The investment case for cervical cancer elimination

Vivien Davis Tsu1,* | Ophira Ginsburg2

1PATH, Seattle, WA, USA
2Department of Population Health, NYU School of Medicine, Laura and Isaac Perlmutter Cancer Center at NYU Langone Medical Center, New York, NY, USA

*Correspondence
Vivien Davis Tsu, PATH, Seattle, WA, USA. Email: vtsu@path.org

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Abstract
We already know what causes cervical cancer, how to prevent it, and how to treat it, even in resource-constrained settings. Inequitable access to human papillomavirus vaccine for girls and screening and precancer treatment for women in low- and middle-income countries is unacceptable on ethical, social, and financial grounds. The burden of cervical cancer falls on the poor and extends beyond the narrow bounds of the family, affecting national economic development and community life, as family resources are drained and poverty tightens its grip. Proven solutions are available and the priorities for the next few years are clear, as shown by the papers in this Supplement. Sustained political commitment and strategic investments in cervical cancer prevention can not only save millions of lives over the next 10 years, but can also pave the way for the broader fight against all cancers.

KEYWORDS
Cervical cancer; Disease elimination; Low-income countries; Prevention

1 | INTRODUCTION

We already know what causes cervical cancer, how to prevent it, and how to treat it, even in resource-constrained settings. Yet, sadly, every two minutes a woman dies of this disease. The global divide in incidence and mortality for cervical cancer could hardly be more stark. The vast majority of women who develop and die of cervical cancer live in low- and middle-income countries (LMICs), where access to primary and secondary prevention—and care for women with invasive disease, including palliative care—remains profoundly limited. The problem fundamentally is social and economic inequality—the solution is, in large part, sustained political commitment.

If the current generation of young adolescent girls can be vaccinated against human papillomavirus (HPV), in 20–30 years as they reach the ages when precancerous lesions would normally appear and take hold, they can expect to be nearly free of the threat of cervical cancer. The good news about cross-protection against HPV types not included in the vaccine and herd immunity for those who missed being vaccinated1,2 and the recent licensing of a 9-valent vaccine that protects against 90% of the types causing cervical cancer suggests we may be closer to elimination of this disease than we dreamed possible 10 years ago when the vaccine was first introduced.3

Despite this exciting prospect and the hard work it will take to make widespread HPV vaccination a reality, we cannot forget the millions of adult women and older adolescent girls who were beyond the priority age for vaccination when it became available in their communities. These women deserve a chance to have the protection that screening and preventive treatment (for precancer) provides—the protection women in wealthy countries have benefitted from for decades. Arguments to rationalize this gross inequity of access in the past—the challenges of providing cytology, insufficient trained specialists, competing burdens of infectious disease and obstetric complications—can no longer be accepted. Without significantly increased screening and preventive treatment services, an estimated 19 million women will die from cervical cancer over the next 40 years.4

There is a backlog of more than 700 million women in low- and lower-middle-income countries who were 20–49 years old in 2015,5 who are or will reach screening age in the next decade who have not been vaccinated and for the most part have never been screened. The
papers in this Supplement highlight the progress that has been made in recent years and, more importantly, the opportunities that governments now have to apply proven clinical tools and health system approaches to redress this inequity.

This final paper in this International Journal of Gynecology and Obstetrics (IJGO) Supplement draws on the insights of the expert contributions of the preceding papers to construct a compelling case for urgent investment in cervical cancer prevention. Targeted investments that build on recent scientific advances and best practices can support and accelerate national efforts to scale-up nascent programs, and ensure essential services are established with sustainable strategies for disadvantaged women who have, for far too long, borne the heaviest portion of the burden of this preventable disease.

2 | THE BURDEN OF CERVICAL CANCER IS ON THE POOR

In 2012 there were 528,000 cases and 266,000 deaths from cervical cancer worldwide, a number of deaths not unlike that of women who died from complications of pregnancy and childbirth. Maternal mortality rates have greatly improved over the last 15 years, dropping from about 529,000 in 2000 to about 303,000 in 2015; this is believed to be due at least in part to efforts to meet the Millennium Development Goals. As with maternal mortality, the distribution of cervical cancer cases is highly skewed, with mortality rates in the Eastern Africa region (27.6 per 100,000: age standardized rate) that are 18 times higher than in regions with the lowest rates—Australia/New Zealand (1.5) and Western Europe (1.8). There are 38 countries where the most common cancer among women is cervical cancer, and most of those countries are in Sub-Saharan Africa. Women in these countries play significant roles in their families, communities, and society at large, as caregivers of children and the elderly, wage earners, and major food producers. The impact of serious illness and premature mortality extends far beyond the narrow bounds of the family, affecting national economic development as well as community life and draining family resources as poverty tightens its grip.

Many wealthy countries have seen cervical cancer incidence and mortality rates fall dramatically in the last two to three decades, particularly where effective population-based screening programs have been established. With the introduction of HPV vaccines and the continued delivery of screening services, these countries are already on the path to elimination of cervical cancer. There are others, however, where screening programs have been weak and changes in sexual lifestyles have increased exposure to HPV, as in Central Asia, or where high HIV rates have exacerbated HPV persistence and progression to cancer, resulting in rates that are unchanged or rising. If there is no substantial change in the incidence of cervical cancer, the overall number of women predicted to develop the disease each year is estimated to grow to 700,000 by 2030, the last year for achieving the Sustainable Development Goal target to reduce by one-third premature mortality from noncommunicable diseases (NCDs), including cancer, cardiovascular disease, diabetes, and chronic respiratory diseases. It is in LMICs where efforts will make the most difference.

3 | PROVEN SOLUTIONS ARE AVAILABLE

The licensure of three HPV vaccines and the growing body of evidence that they can be delivered to young adolescent girls in LMICs, building on existing platforms of national immunization programs, is one of the most exciting developments of the past decade. As noted in the paper by LaMontagne et al., the impact of the vaccine on immunological and disease endpoints has surpassed our expectations, including the benefits of herd immunity for the unvaccinated in communities where vaccine is widely but not universally provided. The safety of the vaccine, despite numerous unsubstantiated claims by vaccine opponents, continues to be judged highly satisfactory by national and global safety authorities after more than 200 million doses have been administered. The change in the dosing schedule from three to two doses (and possibly eventually one dose) has reduced vaccine and delivery costs and eased the burden on over-taxed health systems.

While improvements can always be made, there are now effective technologies for screening and precancer treatment that are feasible even in constrained health systems, and validated programmatic approaches that are supported by international guidelines. Research and program experience over the past 15 years has demonstrated both the strengths and weaknesses of visual inspection with acetic acid (VIA) for screening; with proper training and quality assurance, it is an affordable starting point that enables countries to launch screening programs and build the requisite elements of community education, precancer treatment capacity, and referral links to specialized care, including treatment for invasive cancer and palliative care. However, the moderate sensitivity and variability of VIA, the heavy burden on overworked healthcare providers, and the cultural issue of modesty have also been revealed as major barriers to scaling up high-quality national programs based on VIA. As noted by Ogilvie et al., HPV tests designed to minimize infrastructure demands offer the promise of higher sensitivity and reliability, allowing longer intervals between screening and greater disease reduction. Wherever sufficient resources permit it, the WHO recommends HPV testing as the preferred screening method. The ability to perform HPV testing with samples collected by women themselves is one of the biggest breakthroughs, with the potential to revolutionize screening by removing cultural barriers and reducing demands on health worker time.

Despite these advances in screening technology and delivery, they will have limited impact if screening is not followed by effective treatment where needed, embedded within programs with resource-appropriate management algorithms. Castle et al. point out the exciting advances in thermal coagulation (also known as cold coagulation), which is finding a niche in programs where cryotherapy has proven to be problematic to maintain, especially with the development of two devices designed especially for low-resource settings. Gaps in evidence on use in low-resource settings and recommended clinical guidelines should be filled in the next few years. Basu et al. note that
several basic management algorithms for handling screen-positive women have been developed, although evaluation of their use in routine programs is still needed and is a priority going forward.

Broader health system elements and community actions provide the essential underpinnings for clinical programs. Focused and systematic analyses of health information systems in recent years have identified feasible approaches for incorporating cervical cancer indicators into routine government data systems, whether paper-based or electronic; implementation of these approaches is now the urgent priority. Several countries and agencies have put into practice programs that integrate cervical cancer screening into existing health services, such as those for family planning and HIV/AIDS, while documenting potential benefits and remaining challenges. More such programmatic experiments are needed to identify facilitating factors and favorable environments for integration, and to learn how to ensure that established programs are not compromised and efficiencies are in fact captured. Raising awareness and engaging communities has a long way to go, although the introduction of HPV vaccines in demonstration projects in more than 20 LMICs in recent years has laid some groundwork by introducing information about the burden of cervical cancer and the possibility of preventing it. At least the key messages and appropriate terminology are now much better understood.

Scaling up all these activities to national programs with coverage reaching even the most marginalized populations is the ultimate goal, if we are to achieve elimination of cervical cancer. As Holme et al. report, there is both good news and bad news on this front. Where there were no effective national programs 10 years ago, we now have several countries forging ahead to expand and adapt pilot programs, even with their limited resources. Countries that had services in major urban areas are starting to expand to smaller provincial and district facilities and test potential outreach strategies. However, too many countries are struggling to map out feasible national strategies appropriate for their resources and to identify partners and donors who will help them get started. There was a longstanding belief that screening programs would not be successful unless they could achieve 80% coverage, but modeling has clearly shown that the impact is linear and that every incremental improvement in coverage has a payoff in disease reduction, although it may be somewhat less cost-effective until higher levels of coverage can be achieved. If implemented with careful planning, strategic and sustainable financing, robust monitoring and evaluation, and adequate population coverage, screening programs can reduce cervical cancer incidence and mortality substantially.

Table 1 draws on the papers in this Supplement to summarize highlights of the progress made in the past decade and remaining priorities. Addressing these priorities requires the attention of many different partners at national and global levels. Advocacy will be critical to this effort.

4 | THE RATIONALE FOR INCREASED INVESTMENT NOW

Campos et al. have calculated the cost of a basic program of vaccination, once-in-a-lifetime screening, and cancer treatment (at current levels) for 50 LMICs, rolled out over a 10-year period. To reach 160 million girls with two doses of vaccine and 170 million women with screening and treatment as needed would cost about US $3.2 billion. The program cost for each woman reached with screening averaged US $9, with costs lower in the low-income countries. What has not been calculated is the cost of inaction—the lives lost each year and the escalating health costs to the system of treating late-stage cancers, a cost that will climb as more women demand cancer treatment rather than accepting their fate.

With this targeted investment over the next 10 years, we could prevent 5.2 million cervical cancer cases, 3.7 million deaths, and 21.8 million disability-adjusted life years. By any measure, both vaccination and screening in this basic package are very cost-effective. If we continue to defer action—waiting for better technologies or for successive cohorts of vaccinated girls from this point onward to take care of the problem—we will be sacrificing the current generation of women and girls who did not benefit from HPV vaccines.

In addition to the girls and women who benefit directly, other investments already being made to strengthen health systems—such as upgrading health information systems, expanding the health labor force, and modernizing procurement capacities and supply chains—will have a bigger payoff if we use them wisely to address not only the traditional health issues but also previously unaddressed problems like cervical cancer, with high value for money spent.

Sustained political commitment and strategic investments in cervical cancer prevention can not only save millions of lives over the next 10 years but can also pave the way for the broader fight against all cancers. The smallpox eradication campaign in the 1960s and 1970s revealed the incredible potential that vaccines offer for battling epidemic infectious diseases and heralded the development of national immunization programs. In the same way, the successful control of cervical cancer—the first cancer for which we have effective strategies for both primary and secondary prevention applicable in lower-resource settings—could be the opening salvo in the battle against cancer globally, a fight that will be difficult to turn away from even in countries with the least resources. As Bill Foege, leader of the smallpox campaign, noted: "...we are always faced with making sufficient decisions based on insufficient information. If we had waited until all the answers were available, the work on smallpox eradication would never have started—selecting the target helped develop the appropriate tools and strategy." In the case of cervical cancer, many of the answers and tools are already available; consensus on the target is emerging—elimination of cervical cancer as a public health problem.

AUTHOR CONTRIBUTIONS

Both VT and OG developed the original concept. VT created the first draft. Both authors contributed suggestions and reviewed the final paper.

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| TABLE 1 | Overview of progress and priorities for cervical cancer prevention. |
|----------------------|---------------------------------------------------------------|
| **Recent progress** | **Near-term priorities** |
| **Primary prevention** | | |
| HPV vaccine advances and scaling up | • Gavi negotiated low vaccine price for eligible countries • PAHO negotiated low price for Americas • >20 LMICs have done demonstration projects, starting to move to national scale • Two-dose regimen approved • Nine-valent vaccine approved | • More countries move to national scale • Document viable models of delivery • Evaluate effectiveness of one-dose regimen • Countries use existing tools and knowledge for effective planning • Disseminate growing body of evidence on impact • Reach 30 million girls in LMICs |
| **Screening and precancer treatment** | | |
| Screening technologies | • Self-collecting specimens for HPV testing is culturally acceptable and greatly reduces burden on health system • VIA is useful starting place | • Establish quality assurance protocols for HPV testing • Learn from experience with current tests to prepare for better tests that are coming |
| Precancer treatment | • Recognition of role for thermal coagulation • Development of devices better suited to needs of LMICs | • Incorporate thermal coagulation into global and national guidelines • Standardize clinical practices and training for thermal coagulation |
| Management algorithms | • Initial guidance for managing screen-positive women is available, but mostly from models • Good evidence for screen and treat safety and effectiveness | • Establish evidence-based algorithms for general and HIV+ populations based on program experience • Match algorithms to resource levels |
| Scaling up screening | • Several countries have successfully expanded, but it has taken time and is still not national • Countries learning from others in their regions • National political support for scaling up is growing—e.g., First Ladies’ initiatives | • Another 5–10 countries have pilots that could be expanded • Transition from pilot to national requires changes to information systems, supply lists, training, financing and quality control systems • Underlying problems with staff turnover and shortages need attention |
| Supportive health systems for cervical cancer prevention | | |
| Better data systems | • Common indicators have been identified • More systems are electronic • mHealth tools look promising • WHO Global Joint Reporting form for immunizations includes HPV vaccine | • All countries need to incorporate screening indicators into national data, since it is one of the indicators for the NCD initiative • Data on treatment are needed to monitor follow-up of screen-positive women |
| Integration with other services | • Services under PEPFAR have included cervical cancer prevention for HIV+ women in several countries • Three large family planning organizations have incorporated screening in their services in multiple countries • Pink Ribbon Red Ribbon has supported integrated HIV/cervical cancer prevention services in five African countries | • Remove arbitrary barriers and enhance coordination between programs that serve same clientele and use overlapping resources • Identify and evaluate integration models that optimize resource use and convenience for women |
| Financing | • Overall package of cervical cancer prevention services for next 10 years has been costed • WHO/CDC costing tool developed to help countries create national cervical cancer prevention and control budgets • Global Fund now allows countries to include cervical cancer prevention services in their programs • Countries can include cervical cancer prevention in their Global Financing Facility requests | • Identify more funds (from national and donor sources) to cover start-up and expansion costs of equipment and training for screening • Negotiate lower prices for HPV vaccine for non-Gavi countries • Negotiate lower/tiered prices for HPV tests and precancer treatment devices |
| Communication and advocacy | • Good evidence available for communication messages and channels for vaccine, more limited for screening • Global coalitions for advocacy established, more limited at national level | • Strengthen cross-sectoral advocacy partnerships • Harmonize advocacy messages globally • Strengthen capacity of national champions and encourage national coalition building • Focus vaccine and screening messages on cancer prevention, not HPV infection |

LMICs, low- and middle-income countries; HPV, human papillomavirus; VIA, visual inspection with acetic acid; NCD, noncommunicable disease.
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CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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