24 for self-sampling at home and pick up at pharmacies, respectively).

### Table 1. Results of participation, by arm, centre, and mode of participation
Table 2. Results of participation, by arm and age group

| 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 |
| <39       | N    | N  | %   | N    | N  | %   | N    | N  | %   | RR  | CI (95%) | RR  | CI (95%) |
| 1112      | 134  | 12.1 | 1029 | 271  | 26.3 | 964 | 129  | 13.4 | 2.19 | 1.77–2.71 | 1.11 | 0.87–1.42 |
| 39–49     | 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 |

A

Centre | RR (95% CI) | Weight %
--- | --- | ---
Abruzzo | 0.98 (0.83, 1.15) | 17.26 |
Roma G | 4.94 (3.49, 7.00) | 15.92 |
Este | 2.62 (2.02, 3.40) | 16.66 |
Pieve di Soligo | 1.43 (1.17, 1.75) | 17.04 |
Molise | 2.29 (1.77, 2.94) | 16.71 |
Bologna | 1.68 (1.26, 2.25) | 16.40 |
Overall | 2.00 (1.30, 3.10) | 100.00 |

B

Centre | RR (95% CI) | Weight %
--- | --- | ---
Abruzzo | 0.72 (0.60, 0.86) | 17.48 |
Roma G | 3.75 (2.62, 5.35) | 16.37 |
Este | 1.23 (0.91, 1.67) | 16.76 |
Pieve di Soligo | 0.62 (0.47, 0.81) | 17.00 |
Molise | 0.97 (0.72, 1.32) | 16.76 |
Bologna | 0.53 (0.34, 0.83) | 15.61 |
Overall | 1.01 (0.62, 1.65) | 100.00 |

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 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.

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

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 filled 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).

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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 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 follow-up procedures was about 97% in the most recent Dutch trial (Bosgraaf et al, 2015), conducted in an organised screening programme with a strong central management of the ascertainment, 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

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

| Centre          | Samples* | 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      | 0     | 1                   |
| Pieve di Soligo | 114      | 114          | 3       | 7       | 2              | 2       | 2      | 2     | 0                   |
| Molise          | 77       | 77           | 1       | 12      | 0              | 0       | 0      | 0     | 1                   |
| Total           | 235      | 235          | 5       | 19      | 2              | 2       | 2      | 2     | 2                   |

*10 samples were unsuitable for HPV testing.
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 (Bortozzo 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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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 km² | 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)

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

| Age group | HPV test at clinic | Self-sampling at home | Self-sampling pharmacy | Pap test at clinic | Total |
|-----------|--------------------|-----------------------|------------------------|--------------------|-------|
|           | 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

| Age group | HPV test at clinic | Self-sampling at home | Self-sampling pharmacy | Pap test at clinic | Total |
|-----------|--------------------|-----------------------|------------------------|--------------------|-------|
|           | 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 |
|           | 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 | Total |
|----------|---------------|-----------------------|------------------------|-------|
|          | N             | %                     | N                      | 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 | 12041 |

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).