Effect of self-collection of HPV DNA offered by community health workers at home visits on uptake of screening for cervical cancer (the EMA study): a population-based cluster-randomised trial

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Summary

Background Control of cervical cancer in developing countries has been hampered by a failure to achieve high screening uptake. HPV DNA self-collection could increase screening coverage, but implementation of this technology is difficult in countries of middle and low income. We investigated whether offering HPV DNA self-collection during routine home visits by community health workers could increase cervical screening.

Methods We did a population-based cluster-randomised trial in the province of Jujuy, Argentina, between July 1, 2012, and Dec 31, 2012. Community health workers were eligible for the study if they scored highly on a performance score, and women aged 30 years or older were eligible for enrolment by the community health worker. 200 community health workers were randomly allocated in a 1:1 ratio to either the intervention group (offered women the chance to self-collect a sample for cervical screening during a home visit) or the control group (advised women to attend a health clinic for cervical screening). The primary outcome was screening uptake, measured as the proportion of women having any HPV screening test within 6 months of the community health worker visit. Analysis was by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT02095561.

Findings 100 community health workers were randomly allocated to the intervention group and 100 were assigned to the control group; nine did not take part. 191 participating community health workers (94 in the intervention group and 97 in the control group) initially contacted 7650 women; of 3632 women contacted by community health workers in the intervention group, 3049 agreed to participate; of 4018 women contacted by community health workers in the control group, 2964 agreed to participate. 2618 (86%) of 3049 women in the intervention group had any HPV test within 6 months of the community health worker visit, compared with 599 (20%) of 2964 in the control group (risk ratio 4·02, 95% CI 3·44–4·71).

Interpretation Offering self-collection of samples for HPV testing by community health workers during home visits resulted in a four-fold increase in screening uptake, showing that this strategy is effective to improve cervical screening coverage. This intervention reduces women's barriers to screening and results in a substantial and rapid increase in coverage. Our findings suggest that HPV testing could be extended throughout Argentina and in other countries to increase cervical screening coverage.

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See **Online** for a podcast interview with Silvina Arrossi

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Introduction

A key factor that has hampered control of cervical cancer in developing countries is failure to achieve high screening uptake; recruitment through opportunistic screening and promotion has been insufficient, particularly among women from poor populations.[1,2] In Argentina, more than 60% of women with low education have not had a Papanicolaou (Pap) test in the past 2 years.[3]

In recent years, testing for human papillomavirus (HPV) DNA has changed the scenario. This new technology is more effective than cytology for the detection of precursors of cervical cancer and offers the possibility of reducing screening frequency.[4] Through self-collection, HPV DNA testing could reduce barriers to screening and increase coverage.[5] The method is highly accurate[6,7] and is acceptable for women in different countries.[8–10] Nonetheless, translation of this acceptability into packages of care for public health systems remains a major challenge. Effectiveness of HPV self-collection relies on several programmatic issues, including delivery and transport of sample collection kits and referral of women.[11] Delivering sample containers and returning samples via the postal system has been proposed,[7,12,13] but this strategy is not feasible in most developing countries.

To address complex health problems such as low coverage, technological changes need to be integrated

with social innovations to ensure that the new technology is actually implemented among the population that needs it most.[14] Therefore, to achieve the highest effect, self-collection must be implemented with social developments that allow the innovation to be scaled in the specific contexts of countries of middle-to-low income.

The increasing role of community health workers to address the challenge of delivering services to underserved populations through education, outreach, and counselling is now recognised.[15–17] However, community health work has been mainly oriented to maternal and child care and control of communicable diseases.[17] The effectiveness of home promotion activities by community health workers to increase demand for cytological screening[18–22] has been limited, because those outreach efforts cannot translate into screening owing to access barriers to health care.

We postulated that a real difference could be made in control of cervical cancer by combining a new technology (HPV DNA testing) with a social innovation (incorporation of self-collection into routine home visits by community health workers). To evaluate this combination, we did the self-collection modality study (known as the EMA study), a population-based cluster-randomised trial set in Jujuy, an Argentinean province with one of the highest rates of mortality from cervical cancer nationally.[23] In Jujuy, primary HPV testing was introduced in 2011[24] and, despite important efforts of the province to promote screening, estimated coverage is around 50%.[3]

Methods

Setting and participants

Jujuy is located in northwest Argentina; 85% of the population live in urban areas. The public health system includes a main hospital and 270 primary health-care centres. Since 2012, HPV DNA testing has been the primary screening test for cervical cancer, available for all women aged 30 years or older who attend public health centres. The primary health-care system employs about 700 paid full-time community health workers who visit about 110 000 households twice a year for health-related tasks such as immunisation and promotion of maternal and child health. The performance of community health workers is evaluated annually and scored as good or suboptimum by supervisors in the primary health-care system, according to achievement of established goals (eg, the number of home visits).

We regarded community health workers as clusters in the study and judged them eligible if they were working in Jujuy's public health system in July, 2012, and had received a good performance score in 2011. Community health workers in rural areas of Jujuy are assigned a mean of 52 women (aged ≥30 years), whereas those working in urban areas have on average 155 women assigned to them.

A woman was eligible for the study if she was 30 years or older and living in a household visited by community health workers. Women at home during the routine visit were invited to participate but excluded if they had had a previous HPV DNA test, a hysterectomy, or treatment for premalignant or malignant disease, were pregnant, or had a mental disability.

All women gave written informed consent. The bioethics review committee of Jujuy's Ministry of Health approved the study.

Randomisation and masking

Of 698 community health workers working in the Jujuy primary health-care system, 488 were eligible and were stratified into four groups according to sex and setting (either urban or rural). We selected at random (using a computer-generated random number list) a stratified sample of 200 community health workers, with proportional allocation to strata. Within strata, we assigned community health workers at random, in a 1:1 ratio, to either the intervention group or control group. We also used a computer-generated random number list for the intervention allocation. All selected community health workers were informed about the study by the head of the primary health-care system. Masking of intervention and outcome assessments was not feasible.

Procedures

We provided training for all community health workers on cervical cancer prevention and HPV DNA testing, and informed them about the EMA study objectives and protocol. For community health workers allocated to the intervention group, we also included a training module on communication strategies to instruct women on self-collection. In total, for all community health workers, we held two 1-day workshops, which were led by EMA team members.

Community health workers from both groups identified eligible women during their routine home visits, explained the aims of the study, and obtained written informed consent; they also talked to women about cervical cancer prevention and HPV DNA testing. Community health workers allocated to the control group advised women to seek cervical screening at health centres; women were free to go to any one of 270 provincial health centres. Community health workers assigned to the intervention group offered women self-collection and provided education and a leaflet on how to do the procedure. They asked women if they accepted self-collection and recorded the answer on a questionnaire. Women accepting self-collection could deliver the sample immediately or the day after, in which case community health workers revisited them. Women who did not choose self-collection were encouraged to get screened at health centres. Table 1 shows details of the intervention components.

Women self-collected samples with a cervical sampler kit (Qiagen, Gaithersburg, MD, USA), which comprised a cervical brush, specimen container, and transport medium. Community health workers received these kits

at the training workshops; if they needed additional units they could obtain them from health centres or the provincial programme headquarters. During the visit, community health workers instructed women how to insert the head of the brush into the vagina and place it into the container. They labelled the specimen container with the woman's name and her unique national identifier number. Community health workers transported specimens at room temperature to health centres; from here they were sent to the provincial HPV laboratory, usually once a week, by the health centre or second-level hospital. Specimens arriving at the laboratory more than 14 days after collection were not processed. At the laboratory, technicians analysed the HPV DNA status for 13 high-risk HPV types using hybrid-capture 2, following the manufacturer's instructions.

According to national guidelines,[25] cytological samples are taken at the same time that clinician-collected HPV testing is done, but the sample is only read if the woman is HPV-positive; women with samples that include atypical cells of undetermined significance or more (ASCUS+) are referred for colposcopy. We referred women who provided a self-collected sample and were HPV-positive for colposcopy and biopsy (if needed), which avoided an additional visit for cytological triage. Women from both the intervention and control groups went to health centres to receive their test results. Colposcopies were done by colposcopists from the public health system who received specific training on the project protocol and also a refresher course to unify colposcopic classification and diagnostic criteria. On average, distance to travel to colposcopy units was 19 km (SD 27, range 1–211). Biopsy findings were reported according to cervical intraepithelial neoplasia (CIN) terminology. Identified cases of CIN2+ were treated according to standard protocols (LEEP for CIN).[25] We advised HPV-negative women to repeat screening within 3 years.

A national screening information system (SITAM) records data on screening tests and diagnostic procedures done within the public health system. SITAM was linked to the study database to identify women with HPV tests and other procedures and to extract information about Pap testing in the past 4 years. We also obtained information on patients' education and health insurance from the primary health care system database and from the questionnaire that was administered by community health workers during enrolment of women. For the intervention group, we also included a question about self-sampling acceptability.

Outcome measures

The primary outcome was screening uptake, defined at the individual participant level as the proportion of women with any HPV test (self-collected or clinician-collected) registered in SITAM within 6 months after the community health worker visit. We also analysed screening uptake at community health worker (cluster) level, which we defined as the proportion of women with any HPV test per community health worker. We did the primary analysis by intention to treat.

	Intervention cluster	Control cluster
Promotion of HPV testing at health centres	✓	✓
HPV test kits included among community health workers' home visit materials	✓	x
Education materials about self-collection included among home visit materials	✓	x
Offering of self-collection	✓	x
Delivering of samples to health centres, to be transported to the HPV laboratory	✓	x

Table 1: **Intervention components**

We measured several secondary outcomes at the individual participant level. First, we analysed reported acceptability—ie, the proportion of women from the intervention group who, according to the questionnaire, accepted self-collection, independently of whether or not they were indeed tested. Second, we assessed HPV positivity. Finally, we investigated detection of CIN2+ disease, defined as the proportion of women with histologically confirmed CIN2+ disease during the follow-up period (until Dec 31, 2013) out of the total number of women tested with each type of test (self-collected or clinician-collected). Additionally, we reported the number of CIN2+ cases per 1000 women in each study group.

Statistical analysis

We designed the EMA study to have more than 90% power to detect a 10% increase in screening uptake for the intervention group, compared with a 50% screening uptake in the control group (two-sided α of 0·05). Based on primary health-care system records for the years 2011–12, we estimated that community health workers would enrol an average of 30 women in 6 months. We included correlation induced by community health workers in our sample size calculations, assuming an intraclass correlation coefficient of 0·10, which resulted in a sample of 100 community health workers per study group and a total of about 6000 women enrolled.

To account for the cluster design, we used two analytical strategies. First, at the level of the individual participant, we assessed the intervention effect using generalised linear models, log link, and Poisson distribution, taking into account data clustering.[26] We report risk ratios and 95% CIs. To analyse effect modification, we fitted a model including Pap testing in the past 4 years and Pap study group interaction. We fitted the same generalised linear model described above to evaluate the association between self-collection (self-collected tests registered in SITAM) and community health worker characteristics (sex, urban or rural work

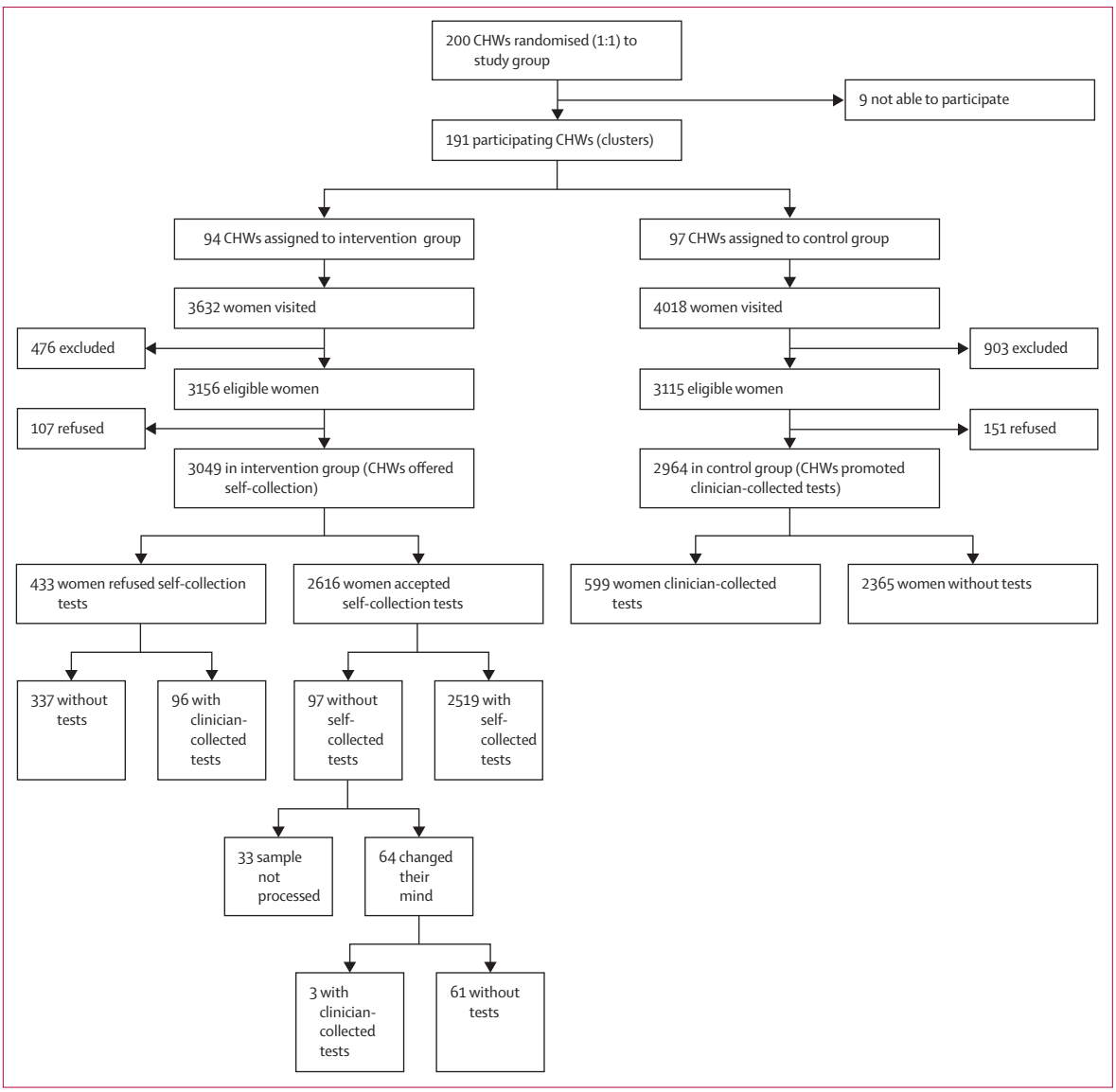

Figure 1: **Trial profile**
CHW=community health worker.

setting), after adjusting for women's age, health insurance, education level, and a Pap test in the past 4 years. Second, we estimated screening uptake using the community health worker as the unit of analysis—ie, defining the proportion of screened women per community health worker—and we compared study groups with the Kruskal-Wallis test. To assess potential bias attributable to the randomised community health workers who did not participate, we reanalysed data assuming a nil proportion of women tested for these community health workers. We compared detection of CIN2+ disease and CIN2+ cases per 1000 women with Fisher's exact test. We used SAS version 9.2 for all analyses. This trial is registered with ClinicalTrials.gov, number NCT02095561.

Role of the funding source
Local health personnel participated actively in design and planning of the study. The funder had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results
Between July 1, 2012, and Dec 31, 2012, 200 community health workers were enrolled to the study and randomly allocated in a 1:1 ratio to either the intervention group (n=100) or the control group (n=100; figure 1). Of these, nine did not take part (three men [33%]; four people from rural areas [44%]), for reasons including illness and

	Total population	Intervention group	Control group
Community health workers			
Total (n)	191	94	97
Sex			
Men	45 (24%)	21 (22%)	24 (25%)
Women	146 (76%)	73 (78%)	73 (75%)
Area*			
Urban	133 (70%)	67 (72%)	66 (68%)
Rural	57 (30%)	26 (28%)	31 (32%)
Women			
Total (n)	6013	3049	2964
Age (years)			
30–39	2536 (42%)	1294 (42%)	1242 (42%)
40–49	1582 (26%)	784 (26%)	798 (27%)
50–64	1509 (25%)	762 (25%)	747 (25%)
≥65	386 (6%)	209 (7%)	177 (6%)
Education†			
Never went to school, or primary education incomplete	960 (17%)	488 (17%)	472 (17%)
Primary complete but secondary incomplete	2664 (48%)	1373 (48%)	1291 (47%)
Secondary complete	1193 (21%)	600 (21%)	593 (22%)
Tertiary (incomplete or complete)	782 (14%)	401 (14%)	381 (14%)
Health insurance‡			
Public system	3027 (53%)	1472 (51%)	1555 (56%)
Private or social security	2650 (47%)	1409 (49%)	1241 (44%)
Pap test in past 4 years			
Yes	1727 (29%)	889 (29%)	838 (28%)
No	4286 (71%)	2160 (71%)	2126 (72%)

Pap=Papanicolaou. *Data missing for one community health worker. †Data missing for 414 women. ‡Data missing for 336 women.

Table 2: **Characteristics of community health workers and women**

	Women tested/ total women (%)	Risk ratio (95% CI)	p
All women*			
Control group	599/2964 (20%)	..	..
Intervention group	2618/3049 (86%)	4·02 (3·44–4·71)	<0·0001
Women with no Pap test in past 4 years			
Control group	336/2126 (16%)	..	..
Intervention group	1874/2160 (87%)	4·98 (4·12–6·02)	<0·0001
Women with a Pap test in past 4 years			
Control group	336/838 (40%)	..	..
Intervention group	771/889 (87%)	2·76 (2·39–3·20)	<0·0001

Risk ratios, 95% CIs, and p values based on a modified Poisson generalised linear model, taking into account the clustering induced by community health workers. Pap=Papanicolaou. *Intracluster correlation coefficient for the primary outcome, 0·098.

Table 3: **Primary outcome of screening uptake by women**

maternity leave. Therefore, 94 community health workers were in the intervention group and 97 were in the control group. Community health workers who agreed to participate were predominantly women (146, 76%) and worked in urban settings (133, 70%; table 2). No difference was noted in sex (p=0·45) or setting (p=0·15) between participating community health workers and those who declined to participate.

The 191 participating community health workers contacted 7650 women in total. Of 3632 women initially contacted by community health workers allocated to the intervention group, 3156 were eligible and 3049 (97%) agreed to participate. Of 4018 women initially contacted by community health workers assigned to the control group, 3115 were eligible and 2964 (95%) agreed to participate. When compared with enrolled women, those who did not participate (n=258) were older (age 30–39 years, 19%; 40–49 years, 26%; 50–64 years, 31%; and ≥65 years, 23%; p<0·0001). The mean number of women enrolled by community health workers allocated to the intervention group was 32·4 (SD 26·8, range 1–107), and for those assigned to the control group, the mean number of women enrolled was 30·6 (25·2, 2–99). Of all enrolled women, 4286 (71%) had not had a Pap test in the past 4 years (table 2).

2616 (86%) of 3049 women in the intervention group accepted self-collection when it was offered to them; of these women, 97 were not tested (figure 1): 64 chose to deliver the sample the day after but changed their mind, and 33 collected the specimen but it was not processed because of logistical problems. 99 women from the intervention group had clinician-collected HPV tests.

2618 (86%) of 3049 women in the intervention group had any HPV test within 6 months of the community health worker visit, compared with 599 (20%) of 2964 in the control group (risk ratio 4·02, 95% CI 3·44–4·71; table 3). 2519 (96%) of 2618 tests in the intervention group were self-collected samples. Having a Pap test in the past 4 years was an effect modifier (p<0·0001); the effect of the intervention was stronger among women who had not had a Pap test in the past 4 years (risk ratio 4·98, 95% CI 4·12–6·02) than among women who had had a Pap test (2·76, 2·39–3·20). Having a self-collected test was not associated with the sex of the community health worker or with an urban or rural work setting (table 4).

Data were also analysed at cluster level, expressing screening uptake as the proportion of women tested per community health worker; figure 2 summarises the results attained by community health workers. Compared with workers assigned to the control group, a remarkable increase was noted in the proportion of women having any HPV test per community health worker allocated to the intervention group (p<0·0001). Furthermore, large variability was recorded in community health worker outcomes. For example, in the intervention group, more than 50% of community health workers were very successful, with more than 91% of women having

	Self-collected tests (n=2519)*	Risk ratio (95% CI)	p
Sex of community health worker			
Men	286 (77%)	1·09 (0·93–1·27)	0·279
Women (reference)	2233 (83%)	..	..
Area†			
Urban	2101 (84%)	0·95 (0·84–1·06)	0·351
Rural (reference)	417 (75%)	..	..

Risk ratios, 95% CIs, and p values are based on a modified Poisson generalised linear model including sex of the community health worker, area, woman's age, education level, health insurance, and Papanicolaou (Pap) test in the past 4 years as fixed effect and taking into account the clustering induced by community health workers. 2798 women in the intervention arm had complete data.
*92 community health workers had at least one woman provide a self-collected test. †Data missing for one community health worker.

Table 4: **Association between characteristics of community health workers and women with self-collected tests**

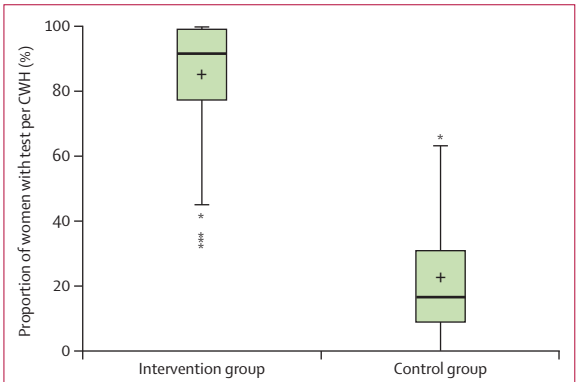

Figure 2: **Screening uptake at cluster level**
94 CHWs were in the intervention group; 97 CHWs were in the control group. Control versus intervention, p<0·0001. The lower and upper end of the green box represent the first and third quartile, respectively; the solid line represents the median; + represents the mean; vertical lines show the range of the Tukey boxplot threshold; outliers are denoted with asterisks.

cervical screening; however, 25% of community health workers had a comparatively low performance, with less than 78% of women having any HPV test. Including all randomly allocated community health workers, and imputing zero women with tests to non-participant community health workers, produced comparable results.

Follow-up ended on Dec 31, 2013, 12 months after the last woman was enrolled. Median follow-up was 84 days (IQR 45–142). Of 2519 women in the intervention group with a self-collected specimen and an HPV test result, 298 (12%) tested positive for HPV. Of these women, 232 (78%) attended for colposcopy during the study follow-up period (in 202 [87%] women, colposcopy was done jointly with or after a Pap test): 179 had normal findings and 53 had an abnormal result (figure 3). For these 232 women, the average time from receiving their HPV test result to having colposcopy was 100 days (SD 67, range 6–305). Another 33 women had colposcopies done in the private sector, which were not included in the CIN2+ calculation. 48 biopsy procedures were done (five women with abnormal colposcopy had no biopsy results).

CIN2+ disease was detected in 29 (1·15%) of 2519 women in the intervention group who provided a self-collected sample and had a test result. Of these 29 women, 21 (72%) had been treated by Dec 31, 2013 (mean time from diagnosis to treatment was 91 days, SD 76, range 11–272). When results of cytology from this group were used to recalculate the number of cases of CIN2+ detected after cytological triage, as was done in the control group, 24 CIN2+ lesions were detected by self-collection.

Of 698 women with clinician-collected tests (99 from the intervention group and 599 controls), 81 (12%) tested positive for HPV; 32 of these women had ASCUS+. Women who had a clinician-collected HPV test and were positive for HPV were referred for colposcopy only if they had abnormal findings on cytology. 23 (72%) of 32 women with ASCUS+ had colposcopy during the study follow-up period: eight had normal results and 15 had abnormal findings on biopsy. For these patients, the mean time from receiving their HPV test result to having colposcopy was 68 days (SD 43, range 7–144). Of the 698 women with clinician-collected tests, nine (1·29%) had CIN2+ disease detected. Six (67%) women had been treated by Dec 31, 2013 (mean time from diagnosis to treatment was 80 days, SD 92, range 10–242). Differences in HPV positivity and CIN2+ detection between methods (self-collection and clinician-collection) were not significant. In total, 31 women with CIN2+ disease were detected in the intervention group (29 with self-collected tests and two with clinician-collected tests) compared with seven in the control group (10·2 CIN2-positive cases per 1000 participant women *vs* 2·4 per 1000 controls; p=0·0002).

Discussion

The main objective of the EMA study was to assess the effect on cervical cancer screening uptake of offering self-collection of samples for HPV testing by community health workers during home visits. This intervention resulted in a four-fold increase in screening uptake, showing that it is an effective strategy to improve cervical screening coverage. Furthermore, offering women self-collection resulted in detection of almost five times more cases of CIN2+ disease than usual. A cluster design, with the community health worker as the unit of randomisation, was chosen to minimise contamination and make the study logistically feasible. As far as we know, the EMA study is the first of its kind to be done in a programmatic real-world context in a low-resource region. The study was implemented in Jujuy, the first Argentinean province to introduce primary HPV testing for cervical cancer screening.

Several randomised trials in developed countries have compared the effect of sending self-sampler kits via the

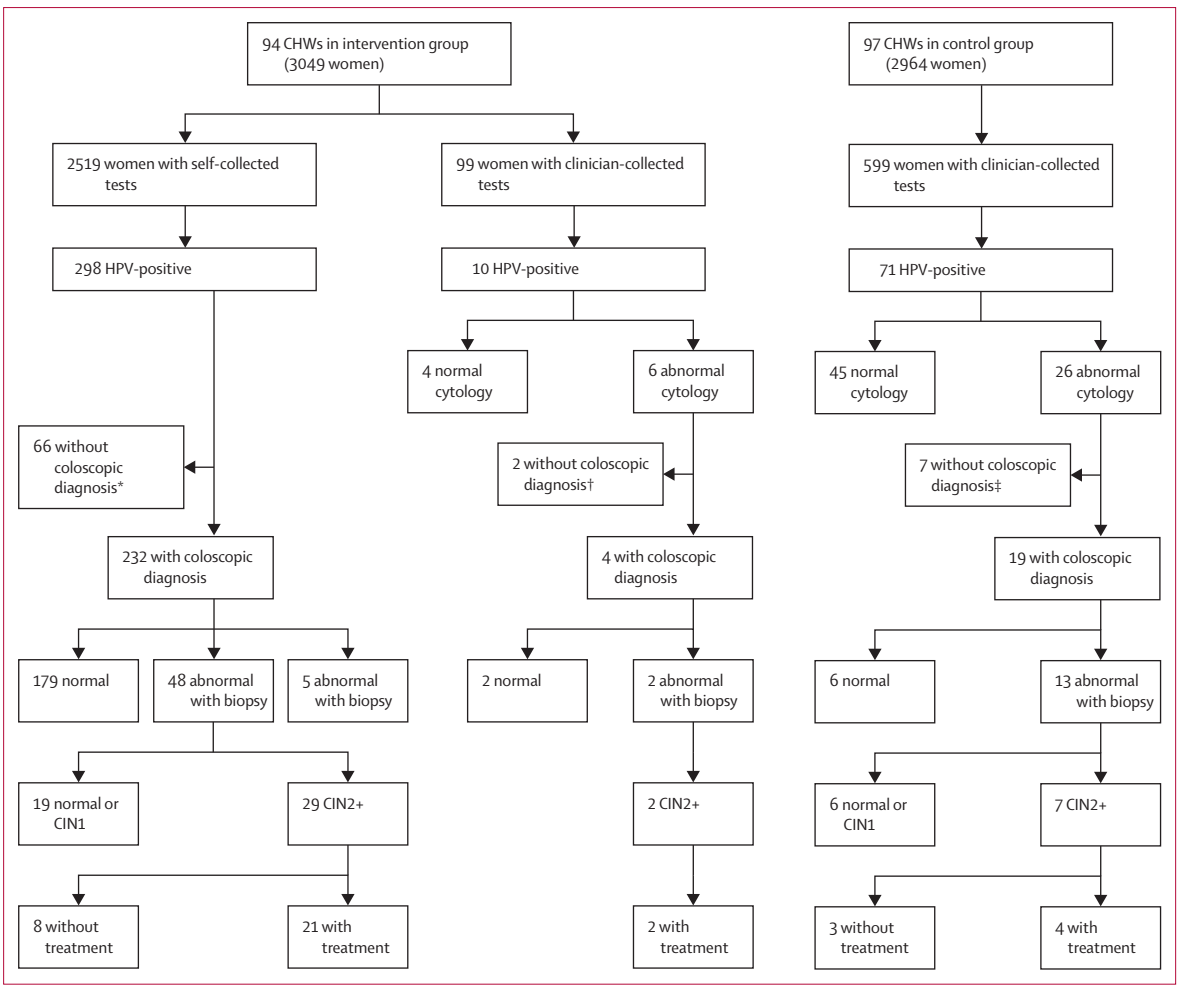

Figure 3: **Follow-up of women positive for high-risk HPV**
CHW=community health worker. HPV=human papillomavirus. *33 tested by private service, five negative Pap test, three moved, four refused or could not have treatment, one died, 20 no data available. †One moved, one no data available. ‡One moved, one refused treatment, five no data available.

postal system instead of sending a letter inviting the woman for cytology,[5,8,12,13,27] with low-to-moderate effects reported. In one study,[8] a 40% increase in adherence was seen in some locations. In developing countries, this strategy is not feasible because of limitations of the postal system and few reliable addresses. Additionally, the absence of face-to-face explanation of self-collection and how to do it might strongly limit acceptability and uptake, particularly among women of low education.

Findings of non-randomised studies from developing countries showed the high potential effect of self-collection offered through home visits to increase cervical cancer screening uptake.[9,28] In a study from Chile,[9] in which two community health workers received a small economic incentive per visit, 86·5% screening uptake was reported. In our study, offering self-sampling was an additional task in community health worker activities, with no incentive provided. In fact, key project components (sample transportation and processing, result communication, and referral for diagnosis or treatment) were done in a programmatic real-world setting and were subject to staff constraints and competing demands of public health care. Our study reflects what can be realistically achieved with self-collection delivered by community health workers to increase screening uptake.

With our study design we were able to distinguish the effects of the community health worker from the intervention, because we compared women receiving the intervention with a control group who were only advised by the community health worker to attend a clinic for clinician-collected HPV testing. Door-to-door canvassing is believed to be a moderately effective way of recruiting women for cancer control programmes,[20,29] depending on intensity and uptake definition. In a study among Chinese women in the USA, significant differences were noted between intervention and control groups with respect to planned, but not actual, screening,[30] suggesting that community health workers succeeded in creating awareness but not in reducing barriers. In our study, the

Panel: **Research in context**

Systematic review

To define the study protocol, we searched PubMed between January, 2002, and December, 2012, with the key terms "cervical cancer", "vaginal self-sampling", "HPV testing", "cervical cancer screening", "clinical trials", "self-collection", "community health workers", and "primary health care"; publications retrieved were reviewed for quality and relevance. We later extended the PubMed search to April, 2014, when writing the report. We only included studies written in English and Spanish. Much of the evidence about the effect of HPV self-collection on screening uptake comes from developed countries, using postal systems,[7,12,13] an approach that is not feasible in developing countries. We did not find any randomised study in which the effectiveness of self-collection offered by community health workers during home visits was evaluated in a programmatic setting.

Interpretation

In the EMA study, HPV self-collection offered by community health workers at home visits was acceptable and highly effective at increasing screening uptake. Even though self-collection led to a small reduction in the proportion of cases of CIN2+ disease detected, by comparison with clinician-collected tests, increased screening uptake allowed for the detection of a significantly larger number of cases of CIN2+ disease. HPV self-collection offered by community health workers as a primary health care task reduces women's barriers to screening and results in a substantial and rapid increase in coverage.

intervention resulted in 85·9% of women having an HPV test, compared with 20·2% in the control group, and this higher proportion was mainly attributable to self-collection. In Jujuy, HPV testing has been established as the primary screening test for cervical cancer, which is offered free of charge in all public health centres. Our study findings suggest that, despite the test's availability, women in the control group faced barriers to get tested. These barriers would be reduced by the offer of HPV self-collection at home. The effect of the intervention was strongest in the subgroup of women who had not had a Pap test in the past 4 years, suggesting that whereas self-collection was effective to change behaviour in screening under-users, promotion of testing at health centres was more effective among women who usually get screened. These results show that synergy between two innovations—HPV self-collection and reorganisation of roles of community health workers—can result in a substantial increase in cervical screening uptake. Moreover, cervical cancer prevention can be integrated into the role of the community health worker as part of primary health-care system activities. However, incorporating too many tasks into community health worker activities can result in job stress and reduced effectiveness of their work. To avoid work overload, HPV self-collection should be incorporated into community health worker activities after careful consideration of what they can realistically achieve in every specific context, and after consideration of other competing responsibilities.[17]

In our study, only 1·3% of women who self-collected a sample were not tested for HPV, suggesting few logistical problems. Importantly, findings show that self-sampling can be offered effectively by male community health workers, because similar results were obtained for male and female community health workers. Thus, male community health workers were effective in overcoming gender and subjective barriers—ie, embarrassment.

Screening programmes with high coverage will not result in a decrease in disease burden if women are not diagnosed and treated; therefore, self-collection must be implemented once diagnostic and treatment services are in place. In our study, 88% of self-collected HPV-positive women had colposcopy, and 85% of women with a histological diagnosis of CIN2+ were treated. This figure is higher than that reported for Jujuy's previous cytology-based programme (70%)[31] and is similar to that reported in a Chilean study,[9] which indicates that although women who self-collected did not have initial contact with medical providers, and the average time between the test result and colposcopy was somewhat longer, the referral system worked adequately and community health workers were an effective link between women and diagnostic services. Furthermore, a high level of colposcopic diagnoses was achieved despite referral of all self-collected HPV-positive women. This approach might not be feasible in many middle-income settings, where availability of colposcopy is limited.[32] Cytological or visual triage might be an option, but would need an additional visit to the health centre, thus reducing the advantage of self-collection. WHO guidelines include treating HPV-positive women immediately with cryotherapy,[33] and this procedure can be an option in settings with reduced diagnostic facilities.

Our trial was not designed to assess differences in detection rates between methods (self-collection and clinician-collection). The proportion of CIN2+ disease detected by self-collection was 11% lower than that detected when clinicians collected samples, which is similar to data reported in a meta-analysis.[7] Women with HPV-positive clinician-collected tests were referred for colposcopy when they had abnormal cytological findings, whereas those with self-collected tests were referred for colposcopy only if they were HPV-positive. However, in the intervention group, most colposcopists also did a Pap test before or together with colposcopy. Therefore, the proportion of detected CIN2+ disease that was reported for self-collection cannot be attributed to the original triage protocol. When data for cytology from this group were used to recalculate CIN2+ cases detected by cytological triage, as was done in the control group, at least twice as many lesions were still detected by self-collection.

Despite the slightly lower proportion of CIN2+ cases detected after self-collection, the remarkable gain in screening uptake attributable to the intervention resulted in almost five times as many CIN2+ cases being detected. Self-collection has been recommended for salvage of screening under-users.[7] In our study, self-collection was offered to women irrespective of their attendance status, although 71% had no cervical screening registered in the previous 4 years. In many countries, gains in coverage

could largely outweigh loss in self-collected test performance, particularly considering the enormous difficulties faced by most programmes to achieve good coverage rates. Thus, in settings where achieving high coverage is especially difficult, self-collection might be regarded as an option for all women. Women's preference should also be considered, and the potential personal gain from self-collection in terms of autonomy, privacy, time, and self-esteem.[34] In our study, women were given the possibility to choose; most women accepted self-collection, suggesting that women highly value the actual possibility of being tested with no delays. More evidence is needed about women's preferences on this subject.

In our study, eligible women who did not take part in the study differed from participants with respect to age distribution; non-participants might also have differed in relation to other baseline variables and measured outcomes. This diversity might limit the generalisability of our results, although by a very small amount in view of the high proportion of eligible women who did participate (97%). Moreover, the community health workers selected were among the best-performing, recognising the need for a specific level of motivation and skills. Inclusion of all community health workers would probably decrease effectiveness of the strategy, which can be compensated for by training and close supervision. Thus, the cost and feasibility of including strong training and monitoring components have to be considered when evaluating self-collection as a programmatic strategy.

The high effect on screening coverage noted by our study was obtained by community health workers that are part of the Jujuy primary health-care system and, therefore, a question remains about how this experience can be replicated in other settings. Community health workers are active in many countries and offer a wide range of health services, from promotion of antenatal care and breastfeeding to preventive health education on malaria, tuberculosis, and sexually transmitted diseases.[15–17] In many settings, these workers have had a key role in the decline of health-related metrics such as maternal and child mortality.[35] Therefore, incorporation of HPV self-collection into the activities of community health workers could be feasible, as long as HPV testing is available and key components of a cervical cancer prevention programme are organised. In Jujuy, an information system and a diagnosis and treatment infrastructure existed already as part of the provincial programme.

HPV self-collection offered by community health workers in a programmatic setting is highly effective at increasing uptake of cervical screening, allowing for many more women to be detected with disease. Our study provides key evidence to delineate extension of HPV testing in Argentina, and for countries to increase screening coverage.

Contributors

SA had the original idea for the trial, secured research support, was the principal investigator and study coordinator, and wrote the report. LT was responsible for day-to-day trial management. LO was the trial statistician, developed a statistical plan and did the analysis, and produced the figures and tables (in consultation with coauthors). MC was responsible for design of communication and training materials. MC and PB trained community health workers. PB and AM were in charge of coordination and supervision of community health workers. AC was site principal investigator and helped write the report. RH contributed to study design, data analysis, and writing of the report. RL contributed to study design, data interpretation, and writing of the report.

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Declaration of interests

We declare no competing interests.

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References

1 International Agency for Research on Cancer. IARC handbooks of cancer prevention: volume 10—cervix cancer screening. 2005. http://www.iarc.fr/en/publications/pdfs-online/prev/handbook10/HANDBOOK10.pdf (accessed Dec 5, 2014).

2 PAHO. Cancer in the Americas: country profiles 2013. Washington: Pan American Health Organization, 2013. http://www.paho.org/hq/index.php?option=com_docman&task=doc_download&gid=23456&Itemid= (accessed Dec 5, 2014).

3 Arrossi S, Paolino M, Sankaranarayanan R. Challenges faced by cervical cancer prevention programs in developing countries: a situational analysis of program organization in Argentina. *Rev Panam Salud Publica* 2010; **28:** 249–57.

4 Sankaranarayanan R, Nene B, Shastri S, et al. HPV screening for cervical cancer in rural India. *N Engl J Med* 2009; **360:** 1385–94.

5 Gök M, Heideman DA, van Kemenade FJ, et al. HPV testing on self collected cervicovaginal lavage specimens as screening method for women who do not attend cervical screening: cohort study. *BMJ* 2010; **340:** c1040.

6 Lazcano-Ponce E, Lorincz AT, Cruz-Valdez A, et al. Self-collection of vaginal specimens for human papillomavirus testing in cervical cancer prevention (MARCH): a community-based randomised controlled trial. *Lancet* 2011; **378:** 1868–73.

7 Arbyn M, Verdoodt F, Snijders PJF, et al. Accuracy of human papillomavirus testing on self-collected versus clinician-collected samples: a meta-analysis. *Lancet Oncol* 2014; **15:** 172–83.

8 Rossi PG, Marsili LM, Camilloni L, et al. The effect of self-sampled HPV testing on participation to cervical cancer screening in Italy: a randomised controlled trial (ISRCTN96071600). *Br J Cancer* 2011; **104:** 248–54.

9 Léniz J, Barriga MI, Lagos M, Ibáñez C, Puschel K, Ferreccio C. Autotoma vaginal para detección de virus del papiloma humano en mujeres no adherentes a tamizaje con Papanicolaou en Chile. *Salud Publica Mex* 2013; **55:** 162–69.

10 Zehbe I, Moeller H, Severini A, et al. Feasibility of self-sampling and human papillomavirus testing for cervical cancer screening in First Nation women from Northwest Ontario, Canada: a pilot study. *BMJ Open* 2011; **1:** e000030.

11 Gravitt PE, Rositch AF. HPV self-testing and cervical cancer screening coverage. *Lancet Oncol* 2014; **15:** 128–29.

12 Szarewski A, Cadman L, Mesher D, et al. HPV self-sampling as an alternative strategy in non-attenders for cervical screening: a randomised controlled trial. *Br J Cancer* 2011; **104:** 915–20.

13 Virtanen A, Nieminen P, Luostarinen T, Anttila A. Self-sample HPV tests as an intervention for nonattendees of cervical cancer screening in Finland: a randomized trial. *Cancer Epidemiol Biomarkers Prev* 2011; **20:** 1960–69.

14 Grand Challenges Canada/Grand Défis Canada. Integrated innovation. September 2010. http://www.grandchallenges.ca/wp-content/uploads/integratedinnovation_EN.pdf (accessed May 20, 2014).

15 El Arifeen S, Christou A, Reichenbach L, et al. Community-based approaches and partnerships: innovations in health-service delivery in Bangladesh. *Lancet* 2013; **382:** 2012–26.

16 Perry HB, Zullinger R, Rogers MM. Community health workers in low-, middle-, and high-income countries: an overview of their history, recent evolution, and current effectiveness. *Annu Rev Public Health* 2014; **35:** 399–421.

17 WHO, Global Health Workforce Alliance. Global experience of community health workers for delivery of health related Millennium Development Goals: a systematic review, country case studies, and recommendations for integration into national health systems. 2010. http://www.who.int/workforcealliance/knowledge/publications/CHW_FullReport_2010.pdf (accessed May 20, 2014).

18 Passkett ED, McLaughlin JM, Lehman AM, Katz ML, Tatum CM, Oliveri JM. Evaluating the efficacy of lay health advisors for increasing risk-appropriate Pap test screening: a randomized controlled trial among Ohio Appalachian women. *Cancer Epidemiol Biomarkers Prev* 2011; **20:** 835–43.

19 Lu M, Moritz S, Lorenzetti D, Sykes L, Strauss S, Quan H. A systematic review of interventions to increase breast and cervical cancer screening uptake among Asian women. *BMC Public Health* 2012; **12:** 413.

20 Everett T, Bryant A, Griffin MF, Martin-Hirsch PP, Forbes CA, Jepson RG. Interventions targeted at women to encourage the uptake of cervical screening. *Cochrane Database Syst Rev* 2011; **5:** CD002834.

21 Sabatino SA, Lawrence B, Elder R, et al, and the Community Preventive Services Task Force. Effectiveness of interventions to increase screening for breast, cervical, and colorectal cancers: nine updated systematic reviews for the guide to community preventive services. *Am J Prev Med* 2012; **43:** 97–118.

22 Baron RC, Rimer BK, Coates RJ, et al. Task force on community preventive services, client-directed interventions to increase community access to breast, cervical, and colorectal cancer screening a systematic review *Am J Prev Med* 2008. **35:** S56–66.

23 Ministerio de Salud. Programa Nacional de Prevención de Cáncer Cervicouterino. http://www.msal.gov.ar/cancer-cervico-uterino/images/stories/3-equipos-salud/pdf/201405_2.3_Mortalidad-cncer-cuello-trienios-06-08-09-11.pdf (accessed Dec 30, 2014).

24 Presidencia de la Nación. Resolución 1472/2011: "Proyecto Demostración para la incorporación de la Prueba de HPV como Tamizaje Primario". Sept 26, 2011. http://www.boletinoficial.gov.ar/Inicio/index.castle?s=1&fea=26/09/2011 (accessed May 20, 2014).

25 Ministerio de Salud de la Nación. Prevención del cáncer de cérvico-uterino: recomendaciones para el tamizaje, seguimiento y tratamiento de mujeres para la prevención del cáncer cervicouterino en el marco de la incorporación de la prueba de VPH. http://www.msal.gov.ar/inc/images/stories/downloads/publicaciones/equipo_medico/Cancer_Cervico_Uterino/Recomendaciones_para_el_tamizaje.pdf (accessed May 20, 2014).

26 Zou GY, Donner A. Extension of the modified Poisson regression model to prospective studies with correlated binary data. *Stat Methods Med Res* 2013; **22:** 661–70.

27 Sancho-Garnier H, Tamalet C, Halfon P, et al. HPV self-sampling or the Pap-smear: a randomized study among cervical screening nonattenders from lower socioeconomic groups in France. *Int J Cancer* 2013; **133:** 2681–87.

28 Abuelo CE, Levinson KL, Salmeron J, Sologuren CV, Fernandez MJ, Belinson JL. The Peru Cervical Cancer Screening Study (PERCAPS): the design and implementation of a mother/daughter screen, treat, and vaccinate program in the Peruvian jungle. *J Community Health* 2014; **39:** 409–15.

29 Wells KJ, Luque JS, Miladinovic B, et al. Do community health worker interventions improve rates of screening mammography in the United States? A systematic review. *Cancer Epidemiol Biomarkers Prev* 2011; **20:** 1580–98.

30 Taylor VM, Hislop TG, Jackson JC, et al. A randomized controlled trial of interventions to promote cervical cancer screening among Chinese women in North America. *J Natl Cancer Inst* 2002; **94:** 670–77.

31 Paolino M, Arrossi S. Análisis de los motivos del abandono del proceso de seguimiento y tratamiento por parte de mujeres con lesiones precursoras de cáncer de cuello uterino en la provincia de Jujuy: implicancias para la gestión. *Salud Colect* 2012; **8:** 247–61.

32 Almonte M, Murillo R, Sánchez GI, et al. Nuevos paradigmas y desafíos en la prevención y control del cáncer de cuello uterino en América Latina. *Salud Publica Méx* 2010; **52:** 544–59.

33 WHO. WHO guidelines for screening and treatment of precancerous lesions for cervical cancer prevention. 2013. http://apps.who.int/iris/bitstream/10665/94830/1/9789241548694_eng.pdf (accessed Oct 24, 2014).

34 Flores Y, Bishai D, Lazcano E, et al. Improving cervical cancer screening in Mexico: results from the Morelos HPV Study. *Salud Publica Mex* 2003; **45:** S388–98.

35 Haines A, Sanders D, Lehmann U, et al. Achieving child survival goals: potential contribution of community health workers. *Lancet* 2007; **369:** 2121–31.