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Correspondence

Human papillomavirus screening for low and middle-income countries

Worldwide, more than 85% of cervical cancer deaths occur in low and middle-income countries (LMICs) (Ferlay et al., 2013). We are concerned by Mark Schiffman's claim that "cervical cytology, which must be frequently repeated to achieve sufficient sensitivity, has failed to extend beyond high-resource environments despite many decades of Public Health effort." (Schiffman, 2017) Schiffman's claim overlooks the example of cervical cytology screening in Vietnam, (Suba et al., 2001; Suba et al., 2012) which Schiffman acknowledged to be a success in 2011 (Suba et al., 2011). Schiffman's claim that cervical cytology screening has encountered only failure in LMICs is therefore inaccurate, yet exemplifies inaccurate statements from other international experts that undermine political support for cervical cytology screening in LMICs. For example, since at least 2001, international experts with the Alliance for Cervical Cancer Prevention have stated that they are "loath" to recommend the introduction of cervical cytology screening to LMICs, (Suba et al., 2012) and have persisted in reiterating false claims that cervical cytology screening is not feasible in LMICs (Tsu and Jeronimo, 2016).

In 2011, Schiffman also acknowledged that "no clinically validated [human papillomavirus (HPV)] test is commercially available that is inexpensive enough to allow widespread implementation in LMICs." (Suba et al., 2011) We ask Schiffman to state whether there is, currently, a clinically validated HPV test that is inexpensive enough to allow widespread implementation in LMICs. If such an HPV test is available, we ask Schiffman to specify its manufacturer and its price. If no such HPV test is currently available, then recommendations to implement HPV screening in LMICs remain unrealistic. Moreover, given current opposition from international experts to implementing cytology screening in LMICs, visual screening methods become, by default, the only feasible screening methods for LMICs empowered by the political support of recommendations from international experts. Even in the hands of international experts, visual screening methods have proven problematic (Suba et al., 2017).

In LMICs, cytology, in addition to its traditional role as a primary screening test, will also be useful for screening younger women in future HPV-based screening programs and for triage of women with positive HPV primary screening tests (Suba et al., 2012). We ask Schiffman to acknowledge that cytology is a feasible and highly appropriate screening method for LMICs during the technological transition to HPV screening. In the absence of such positive recommendations from international experts, the technological transition toward HPV screening in LMICs is likely to remain highly inefficient.

Conflicts of interest

None.

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Eric J. Suba
Kaiser Permanente Medical Center, San Francisco, CA, United States
Corresponding author.
E-mail address: eric.suba@kp.org.

Matthew A. Zarka
Mayo Clinic, Scottsdale, AZ, United States

Stephen S. Raab
University of Mississippi Medical Center, Jackson, MS, United States

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In response to: Human papillomavirus screening for low and middle-income countries

I thank Dr. Suba and colleagues (Suba et al., 2017) for their comments on my editorial (Schiffman, 2017), which supported the increasing use of human papillomavirus (HPV) testing for cervical screening. They endorse greater use of cytology-based screening ("Pap tests") in low- and middle-income countries (LMICs), and question the availability of HPV tests for low-income settings.

While the editorial concentrated on the advantages of HPV testing, I did *not* claim (and I do not believe) that cervical cytology "has encountered only failure in LMICs". Rather, I observed that, many decades after the successful introduction of cervical cytology in high-resource countries, most women in LMICs remain unscreened or under-screened. I expressed my personal view that HPV testing has greater promise than cytology for future widespread screening globally, particularly in concert with efforts to increase HPV vaccine uptake and impact.

The main reasons are the following. In general, HPV testing is more reproducible and less subjective than cytology (Castle et al., 2004; Stoler and Schiffman, 2001), and it can be automated. The feasibility of using self-sampled cervicovaginal specimens for HPV testing permits new outreach strategies (Cuzick et al., 2012). Also, because of its greater clinical sensitivity, HPV testing better increases long-term negative predictive value (reassurance against getting cervical cancer) permitting fewer rounds of screening (Gage et al., 2014). This could be a critical advantage in LMICs because cervical screening competes with many other health priorities for limited public health resources. The lifetime risk of death or morbidity from cervical cancer is less than a few percent, i.e., the great majority of women in any LMIC population do not benefit (Day, 1992) from either HPV vaccination or cervical screening. Therefore, to make screening for cervical cancer a legitimate priority, restricting the lifetime number of visits (and vaccine doses) is important.

Moreover, it is firmly established, I believe, that gradual uptake of vaccination will worsen the predictive value of cytology screening, further favoring a switch to HPV tests that distinguish the vaccine-targeted types from the remaining high-risk types (Franco et al., 2009). Positive predictive value of cytology will inevitably fall as vaccination reduces the numbers of screening targets (precancer) much more than it reduces the equivocal/minimal abnormalities that make up the great majority of non-normal cytologic results.

While I am hopeful about the role of HPV testing in LMICs, I recognize the concerns raised by Dr. Suba and colleagues. They question HPV test availability and affordability and, as of this moment, I think they are right. Establishing an adequate set of suitable tests will take a few more years (n.b., establishing a new high quality cytology effort in a place where it does not currently exist would take a few years, as well). Currently available and soon-to-be-available HPV test options vary by economic level and, not surprisingly, finding good options for low resource settings is the most challenging task. In defining what tests are available, I believe that it is fair to consider HPV tests that are "almost validated" as well as those on the market today. And, in considering affordability, prices are not fixed in HPV diagnostics sales, as assay prices tend to decline dramatically with volume. Although I am not privy to how inexpensive these tests could become if widely used, I would estimate informally based on experiences to date that a price of considerably less than $10 per test is at the very upper end of affordable for low-middle or low resource regions, and <$5 per test (hopefully even lower) is a good target.

So, which tests are available and affordable? Experience with Qiagen careHPV™ has suggested that it is accurate, reproducible, and can be taught easily in low-resource settings. Based on our research experience (Gage et al., 2012), I personally see it as a proof-of-principle technology rather than a scalable "solution". To cite another available inexpensive *commercial* assay, we have validated H13 (Hybribio, Hong Kong) and are involved with projects using it in West Africa and Latin America (Fokom Domgue et al., n.d.). Having multiple competing tests will be important, and again I agree that we need considerably more.

There are numerous research efforts underway to produce low-cost, simple yet accurate HPV tests in the price range just mentioned, which could be used at least in low-middle and high-middle resource settings. At the U.S. National Cancer Institute, we have developed and validated an "open source" next-generation HPV typing assay for high-volume epidemiologic and public health use, and will begin to release the protocol freely to interested groups starting later this year (Wagner, 2017). This next-generation-sequencing based method would work most cost-effectively in dense population centers; its very high-throughput capacity would ultimately lead to low cost per screening but the establishment of the program would require a well-equipped laboratory with substantial initial capital investment (in the kind of facility that might be found in a large urban center in a middle-income country). Separately, we continue to work with several other (non-profit) groups dedicated to creation of very low-cost practical HPV tests for use in low-technology settings, with point-of-care potential a major objective.

While I agree with the need for more HPV tests, in my own view, the eventual availability of practical HPV tests is in plain sight. I am more concerned about the limitations imposed by two other issues affecting all cervical screening methods, i.e., making sure there are adequate methods and strategies for deciding which screen-positive women need treatment ("triage" which, to me, includes colposcopy) (Tota et al., 2017), and insuring that inexpensive, safe and effective treatments are available (WHO Guidelines Approved by the Guidelines Review Committee, 2013; Coleman et al., 2016).

With regard to triage, I personally agree with Dr. Suba and colleagues that cytology, where established, is an excellent triage method among HPV-positive women (Schiffman et al., 2016). It is worth noting that for the purpose of triage, automated cytology or automated dual-stain technologies can already match the performance of conventionally interpreted cytology (Schiffman et al., 2017). Affordability will be a

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crucial factor in determining whether and where cervical screening and triage can/should be entirely automated.

A reasonable concern in transitioning from cytology to HPV testing as the primary cervical screening method is a loss of widespread local competence and control, and reliance on proprietary technology whose price might exceed local resources. In our own efforts, we are striving to encourage a host of competing HPV testing and triage options, focused on public health use, that would serve to keep costs low and availability high.

I believe that most of my colleagues that have spent careers working on cervical cancer prevention are eager to move beyond our present state of stagnant coverage using cytology, are very reluctant to promote an inaccurate method like visual inspection with acetic acid, and are impatiently validating very promising but not fully available HPV-based methods and strategies. We want full-blown dissemination and implementation, the sooner the better. I believe that multiple HPV tests will be ready within a very few years. Our shared goal and responsibility is to see cervical cancer incidence and mortality decline as the result of widely accessible vaccination and screening, regardless of which specific technologies serve the purpose.

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Mark Schiffman

Division of Cancer Epidemiology and Genetics, National Cancer Institute, 9609 Medical Center Drive, Rockville, MD 20850, USA

E-mail address: schiffmm@mail.nih.gov.

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