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. 2618 (86%) of 3049 women 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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with social innovations to ensure that the new technology is actually implemented among the population that needs it most. 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. However, community health work has been mainly oriented to maternal and child care and control of communicable diseases. The effectiveness of home promotion activities by community health workers to increase demand for cytological screening 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 Argentine province with one of the highest rates of mortality from cervical cancer nationally. In Jujuy, primary HPV testing was introduced in 2011 and, despite important efforts of the province to promote screening, estimated coverage is around 50%.

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.

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.6 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
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...
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. 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; 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; 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; 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; 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; 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; 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; 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; 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; 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; figure 2 summarises the results attained by community health workers.

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...
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 Argentinian 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
postal system instead of sending a letter inviting the woman for cytology, with low-to-moderate effects reported. In one study, 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. In a study from Chile, 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, 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, suggesting that community health workers succeeded in creating awareness but not in reducing barriers. In our study, the
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.

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%) and is similar to that reported in a Chilean study, 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. 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, 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. 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. 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. 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. In many settings, these workers have had a key role in the decline of health-related metrics such as maternal and child mortality.

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