HEALTH
WOMEN'S HEALTH

PERSPECTIVE PAPER

Benefits and Costs of the Women's Health Targets for the Post-2015 Development Agenda

Dara Lee Luca

Alyssa Shiraishi Lubet

Kristine Husøy Onarheim

David E. Bloom

Johanne Helene Iversen

Elizabeth Mitgang

Klaus Prettner

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Post-2015 Consensus

Dara Lee Luca
Harvard School of Public Health

Alyssa Shiraishi Lubet
Harvard School of Public Health

Kristine Husøy Onarheim
University of Bergen

David E. Bloom
Harvard School of Public Health

Johanne Helene Iversen
University of Bergen

Elizabeth Mitgang
Harvard School of Public Health

Klaus Prettner
Vienna University of Technology

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Introduction[1]

Economists have long recognized the positive association between population health and income per capita. Traditionally, this association was viewed as reflective of a causal link from income to health. In recent years, robust evidence has been offered in support of the view that the association also reflects a reverse causal link from population health to income, along with much theoretical and empirical work focused on the various pathways through which health can lead to the cultivation of human capital and the concomitant growth of income. However, this growing body of research has yet to identify the specific and essential role of women's health as a driver of economic growth. In order to inform future global health investment, the contribution of women's health – both in terms of their own health status as well as the contribution women make to the health, productivity, and economic well-being of family and community members – necessitates further inquiry.

In this paper, we argue that there are strong reasons to believe that female-specific health interventions are a sound investment for promoting economic well-being at both individual and population levels. In particular, we focus on vaccination against human papilloma virus (HPV), largely motivated by the substantial cervical cancer burden borne by women in resource-poor countries during what is often the most productive years of their lives. Herein we argue that diminishing the lifetime risk of cervical cancer and HPV-related disease by 40% (representing nearly 3 million deaths) through increased HPV vaccination coverage in developing countries is a worthy goal – on grounds of economic rationality – for inclusion in the post-2015 global development agenda.

In the next section, we provide background information on cervical cancer, cervical cancer screening, and HPV vaccination. The following section provides a conceptual framework and supporting evidence on the potential impact of HPV vaccination on women's health and on the health and well-being of their families and communities. Finally, we compare benefit-cost ratios of spending on HPV vaccination against other previously studied female-specific health interventions, and conclude that HPV vaccination deserves serious consideration as a cost-beneficial health strategy.

Background
Cervical Cancer in a Global Context
Globally, cervical cancer is the fourth most common cancer among women, with more than half a million cases diagnosed every year and more than 200,000 deaths annually reported worldwide. The burden of cervical cancer is disproportionately high in the developing world: about 85 per cent of cervical cancer cases occur in less developed countries, where the disease represents the second deadliest cancer among women (following breast cancer) [1]. The impact of the disease is further accentuated by the young average age at death, often when women are most likely to be bearing children, raising and supporting

families, and participating in the workforce [2]. For these reasons, cervical cancer conveys potentially large negative familial and societal externalities, particularly detrimental to children of affected women.

In developed countries, adequate health system infrastructure, resources, and personnel have reduced the cervical cancer burden substantially, primarily through widespread screening and HPV vaccination programs. In contrast, fundamental challenges remain in developing countries [3].Virtually all cervical cancer cases are related to HPV infection, a sexually transmitted virus that can cause different types of cancer in both women and men [4]. Oncogenic ("high-risk") HPV infections can cause various cancers, while non-oncogenic ("low-risk") types are responsible for genital warts and, rarely, recurrent respiratory papillomatosis. It should be emphasized that the majority of women with HPV do not develop cervical cancer; rather, women become susceptible to developing cervical cancer following HPV infection, and other environmental factors are required for the cancer to develop.

Cervical Cancer Prevention: HPV Vaccination

In 2006, two vaccines[2] that protect against HPV came to market. Studies show that both vaccines are safe and highly effective in preventing HPV 16 and HPV 18 – responsible for around 70 percent of cervical cancer – among girls who have not been previously infected with these types of HPV [5-7]. Immunizing girls before they begin to initiate sexual activity is a key strategy for preventing cervical cancer. The two vaccines have been licensed in over 100 countries as of 2014, and the list continues to grow [8].

The HPV vaccination series requires three doses over six months; thereafter, the vaccine has been shown to remain effective for at least five years (dependent upon full compliance with the vaccine schedule). Recent and ongoing research suggests that the vaccine remains efficacious even when fewer than three doses are administered [9]. The American Cancer Society (ACS) recommends routine HPV vaccination for females aged 11 to 12 years, as well as for females aged 13 to 18 years to complete missed vaccination opportunities and finish the series [10]. The ACS also recommends screening according to the age-specific recommendations for the general population, including for women at any age with a history of HPV vaccination.

The market price of the HPV vaccine is considerably higher than prices for the traditional vaccines included in WHO's Expanded Program on Immunization (EPI), such as those for polio and measles. The price difference can be partly attributed to the complex, patent-protected technologies involved in producing HPV vaccines [11, 12]. Vaccine prices differ not just by vaccine composition, but also by market. A recent and encouraging breakthrough comes as a result of the efforts of the Global Alliance of Vaccines and

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[2] Gardasil©, manufactured by Merck&Co., is a quadrivalent vaccine licensed to protect against HPV 16/18-related cervical, anal, vaginal, and vulvar precancers and cancers, and HPV 6/11-related genital warts; it provides protection against 70% of cervical cancer cases. Cervarix©, produced by GlaxoSmithKline, is a bivalent vaccine that protects against HPV types 16/18.

Immunization (GAVI), which has successfully negotiated with manufacturers to lower the price of the quadrivalent vaccine to US $4.50 per dose for GAVI-eligible countries [8]. By comparison, the market price for the same vaccine in high-income countries such as the US is upwards of $300 for the series [13]. This dramatic price reduction in GAVI-eligible countries will likely play a major role in facilitating the expansion of HPV vaccine coverage, including in many countries that are heavily burdened by cervical cancer.

Cervical Cancer Prevention: Screening

The Papanicolaou test, commonly referred to as the "Pap test" or "Pap smear," is one of the most reliable and widely used cervical cancer screening tests available, and it is also relatively low-cost [14]. The test is conducted during a pelvic examination in which cells are collected from the cervix and analyzed under a microscope for evidence of precancers. Through such screening programs, cell changes on the cervix can be detected and treated appropriately before potentially developing into cervical cancer. Screening guidelines vary by country, but in general, screening is recommended to start at about the age of 20 or 25, continue until about the age of 50 or 60, and occur every three to five years [15].

Widespread screening and subsequent diagnosis of pre-cancerous lesions and early-stage cancer has led to a dramatic drop in cervical cancer rates and deaths in developed countries [16, 17]. However, the same trend has not been observed in developing countries [18]. Screening programs have been implemented in developing countries since the early 1980's, yet have failed to reduce cervical cancer mortality rates, in part due to lack of information, access, and infrastructure [19]. Conventional cytology screening is resource- and time-intensive, requiring up to three visits involving trained cytotechnologists, laboratory accessibility for evaluating samples, methods to contact the patient with results, and treatment options if abnormal results are found. In 2002, the WHO estimated that only 5% of women in developing countries were screened appropriately [20].

There has hence been considerable interest in alternative methods for cervical cancer screening, such as visual inspection with acetic acid (VIA) and DNA testing for HPV. VIA is as effective as Pap tests in detecting pre-cancerous cells [21], but holds an advantage over Pap tests due to its ease of use and lower cost. VIA also has the advantage of a "screen-and-treat" feature, whereby acetic acid elicits aceto-whitening in the presence of cervical intraepithelial neoplasia (CIN), or premalignant growth, which can be detected and treated in the same visit [19].

While both Pap and VIA tests are effective and relatively low-cost cervical cancer screening methods, it is still a challenge to expand screening coverage on a wide-scale to developing countries. It is not clear given the current evidence that pushing VIA as an alternative to Pap tests would necessarily succeed in substantially reducing cervical cancer incidence, as critical barriers remain both within and outside the healthcare system. In the absence of a vaccine, all HPV-related health outcomes require treatment and care. These outcomes depend on patients having the time and resources needed to travel to appointments, receive treatments, and recover. Given the high costs of treatment in developing countries

[19], relying on screening programs and subsequent treatment may not be the optimal strategy for tackling cervical cancer.

We therefore argue that wide-scale implementation of HPV vaccination programs, specifically through programs at schools, may be more effective in reducing cervical cancer incidence in developing countries. Ideally, screening using VIA should also be continued in conjunction with vaccination, as recommended in most developed countries. However, screening women within 5–10 years of first sexual intercourse, as currently recommended by guidelines in many developed countries, may not be efficient; the risk of finding benign HPV infections is very high, while the risk of cancer is very low during this period. Combined with increased coverage of vaccination, we recommend that screening begin closer to peak ages of cervical cancer risk. In general, among unscreened populations, the onset of cervical cancer begins around age 35 and peaks near age 65 [22], after which incidence rates decline dramatically.

Conceptual Framework and Supporting Evidence

In this section, we consider the full economic benefits of increasing HPV vaccination. Following the framework set forth in Bärnighausen et al. [23, 24], we categorize the benefits into the more traditional scope of healthcare cost savings, care-related productivity gains, and direct health gains. We also include a broadened scope of benefits, including outcome-related productivity gains, behavior-related productivity gains, community health, and economic externalities.

Direct Health Gains

This category of benefit refers to a reduction in disease or mortality resulting from vaccination. Increasing HPV vaccination may directly reduce morbidity and mortality from HPV types 16/18, 6/11 and other related HPV types through cross-protection. Furthermore, because HPV infection may increase an individual's risk of acquiring HIV [25, 26], it is plausible to consider further the role HPV vaccination could serve in providing cross-protection against other sexually transmitted infections (STI) (also see Figure 1). Anal cancer, 90 percent of which is caused by HPV, could be averted either via the direct vaccination of men or through cross-protection from vaccinating women. HPV vaccination could also lead to fewer vaginal and vulvar cancers, roughly 40 percent of which are caused by HPV. Finally, the mental health strain that accompanies disease and treatment should also be considered. Studies have shown that cervical cancer survivors may suffer from the lingering effects of depression for many years after treatment [27].
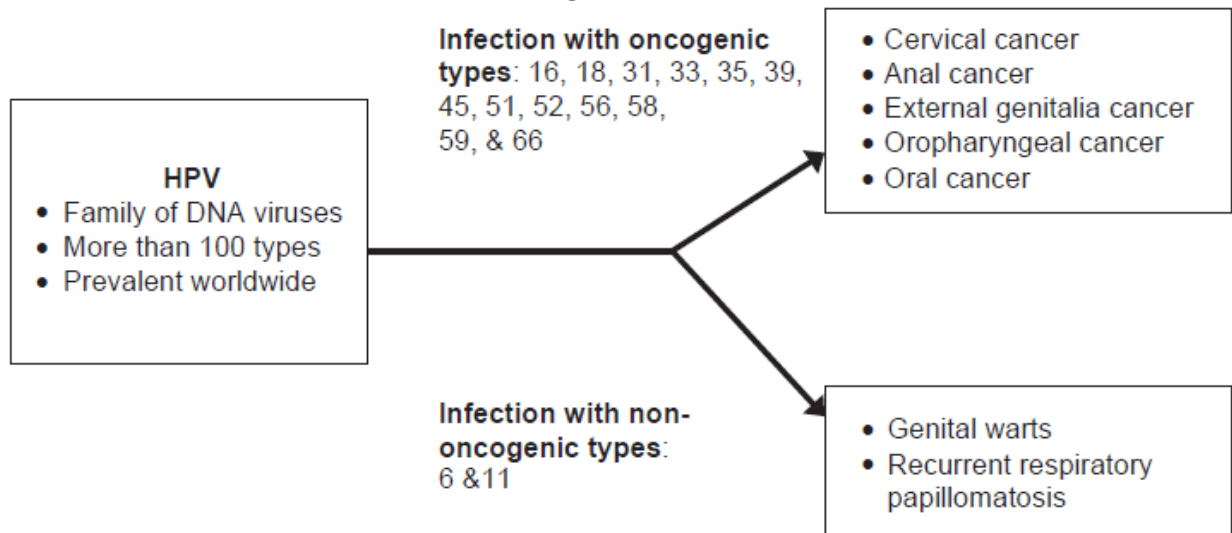
Figure 1 depicts the HPV virus family, comprised of more than 100 related viruses, and enumerates the health complications specific to oncogenic and non-oncogenic types, respectively. Source: Bärnighausen et al., 2012

Healthcare Cost Savings

In general terms, healthcare cost savings refer to the savings of medical expenditures that result when vaccination prevents episodes of illness. In the specific case of HPV vaccination, healthcare cost savings can result from avoiding direct medical costs (e.g., medications, doctor visits, lab costs, hospitalizations) and direct, non-medical costs (e.g., transport) because vaccination can prevent illness related to HPV types 16/18, 6/11, as well as other HPV types through cross-protection. There may also be health cost savings in other dimensions realized from averted treatment of mental health strains, other cancers, and other STIs via increasing HPV vaccination. This category of benefit is almost universally accounted for in economic evaluations of vaccination, including the studies we reference below.

Care-related productivity gains

There is an opportunity cost to seeking treatment, receiving care, or recovering from HPV-related health outcomes in the absence of a vaccine: time away from wage-earning work for both the individual receiving care and the caregiver. Family, friends, and others may participate in caregiving; both adults and children are caregivers for people with HPV-related disease. In the presence of higher HPV vaccination coverage, there could be productivity gains from averted missed work for vaccinated individuals, as well as averted missed work for potential caregivers.

Outcome-related productivity gains

It is not uncommon for patients with HPV-related cancers to disengage from the workforce temporarily or permanently leading to lost productivity and income. Furthermore, HPV-

related disease tends to strike during economically active years. In particular, age-specific incidence and mortality owing to cervical cancer often overlap with the age range when the majority of women are economically active in many countries. While patterns differ by country, the data suggest that withdrawal from the workforce could hurt productivity at both the household and national levels. In the presence of a vaccine that prevents cervical cancer resulting from HPV infection, these losses in future earnings and productivity would be mitigated. Other potential gains could result from the prevention of HPV-related disease, such as anal cancer in men. In sum, outcome-related productivity gains may occur through fewer averted care-seeking episodes, translating into fewer career interruptions and impacts, higher lifetime hours worked (length of the productive period), as well as higher productivity and earnings per hour worked. These substantive gains in productivity from avoiding HPV-related disease are typically not taken into account in cost-effective analyses of HPV vaccination.

Behavior-related productivity gains

Behavior-related productivity gains can result when vaccination improves health and survival, and thereby changes individual behavior in a way that impacts productivity. With regard to HPV vaccination, there are two main ways that behavior-related productivity effects can play out. First, reduced risk of HPV through vaccination may impact educational choices and investment for young adults and household members (children) of the vaccinated person. Second, reduced risk of HPV through vaccination could also impact protective behavior. There is already well-established evidence that household-level behavior changes as a result of cervical cancer. In one study, researchers identified decreased daily food consumption among patients undergoing treatment for cervical cancer in Argentina [28]. Among these households, a host of education-related impacts were also incurred, including absenteeism and difficulty paying for education. With a successful vaccination program, and a subsequent reduction in cervical cancer, we anticipate these negative behavior effects to be mitigated. Human capital investments in women could also be positively impacted as a result of women's improved longevity and health [29].

Community health and economic externalities

Positive externalities include improved health outcomes among unvaccinated community members. These include vaccination-related herd immunity effects that result from unvaccinated members of a community gaining protection against a disease through sufficient vaccination coverage of surrounding community members [30, 31]. With regard to HPV vaccination, the specific community health externalities could include reduced incidence of HPV and HPV-related disease in unvaccinated community members. On a macro level, higher vaccination rates and reduced rates of cancer could potentially make an economy more desirable for foreign direct investment.

Given the sexually-transmitted nature of HPV, herd effects could theoretically be realized in two ways: (1) by vaccinating both males and females, who would confer protection directly to their unvaccinated sexual partners; or (2) by vaccinating just females, which would reduce transmission to their unvaccinated male partners, and, in turn, reduce transmission

to their subsequent, unvaccinated female partners [32], and so on. That said, most existing studies indicate that vaccinating girls along with screening would be more effective than vaccinating both boys and girls [32-35].

Mathematical models can predict the impact of herd effects from HPV vaccination, but recent empirical data have also made it possible to quantify such herd effects. A 2012 study from the US reports a decrease in vaccine-type-specific HPV prevalence in both vaccinated and unvaccinated girls in the vaccinated cohort four years after introduction of the vaccine, suggesting evidence of herd effects in the community [32]. Data from Australia suggest a 44% decline in the incidence of male genital warts as a result of female HPV vaccination [36]. These findings confirm the predictions of mathematical models that there could be significant herd effects resulting from HPV vaccination.

Finally, health benefits may also accrue to children of the vaccinated person via reduction in the incidence of recurrent respiratory papillomatosis (RRP), though it should be noted that while serious, RRP is a rare condition [37]. By reducing HPV-related genital warts in the mothers, the children would no longer be at risk for juvenile onset RRP that occurs as a result of exposure to HPV in the perinatal period [38]. Considering these intergenerational health benefits is not currently standard practice in economic evaluations of HPV vaccination.

Costs of increasing coverage of HPV vaccination
The previous subsections laid out the substantial benefits that could accrue from increased HPV vaccination coverage. We now move on to briefly discuss the related costs and infrastructure that would be needed to substantially scale up HPV vaccination in less-developed countries.

The first thing to consider is the market price of the HPV vaccine. As discussed earlier, while the market price of the HPV vaccine is high, the vaccine is available (as of 2013) at the substantially reduced cost of under $5 in GAVI-eligible countries. However, there are also substantial system costs in order to introduce and operate an immunization program, including costs related to introducing a new vaccine (e.g., investments in cold chain infrastructure and personnel training) as well as costs related to maintaining the vaccine in the national immunization program (e.g., costs of transportation, cold chain maintenance, and wastage). Research suggests that almost half of all systems costs spending are directed towards human resources items [39]. This spending is next followed by investments in cold chain and maintenance, and then vehicles and transportation. In conducting a comprehensive benefit-cost analysis of HPV vaccination, which will require new infrastructure in many countries, it is critical to properly assess the systems costs required.

Given that the HPV vaccine does not align with other routine vaccinations, and that the vaccine is to be given in three doses over 12 months, there could be significant time costs incurred for seeking vaccination against HPV. However, when introduced through a school-based immunization program, these costs would be relatively low for school-aged girls who regularly attend school. There is growing evidence from Africa, Asia, and Latin America

that school-based HPV vaccination programs can be successful [40]. In areas where the rate of school enrollment among girls are low, the time costs would be greater and more involved community-based efforts will be needed to reach young girls.

While adverse effects of vaccination are always a concern, there are reassuringly few minimal adverse events following HPV immunization [5-7, 41]. Further, there is little evidence of risk compensation, i.e., individuals engaging in riskier sexual behavior after receiving the vaccine [42, 43].

Comparison of Benefit-Cost Analyses

We present in Table 1 the benefit-cost ratios of four major female-specific interventions that have been examined in the literature. In addition to HPV vaccination, we also consider screening (with treatment) and family planning programs as comparators. The estimates are drawn from different papers and hence incorporate different assumptions, but we believe that this table provides a sense of the potential value of increasing HPV vaccination.

We first present benefit-cost ratios (BCR) from HPV vaccination, followed by those from Pap smears administered according to current US recommendations (tri-annual between ages of 20 to 65), and penta-annual VIA screening from ages 35-45 (proposed as a more feasible and efficient strategy in low-resource settings). Finally, we present the BCR of family planning programs, which has been previously studied as a CCC intervention and found to be highly cost-effective [44].

As shown in Table 1, the BCRs from vaccination range from 2.7 to 4.9 depending on the region,[3] but the BCRs are consistently higher when compared to the traditional screen-and-treat strategy. The average BCRs of tri-annual Pap tests and penta-annual VIA screening are a magnitude lower at 0.83 and 1.73, respectively. When we assume that the cost per DALY is $5,000, the BCRs are even higher. The main assumption here is that the cost per vaccinated girl is $25 international dollars (I),[4] which includes both the cost of the three-dose vaccine (at I$5 per dose), wastage, freight and supplies, administration, immunization support and programmatic costs [45]. Most existing studies, including ones not reported here, suggest that HPV vaccination would be a cost-effective strategy (i.e., cost of saving one life is less than the country's GDP per capita), if the cost per vaccinated girl were less than I$25. More complex models that take into account interaction effects from both vaccination and screening indicate that vaccination combined with screening at later ages would be even more cost-effective [46-49]. An additional potential benefit that has not been taken into account is the savings that result from reduced frequency of screening.

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[3] The regions featured in this analysis are aggregate figures adopted from the existing studies of Goldie et al. 2008 and Ginsberg et al. 2009, respectively, and reflect data representative of six WHO geographic areas: Africa (Afr), Eastern Mediterranean (Emr), Europe (Eur), Americas (Amr), Western Pacific (Wpr), and South East Asia (Sear).

[4] According to the World Bank, in any given country, an international dollar would buy an equivalent amount of goods and services as that of a U.S. dollar in the United States, and is often used along with purchasing power parity. This hypothetical currency is commonly abbreviated as "I."

While analyzing the BCR is appealing because of its simplicity, we caution that these ratios are aggregated from different sources. Although we attempt to standardize our inputs (e.g., adjusting all costs to 2005 international dollars when possible) there remain significant differences in the details of the assumptions. More importantly, as we emphasized earlier, an economic valuation of HPV vaccination should take into account the broader benefits of vaccination, and hence the estimates in Table 1 should be considered as conservative, lower-bound estimates.

Table 1 - Comparison of Benefit-Cost Ratios

Type of Intervention	Benefit-Cost Ratio (BCR) DALY = $1,000	Benefit-Cost Ratio (BCR) DALY = $5,000	Description of Strategy	Source Study	First Author	Year
Vaccination						
World*	3.39	16.97	Vaccination of 70% a single birth cohort of 9-year-old girls in 2007 with a 100% effective vaccine. Cost per vaccinated girl is I$25.	Health and economic outcomes of HPV 16,18 vaccination in 72 GAVI-eligible countries	Goldie	2008
Afr	3.37	16.85				
Emr	2.74	13.70				
Eur	2.68	13.42				
Amr	4.88	24.41				
Wpr	3.65	18.24				
Sear	3.37	16.86				
VIA (5, 35, 45 years of age) + Treatment						
World*	1.73	8.67	Visual inspection after application of 3-5% acetic acid (VIA) once every five years between the ages of 35 and 45; plus treatment.	Screening, prevention and treatment of cervical cancer—A global and regional generalized cost-effectiveness analysis	Ginsberg	2009
Afr	2.03	10.17				
Emr	1.60	7.99				
Eur	1.39	6.96				
Amr	1.57	7.83				
Wpr	0.99	4.96				
Sear	2.53	12.65				
Pap Smear (3, 20, 65) + Treatment						
World*	0.83	4.16	Adminstration of pap smear once every three years between the ages of 20 and 65; plus treatment.			
Afr	0.94	4.70				
Emr	0.56	2.78				
Eur	0.64	3.19				
Amr	0.83	4.13				
Wpr	0.37	1.87				
Sear	1.46	7.28				
Family Planning						
World**	30.00	50.00	Family planning programs broadly refer to programs that provide information about contraception, as well as contraceptives themselves and related reproductive health services	Copenhagen Consensus 2012: Challenge Paper on "Population Growth"	Kohler	2012

Notes: All data are discounted at a rate of 3%.

*The world averages for "VIA+Treatment" and "Pap Smear+Treatment" are weighted figures based on the number of countries included in each author's analysis.

** These figures reflect Kohler's lower bound benefit-cost ratios, which account only for reduced infant and maternal mortality (not income growth realized through life cycle, distributional, and intergenerational benefits). When these additional income growth benefits are considered, Kohler's BCRs increase dramatically to 90 and 150, respectively. We hypothesize that capturing similar benefits in the HPV vaccination BCRs would also result in compelling increases across all world regions.

Conclusion

While cervical cancer is one of the most common and deadliest cancers, it is also one of the most preventable [50]. In this note, we present a conceptual framework and supporting evidence that introducing wide-scale HPV vaccination to the developing world will reap substantial rewards. This strategy is consistent with the WHO Global Action Plan 2013-2020, for which one global target is to achieve a 25% relative reduction in risk of premature mortality from cardiovascular diseases, cancer, diabetes, or chronic respiratory diseases [51]. Although the benefit-cost ratio of HPV vaccination is lower than previously studied CCC interventions such as family planning programs, it is also potentially more scalable and replicable, especially if school-based vaccination programs can be implemented and sustained.

A key prior barrier to wider adoption of the HPV vaccination in developing countries was the cost of the vaccine. However, manufacturers have recently dramatically lowered the cost of the vaccine via GAVI to less than $5 per dose for the quadrivalent vaccine. At this cost, existing studies would suggest that HPV vaccination combined with screening could be very cost-effective. Nonetheless, any country considering adoption of an HPV immunization program will need to carefully evaluate the country's disease burden and its existing healthcare infrastructure, and determine whether the country has the necessary resources needed to implement such a program. Other considerations include whether there exist competing and more cost-effective programs, and whether such a program would garner political and public support [52]. For eligible countries, GAVI does provide different forms of support, from developing smaller-scale demonstration projects to national introduction.

To conclude, we believe that scaling up HPV vaccination to 70% coverage – in conjunction with judicious screening guidelines – could be the key to reducing the burden of cervical cancer in developing countries. According to several studies [13, 45, 53, 54] a ten-year vaccination intervention has the potential to decrease the burden of cervical cancer by nearly 3 million deaths. As we illustrate in our conceptual framework, there could be substantial broader economic benefits that are not captured in existing analyses of cervical cancer vaccination. These benefits may present themselves by improving women's health directly, increasing healthcare cost savings, and extending positive externalities on women's immediate communities as well as the broader economy. Our comparison of cost-benefit analyses demonstrates that the average benefit-cost ratio of HPV vaccination across GAVI-eligible regions is around 3.4, but we emphasize that this should be considered a lower-bound estimate as it only captures health cost savings. If we take into account the broader economic and health externality benefits of HPV vaccination, the benefit-cost ratio should increase substantially.

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This paper was written by Dara Lee Luca, Department of Global Health and Population at Harvard School of Public Health, Johanne Helene Iversen, Department of Family Medicine and Dentistry at University of Bergen, Alyssa Shiraishi Lubet, Department of Global Health and Population at Harvard School of Public Health, Elizabeth Mitgang, Department of Global Health and Population at Harvard School of Public Health, Kristine Husøy Onarheim, Department of Global Public Health and Primary Care at University of Bergen, Klaus Prettner, Institute of Mathematical Methods in Economics at Vienna University of Technology, and David E. Bloom, Department of Global Health and Population at Harvard School of Public Health. The project brings together 60 teams of economists with NGOs, international agencies and businesses to identify the targets with the greatest benefit-to-cost ratio for the UN's post-2015 development goals.

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