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WHO should adjust its global strategy for cervical cancer prevention

Eric J Suba ,[1,2] Amber D Donnelly,[3] Dang Van Duong,[4] Ludwing Erick Gonzalez Mena,[5] Greta S Neethling,[6] Nguyen Van Thai[7]

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[1]Global Cervical Cancer Prevention Project, San Francisco, California, USA
[2]Visiting Scholar, Tuskegee University National Center for Bioethics in Research and Health Care, Tuskegee, Alabama, USA
[3]University of Nebraska Medical Center, Omaha, Nebraska, USA
[4]Institute of Cancer Research Cooperation and Community Health Development, Hue City, Viet Nam
[5]Institute for Epidemiological Diagnosis and Reference, Ciudad de Mexico, Mexico
[6]Stellenbosch University Faculty of Medicine and Health Sciences, Cape Town, Western Cape, South Africa
[7]Ho Chi Minh City Oncology Hospital, Ho Chi Minh City, Viet Nam

Correspondence to
Dr Eric J Suba;
eric.suba@gmail.com

INTRODUCTION

Today, 90% of the world's cervical cancer deaths occur among women in low-income and middle-income countries (LMICs). Cervical screening (using visual tests, Pap smears, or human papillomavirus (HPV) tests) and HPV vaccination both prevent cervical cancer. Cervical screening prevents cervical cancer by detecting and eradicating precancerous cervical lesions before they progress to cancers. HPV vaccination prevents cervical cancer by preventing infection of the cervix by carcinogenic types of HPV.

In 2020, the WHO launched a 'Global Strategy to Accelerate the Elimination of Cervical Cancer as a Public Health Problem',[1] which 'states that all countries should adopt HPV-based cervical cancer screening as soon as it is feasible',[2] and advocates that, by 2030, 90% of the world's girls should be vaccinated against HPV, 70% of the world's women should be screened using HPV tests and 90% of women with cervical disease should receive appropriate follow-up care.[1] WHO provides uncertain guidance for LMICs, where HPV screening and vaccination are not widely affordable.

The goal of global cervical cancer prevention efforts should be to save as many lives as quickly as possible.[3] We examine the relationship between that goal and the WHO's Global Strategy.

SUMMARY BOX

⇒ The goal of global cervical cancer prevention efforts should be to save as many lives as quickly as possible. In 2020, the WHO launched a 'Global Strategy to Accelerate the Elimination of Cervical Cancer as a Public Health Problem', which advocates that, by 2030, 90% of the world's girls should be vaccinated against human papillomavirus (HPV), 70% of the world's women should be screened using HPV tests and 90% of women with cervical disease should receive appropriate follow-up care.

⇒ WHO provides uncertain guidance for low-income and middle-income countries (LMICs), where 90% of the world's cervical cancer deaths occur and where HPV screening and HPV vaccination are not widely affordable. Because it does not prevent cervical cancer among women who have previously gotten HPV, HPV vaccination does not offer protection from cervical cancer for most women in LMICs. Quality management for visual screening is problematic. In 2005, the Head of Cancer Screening at the WHO International Agency for Research on Cancer emphasised 'Our results clearly show that good-quality Pap smear screening can be implemented even in a rural setting of a developing country with reasonable investment, while HPV screening does not give any better [disease detection], despite the higher investments'.

⇒ WHO should commit to saving as many lives as quickly as possible and advocate for good-quality Pap smear screening in LMICs until better-quality HPV screening becomes widely affordable in LMICs.

⇒ Iatrogenic delays to Pap screening in LMICs have contributed to at least 500 000 preventable cervical cancer deaths.

HPV VACCINATION

Because it does not prevent cervical cancer among women who have previously gotten HPV, HPV vaccination does not offer protection from cervical cancer for most women in LMICs. The US Preventive Services Task Force has determined that Pap screening reduces cervical cancer rates by 60%–90% within 3 years of introduction, and that those reductions in suffering and death are 'consistent and dramatic across populations'.[4] Because of the decades-long time lag between HPV infection and the development of cancer, universal HPV vaccination of girls, if implemented without cervical screening, will have minimal impact on cervical cancer rates for decades after introduction.[5]

UNICEF advises that HPV vaccine pricing levels remain a significant concern for sustainable financing in LMICs.[6] Some suggest it may be 'necessary to strategically but tragically

'lose' a generation' and forgo establishing cervical screening programmes in LMICs in order to concentrate resources on HPV vaccination to prevent cancer in future generations.[7] Given uncertainties regarding HPV vaccine affordability,[6] several generations of women may be lost if such a strategy is adopted. In 2022, Nepal cancelled the roll-out of its national HPV vaccination programme due to insufficient funds.[8]

CERVICAL SCREENING

Pap screening has been successful in high-income countries but less successful in LMICs.[9] Past failures of Pap screening in LMICs have generated interest in visual screening and HPV screening for LMICs.[9] It is uncertain whether visual screening or HPV screening will succeed where Pap screening has failed.[10] Root cause analysis shows that critical real-world obstacles to successful cervical cancer prevention in LMICs involve human factors far more than technology, and are attributable to lapses of political will and quality management to which all preventive interventions are vulnerable.[10] Comparisons of different screening technologies are inseparable from comparisons of different quality management practices and their associated human factors.

To save as many lives as quickly possible, cervical screening must satisfy three requirements: all women in at-risk demographic groups must receive cervical screening tests as soon as possible; all screening test results must be accurate and all women with abnormal screening test results must receive appropriate follow-up care. We compare the abilities of visual screening, Pap screening and HPV screening to satisfy those three requirements in LMICs.

All women in at-risk demographic groups must receive cervical screening tests as soon as possible

Low coverage rates of women in at-risk demographic groups have been major causes for failures of Pap screening in LMICs.[9 10] Political will for expanding public health services in LMICs is limited, and coverage of at-risk demographic groups is more readily achieved as costs for cervical screening tests decrease.[10] Visual screening tests are inexpensive, but quality management is problematic. Disease-detection rates for visual screening were lower than disease-detection rates for no screening in the hands of visual screening experts funded by the US National Cancer Institute (NCI).[11]

Salary, supply and equipment costs for HPV tests and Pap smears are summarised in tables 1 and 2, respectively. Data in table 1 include prices negotiated through novel procurement strategies by the Clinton Health Access Initiative.[12] The Pap smear is one of the most inexpensive of all medical laboratory tests. In the USA, where cytotechnologists earn ~US$90 000/year and pathologists earn ~US$5 00 000/year, data presented in table 2 imply that costs of salaries, supplies and equipment for a Pap smear total ~US$10. The US Centres for Medicare and Medicaid Services reimburses US$15.15 for a Pap smear,[13] an amount that reimburses overhead costs (eg, laboratory space, administration and information systems) not included in either tables 1 and 2.

For decades, HPV screening has been advocated for LMICs. WHO advises that HPV self-sampling, which eliminates requirements for pelvic examinations, may contribute to acceptability and access to screening services.[1] However, HPV experts who advocate HPV screening for LMICs acknowledge that HPV screening, whether clinician-collected or self-sampled, remains unaffordable for routine implementation in LMICs.[14] The history of the Qiagen careHPV test is cautionary. Since 2004, with support from the Bill & Melinda Gates Foundation (BMGF), the careHPV test has been promoted as an HPV test affordable for LMICs. Supply costs for the careHPV test currently total at least US$10. (table 1) Data presented in tables 1 and 2 suggest that LMIC healthcare workers would receive US-level salaries to implement Pap smear screening for the same investment required to implement HPV screening with US$10 careHPV tests. In Myanmar, supply costs for each careHPV test are more than US$47 because the local distributor 'added a larger profit than permitted',[15] illustrating challenges involved in negotiating stable prices for proprietary technology.

In 2013, WHO policy guidelines stated 'In LMICs, because of the high cost of setting up Pap screening programmes, coverage of screening is very low and alternative screening methods are needed',[16] because 'this traditional screening method requires highly trained human resources and a substantial amount of laboratory equipment'.[16] The 2013 WHO assessment had been refuted in 2005, when the Head of Cancer Screening at the WHO International Agency for Research on Cancer (WHO/IARC), referring to a BMGF-funded study conducted in Osmanabad, India, emphasised 'Our results clearly show that good-quality Pap smear screening can be implemented even in a rural setting of a developing country with reasonable investment, while HPV screening does not give any better [disease detection], despite the higher investments'.[17] Data presented in tables 1 and 2 indicate that laboratory equipment costs for HPV tests exceed those for Pap smears. Technologists who analysed the 32 058 Pap smears collected in Osmanabad were trained for 3 months.[18]

All screening test results must be accurate

The most important performance characteristic of any cervical screening test is its biopsy-confirmed disease-detection rate, which is operator dependent and reliant on locality-specific quality management practices. Based largely on studies of HC2 HPV tests analysed in high-income countries with rigorous quality management practices, WHO/IARC determined that HPV tests yield 10%–20% higher disease detection rates but higher false-positive rates than Pap smears.[19] HC2 HPV tests collected from women in China,[20] Costa Rica[21] and Zimbabwe[22] and shipped to US reference laboratories for analysis demonstrated higher

Table 1 Salary, supply and equipment costs for HPV tests and collection devices (in 2020 US$) (adapted from Demke[12] and Qiagen[24])

Manufacturer	Assay	Pricing accessibility	Instrument prices	Instrument service contract prices	Proprietary reagent prices	Non-proprietary reagent and consumable prices (eg, microtitre plates, micropipettes, etc)	Sample collection device/sample collection medium prices	Medical technologist salaries
Abbot (USA)	RealTime High Risk HPV	22 sub-Saharan African countries*	$160 000	Not included	$5.69	Not included	$0.80	Not included
Hologic (USA)	Aptima HPV	50 Hologic Global Access Initiative Countries	$11.28 (instrument cost included in price per test)			Not included	$0.50	Not included
Roche (Switzerland)	Cobas 4/6/8800 HPV	84 Roche Global Access Programme Countries	$100 000–$600 000	Not included	$7.90	Not included	$2.00	Not included
Qiagen (the Netherlands)	careHPV	Global availability	$10 500	Not included	$4.95–$42†	Not included	$5.28	Not included
	Hybrid Capture 2 (HC2)	Global availability	Not included	Not included	$53	Not included	Not included	Not included
Cepheid (the USA)	Xpert HPV	145 eligible countries	$17 000	Not included	$14.90	Not included	$2.95	Not included

*Angola, Benin, Burkina Faso, Burundi, Cameroon, Chad, Congo, Democratic Republic of the Congo, Ethiopia, Guinea, Kenya, Liberia, Malawi, Mali, Mozambique, Nigeria, Rwanda, Senegal, South Sudan, Tanzania, Togo and Uganda. Other countries may be added on an ad hoc basis.
†The wide range in pricing for careHPV test supplies is explained in the text.
HPV, human papillomavirus.

Table 2 Salary, supply and equipment costs for Pap smears and collection devices (in 2020 US$) (adapted from Suba et al[35])

Category	Item	Cost per pap smear
Salaries	Cytotechnologist screening and interpretation of Pap smear	Cytotechnologist annual salary (in 2020 US$) ÷ 20 000*
	Pathologist interpretation of atypical Pap smear	Pathologist annual salary (in 2020 US$) ÷ 120 000†
Supplies	Modified wooden Ayre spatula	0.06
	Alcohol fixative	0.06
	Pap smear stains	0.07
	Cover slip	0.06
	25 mm × 75 mm glass slide	0.06
	Mounting medium	0.03
Equipment	Microscope	0.04‡

*Assumes a cytotechnologist screens and interprets 20 000 Pap smears per year without any other work responsibilities.
†Assumes 10% of all Pap smears screened by cytotechnologists are atypical and referred to pathologists who spend an average of 10 min interpreting each atypical smear and work 40 hours per week for 50 weeks each year.
‡Assumes a new microscope costs $8000 and is used only to screen and interpret 20 000 Pap smears per year for 10 years.

disease-detection rates but higher false-positive rates than Pap smears analysed in LMIC laboratories.

Two BMGF-funded studies illustrate the importance of using locality-specific disease-detection rate measurements, rather than measurements pooled from other settings, to inform transitions to HPV screening in LMICs. In the BMGF-funded Osmanabad study, which compared HC2 HPV tests analysed in India to Pap smears analysed in India, Pap smears outperformed HC2 HPV tests by demonstrating equivalent disease-detection rates with lower false-positive rates. In a separate BMGF-funded study, which compared Pap smears analysed in Mumbai to HC2 HPV tests analysed in Mumbai, Pap smears again demonstrated equivalent disease-detection rates with lower false-positive rates than HC2 HPV tests.[23] Quality management practices used to assure good-quality Pap smears in India have not been detailed. Based on locality-specific measurements, transitioning from Pap smears to HC2 HPV tests in India would not be desirable because the transition would make cervical screening less accurate but more expensive.

Supplies for each HC2 HPV test are currently priced at US$53 (table 1).[24] Quality management for HPV tests that become widely affordable in LMICs may prove more challenging than that for HC2. WHO/IARC advises 'increased competition resulting in diminishing market share and reductions in the cost of testing might lead HPV test manufacturers to relax their standards of quality. Such a scenario could prove disastrous in many respects, since there are theoretically many more variables that can affect the performance of HPV testing than there are for Pap screening'.[19] Today, more than 90% of HPV tests in the global market have not been evaluated in line with consensus requirements that ensure safe use.[25]

All women with abnormal screening test results must receive appropriate follow-up care

Without appropriate follow-up care, cervical screening is ineffective regardless the screening test used. Good follow-up of women with abnormal Pap smear results has been demonstrated in Cameroon (100% follow-up),[26] China (95% follow-up),[27] Costa Rica (97% follow-up),[21] and Zimbabwe (98% follow-up).[28] Quality management practices used to assure good follow-up in LMICs have not been detailed.

In South Africa, women with high-grade Pap smear results are usually lost to follow-up.[29] Accurate biopsy-confirmed disease-detection rate measurements are not feasible in settings with low follow-up biopsy rates. It is imprudent to advocate transitioning from Pap screening to HPV screening in settings with low follow-up rates, because such transitions may make screening programmes more expensive but no more effective.

Combining visual screening tests with immediate cryotherapy assures 100% follow-up rates but introduces a quality management paradox.[10] Visual screening experts emphasise that close monitoring of disease-detection rates is essential to maintain good standards of visual screening.[30] Visual screening, when combined with immediate cryotherapy, produces no tissue biopsies with which to measure disease-detection rates.[10] Current WHO guidelines recommend that visual screening programmes 'transition rapidly' away from visual screening 'because of the inherent challenges with quality assurance',[31] but do not suggest destinations for that transition in settings where HPV screening is unaffordable.

CONCLUSIONS

Because of quality management challenges inherent to visual screening, and because of uncertainties regarding the affordability and desirability of HPV screening and HPV vaccination in LMICs, Pap smear screening in LMICs is the strategy most likely to achieve the goal of saving as many lives as quickly as possible. Iatrogenic delays to Pap screening in LMICs contribute to preventable cervical cancer deaths. From 1997 to 2015, US NCI funded a pointless study in Mumbai that contributed to at least 500 000 preventable cervical cancer deaths by delaying Pap screening throughout India for 18 years.[11 32]

In 1999, with an initial gift of US$50 million, the BMGF established the Alliance for Cervical Cancer Prevention on the central assumption that novel technologies, rather than Pap screening, are the most likely solution to the problem of cervical cancer in LMICs.[33] In 2000, the Head of Cancer Screening at WHO/IARC, an Alliance member

organisation, stated he would be 'loath' to recommend establishment of Pap screening services in high-risk communities with no cervical screening programmes in place.[34] Current WHO guidelines endorse Pap screening only for communities with Pap screening already in place.[31]

WHO should adjust its Global Strategy for cervical cancer prevention. WHO should accept the WHO/IARC determination that 'good-quality Pap smear screening can be implemented even in a rural setting of a developing country with reasonable investment'[17] and advocate for rapid, immediate expansions of good-quality Pap smear screening in LMICs. Quality management practices that assure good disease-detection rates and good rates of follow-up care for Pap screening in LMICs should be detailed and disseminated.

HPV screening may be integrated into pre-existing Pap screening infrastructure if locality-specific measurements indicate that HPV screening will increase disease-detection rates and increase coverage rates of at-risk demographic groups. After transitions to HPV screening, Pap smears will remain useful for primary screening of younger women and for management of women with positive HPV primary screening tests.[10]

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ORCID iD

Eric J Suba http://orcid.org/0000-0002-0053-3646

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