FINAL REPORT

Study: Women's Acceptability in the Community of a Self-test to Detect Proteinuria to Prevent Pre-Eclampsia/Eclampsia (PE/E)—Component 4 of a Pilot Project
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This report covers:

- Background and Rationale
- Objectives
- Methods
- Sequence of Study Procedures
- Results
- Unanticipated Problem: Causes and Possible Solutions
- Conclusions
- Appendix A: Technical Description of Device

BACKGROUND AND STUDY RATIONALE

To reduce maternal mortality related to pre-eclampsia/eclampsia, a simple, low cost, non-invasive diagnostic test is needed to be widely available in low resource and often rural settings of developing countries. In these settings, many women are often not tested during pregnancy for elevated proteinuria, because they are not able to make it to a health facility. Our new screening test for proteinuria was designed to be prepared by the existing community health agent or volunteer; the health volunteer handles the pen and prepares the test paper and distributes the test paper to the pregnant woman, who then uses the self-test at home.

In the prior phase of testing our proteinuria screening test, the formulation of the proteinuria reagent and the delivery platform in the pen was finalized. In the prior phase, the proteinuria screening test was validated in an antenatal clinic population. The sensitivity, specific, positive predictive value and the negative predictive value was determined to be adequate and suitable for further field testing in the community. In interviews, ANC clients showed high interest in taking the self-test. Therefore, in this phase of the testing of the proteinuria pen platform, we embarked on a community acceptability study.

OBJECTIVES

In the community field study, the specific objectives were to determine the acceptability and feasibility of pregnant women in the community to perform the proteinuria screening self-test and to interpret the color of their test a) in the presence of the existing female community health volunteers (FCHVs) and b) on their own at home (unassisted) 4 weeks later. The hypotheses were that at least 80% of pregnant women visited by FCHV during initial visit about the new self-test would agree to do the new self-test during that visit; and at least 60% would perform the new self-test at home on their own four weeks later and take appropriate action on result.

METHODS

The study design was a descriptive, cross-sectional pilot study of acceptability and feasibility of a proteinuria screening test, using both quantitative and qualitative methods.

Description of the Proteinuria Screening Test and Platform

For a technical description of the proteinuria screening test, please see the description from the Research Plan, in Appendix A.

FCHVs received the proteinuria screening pen with reagent and test strips in Ziplocs, and educational materials in a folder. Jhpiego in collaboration with the MOH asked the FCHV to offer the counseling and self-test to the woman as part of her routine work in the community, during the period of the study.

Educational Messages. The study created educational materials for the FCHV and for the pregnant woman. Pictorially-based *IEC materials for the FCHV* covered: overview of danger signs of the PE/E, the purpose of the new screening test, how to prepare the test strips and pack in Ziploc for each woman and store it in dry place, how to present/discuss the screening to women, how to interpret the colors, the need to remind women to do the self-test again in 4 weeks' time, and how to record data on the study forms. We also emphasized with FCHV the need to strongly urge pregnant women to seek routine ANC. Pictorially-based *IEC materials for the pregnant women* covered: overview of danger signs of the PE/E, the purpose of the new screening test, how to do the self-test by voiding urine on the designated spot on the test strip, how to read the color result for a negative result and positive result, the name and location of the nearest referral clinic in case the test is positive, the reminder to do again in 4 weeks' time, and the need to use routine antenatal care.

Description of the Data Collection

Three types of data were going to be collected. The first was the FCHV Data Collection Form at First Visit, a short pictorial data collection tool that had several questions with dichotomous responses. At this visit, the FCHV was to assign the woman a unique ID number, and record whether the pregnant woman did the self-test and report the color (yellow or "other than yellow"). For women whose test result was "other than yellow", the FCHV was to confirm that she counseled the woman to go to the referral site for further testing, and record whether the woman agreed to do the self-test in 4 weeks' time. On this data collection tool was also a check on the woman's knowledge of what the colors meant: there were five pictures of colors on the spectrum from yellow to green/blue and the woman was to note whether each one was positive or negative.

Two qualitative data collection methods were planned for a second time point, approximately 5 weeks after the first visit. This included a semi-structured Interview of the pregnant woman which was to be conducted by trained interviewer accompanied by the FCHV; and a focus group guide with FCHVs as participants, which was to be conducted by study staff.

A fourth data collection form was developed prior to the start of the study: a register that would be kept at the referral health facility. On this register, providers noted the study participants with a positive result at home who self-referred and arrived at the referral site. On this form, the participant id, the result of a routine Dipstick result and blood pressure screening were recorded.

Jhpiego employed a field supervisor for the study who was in frequent communication with the Village Health Worker and the In-charge of the health post to which the FCHV is assigned, as well as Jhpiego staff at headquarters. Jhpiego staff made weekly trips to the field sites.

Preparation

Referral site: Mangalbare Primary Health Care Center (PHC), (the PHC where prior phase was conducted) received a training session with all key providers to ensure the standard of care for patients with PE/E is in accordance with national guidelines. Mangalbare PHC offers treatment to PE/E cases free of charge. It is a Basic Emergency Obstetric Care (BEmOC) facility, and refers complicated cases to Koshi Zonal Hospital and BPK Institute of Health Sciences.

Training of FCHVs. In each of the three VDCs, Jhpiego arranged for meetings with health authorities and invited the FCHVS to attend the training on the study intervention and data collection tools. The training covered PE/E, and how to do the self-test, prepare and pack self-test strips, how to educate pregnant women using pictorial materials on PE/E, how to do self-test, how to use educate women on action to be taken and how to record data. We emphasized to FCHVs the need to strongly encourage all pregnant women to use antenatal care.

IRB Approval. The study was approved by the Institutional Review Board of the Johns Hopkins School of Public Health and the Nepal Health Research Council.

Contact with pregnant women in the community

First visit. At the woman's house, the FCHV made contact with the pregnant women as she normally would do. The FCHV explained the study to each woman and obtained informed consent. The FCHV educated the woman on PE/E, how to use the new self-test, how to distinguish between the result of yellow for negative and "other than yellow" for positive, and what to do for follow-up. Women were asked to go to the toilet area and void on a test strip paper. When she returned, she was asked the color and what it meant. The FCHV recorded the results, provided more counseling, and left behind additional test strip papers. Women were asked to repeat the test 4 weeks later.

Second visit. About 5-6 weeks after the first visit to the pregnant woman, it was planned that a trained interviewer would accompany the FCHV to see the pregnant woman. The interviewer would ask if the woman did the new self-test on her own at home, and record what was the test result and action taken as reported by the woman. If a woman reported that the self-test was positive and the woman had not yet reached the referral site, the interviewer and FCHV would strongly encourage her to seek care at Mangalbare PHC and offer to accompany her. Women who did the self-test were planned to be interviewed about the experience.

SEQUENCE OF STUDY PROCEDURES

At the start of the data collection process, when results starting coming in, we noticed a high positive rate on the self-test. The high positive rate was approximately 60% to 70% in the beginning. The sequence of events was as follows.

- Training of Female Community Health Volunteer (FCHVs): October 12-14, 2011
- Refresher training of FCHVs after IRB approvals received: October 31
- Start of the Enrollment of Participants: November 1
- Initial Discussion between Baltimore and Field about High Positive Rate: November 3
- Problem Discovered/Confirmed and Participant Enrollment Was Suspended: November 7
- Investigations in Lab and Field began: November 7

- Decision not to continue the study/Study officially terminated (test strips and pens retrieved from FCHVs and women): mid-December.
- Engineering/lab work to re-iterate design of screening test: November 2011 to June 2012

RESULTS

Participants

FCHVs. In each of three participating Village Development Committees (VDC) in Morang District, nine female community health volunteers (FCHVs) were trained and offered the self-test, or **27 FCHVs** total.

Pregnant women. FCHVs recruited pregnant women known to them in their respective VDCs. All women who were recruited to the study consented and performed the self-test (study staff were not aware of any refusals). This high rate of acceptance is believed to be due to the long presence and high standing of the FCHVs in the communities. Overall, prior to the study being suspended, **388 pregnant women** were recruited by the FCHVs and carried out the self-test: 131 in Pathari, 93 in Rajgat, and 164 in Sanischere.

Screening Test Results

Overall, the percent positive on the self-test as determined by pregnant woman and FCHV during the FCHV visit to women's homes was **68%** (262/388). This was quite similar in the three VDCs: 67% (88/131) in Pathari, 69% (64/93) in Rajgat, and 67% (110/164) in Sanischere.

All positive women were referred to Mangalbare health facility by FCHVs. Of these, **58%** (152/262) arrived at the Mangalbare. This figure varied somewhat by VDC: 66% in Pathari, 47% in Rajgat, and 58% in Sanischere. The variation may have been due to geographic distance. Overall, several factors may explain why the percent of women testing positive on the self-test and visiting Mangalbare was not higher: it was harvest time, women may have gone to other health facilities, and since women were not sick, they may not have felt the need to go to the health facility even after strong encouragement.

Dipstick Results at Mangalbare Health Facility

Women carrying the referral card and arriving at Mangalbare PHC were seen quickly in a designated room for further diagnostic testing. Of the women who arrived at the health facility for further testing (n=152, **38%** were Nil on Dipstick, **53%** were Trace, and only **10%** (14 women) were confirmed with elevated protein (6% were 1+, 3% were 2+, <1% were 3+). Blood pressure was checked on all the women using the standard auscultatory method. Only one woman who was 3+ on dipstick also had high blood pressure; all others had normal blood pressure. It was believed that blood pressure equipment accuracy was less than ideal.

Screening Self-test One Month Later

Due to the unanticipated problem with the screening test, all test strips were retrieved from women. Allowing women to perform the self-test one month later on their own was thus not possible. This objective will need to be assessed in a future study.

Anecdotal Qualitative Information

Although we did not have the chance to do in-depth and systematic qualitative data collection with pregnant women at time2, study staff did gather debriefing information from the FCHVs when the study was suspended. FCHVs reported that, in general, pregnant women were excited about the screening test, and learned the importance of testing their urine in pregnancy. Some pregnant women themselves

visited the FCHV to request the screening test, before the FCHV had arrived at their homes. Some mothers-in-law also sought out the screening test for their daughters-in-law from the FCHV. FCHVs were disappointed that some women did not get a chance to be self-tested.

UNANTICIPATED PROBLEM

In this community acceptability study of the proteinuria screening self-test, a higher-than-expected positive rate was found. Once this became clear, we began investigations in the lab and collected reports from the field. We believe that there are several reasons for this unanticipated result, related to end-user related and technology factors:

End-user related factors

a. *Small spot size* of reagent administered from the pen onto the test strip. The test strips in this part of the study were by design prepared by frontline community health workers whereas in the prior ANC clinic validation study, the test strips were prepared by assistant nurse midwives. We found that while strips prepared during community health worker training had correct reagent spot size, many of the actual test strips prepared by community health worker had smaller spot size than was expected, and were smaller than was prepared in the previous nurse made clinic-based validation study. The small spot size appears to accentuate the "wash out" effect. (This means that the pH of the urine on the strip will cause color change regardless of protein presence.)
    - *Solution*: The solution we are working on now and for a future study would be to have a reference, such as a penny coin during training to ensure that the spot size is consistently sufficient. Another alternative we are exploring is a preprinted spot size marked on the strip.

b. *Crescents*. We discovered that community health workers as well as clients were labeling color changes on the periphery of the reagent spot (crescents of color change) as positive even when the rest of the reagent spot had not changed color. We believe that the appearance of "crescents" at the periphery of the spot is another manifestation of wash out effect, as the amount and concentration of reagent at the most peripheral parts of spot would be lower if sufficient reagent was not administered in creating the spot.
    - *Solution:* The solution we are working on now in the lab is to ensure consistent and uniform quantity of reagent delivery by the pen so that it achieves both a suitable size spot, as well as a spot on which the periphery has sufficient reagent concentration. An alternative user-based solution is emphasize during training that crescents are not positive, and a positive result is only to be recorded when there is uniform color change as is depicted in our current training materials.

c. *Preparation of strips.* We know from past studies that regular paper is not suitable for use as test strips because commercial paper, newspapers etc. contain acids which interfere with the test. This is why we used filter paper strips, which do not contain acids. We learned from field reports that the surface on which strips are being made by community health worker s is inconsistent and some prepared strips that were returned tested positive in the lab even with negative known samples of experimental urine.
    - Solution: In future studies, we will be providing clearer instructions to users to prepare strips on a plastic sheet provided for that purpose.

Technology issues:

d. *Stability of reagent*. We have been reexamining the stability of the reagent formulation once it is in the pen, as well as when it is on strips. We noted that some strips that had been stored in zip lock bags by community health workers in the field had much lighter reagent spots than others. One of the chemical agents used in the reagent (Tetrabromophenol Blue) is quite sensitive to light.

e. *"Pen" Platform*. It was discovered in further lab testing that the pen was made of nylon, a permeable substance that had absorbed some of the reagent. This may have altered the concentration of the reagent liquid and may have contributed to some evaporation.
    - Solution: We have submitted our reagent to an independent reference laboratory (Anderson Materials Evaluation, Inc. of Columbia, MD) to examine for stability and are exploring alternatives to the light sensitive reagent.
    - We are also exploring if storage of the reagent strips in a dark container fixes this problem. Conventional strips need to be stored in a light and moisture sealed container.
    - We are investigating alternate pen containers.

CONCLUSIONS

- The community study was well received by local health authorities in Nepal, the facility in-charges, and the FCHVs. Women in the community were also enthusiastic about the ability to self-test for proteinuria.
- The existing FCHV program platform in Nepal was highly effective at reaching hundreds of pregnant women in a short amount of time.
- Pregnant women performed the self-test once they received from FCHVs orientation and education.
- A high positive rate on the screening test was encountered. In the health facility, further diagnostic testing showed that women were mostly "trace" and "nil" on dipstick. Several women with high proteinuria were detected.
- Once we learned of the high positive rate, we performed investigations in the field for user issues and in the laboratory.
- The community study was suspended due to the unanticipated problem. Local partners were kept informed about the issues.
- Currently, in 2012, our engineers with advising from external engineers are exploring a number of solutions to the problems encountered with the pens, reagent, and strips. We expect to have manufactured prototypes prior to future field testing.

APPENDIX A. Technical Description of the Proteinuria Screening Test [Section 11b of the Research Plan - Medical Devices]

The device does not have an IDE. The device is Non-Significant Risk (NSR). Technical information about the device is as follows:

The pens were produced in JHU Lab (101 Clark Hall). The pen is a standard correction pen such as the BIC "White-Out" brand correction pen or the Liquid Paper brand correction pen. The basic design is that of a ball-tip with the body created using a soft, squeezable plastic (most likely polypropylene)[1]. Jhpiego purchased the correction pens, took the pens through a thorough cleaning process. Then pens were rinsed and let to sit overnight in mineral spirits (a chemical similar to paint thinner which removes the correction fluid). This process is repeated several times and then is repeated several more times with water to ensure the pens are clean of the mineral spirits. The pens were labeled to our specifications and filled with our protein reagent (the caps of the pens screw on and off).

The protein reagent consists of a color-changing dye (tetrabromophenol blue, a pH indicator) and a citric acid buffer (composed of sodium citrate and citric acid) dissolved in a solvent composed of water and isopropyl alcohol. The protein reagent is the <u>same used in commercial urine dipsticks</u> (with slight modifications to the concentrations of the components). It screens for albumin.

The reagent had been shown to have a shelf-life of at least 1.5 years at room temperature and we are conducting studies to examine this shelf life at higher temperatures which will be experienced in developing countries. Prior to this study, we did tests of the reagent applied to paper after six months and it was as stable as the reagent in a solution state. The literature also supported this finding.

The individual chemicals have the following HMIS hazard classifications (derived from their individual Material Safety Data Sheets)

HMIS hazard classifications

Component	Health	Flammability	Physical
Water	0	0	0
Isopropyl Alcohol	2	3	0
Citric Acid	2	0	0
Sodium Citrate	0	0	0
Tetrabromophenol Blue (dye)	0	0	0

Notes:
0 corresponds to minimal to no hazard
2 Health Hazard corresponds to Moderate Hazard (temporary or minor injury could occur)
3 Flammability hazard corresponds to Serious Hazard (materials flammable under normal temperature conditions). Note: the solvent contains twice as much water as isopropyl alcohol which should significantly reduce its flammability potential; however, this has not been directly studied in our lab.

[1] It was later noted that the pen material was nylon, an absorbable material.