

Progress in HPV vaccination in low- and lower-middle-income countries

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Abstract

The past 10 years have seen remarkable progress in the global scale-up of human papillomavirus (HPV) vaccinations. Forty-three low- and lower-middle-income countries (LLMICs) have gained experience in delivering this vaccine to young adolescent girls through pilot programs, demonstration programs, and national introductions and most of these have occurred in the last 4 years. The experience of Senegal is summarized as an illustrative country case study. Publication of numerous delivery experiences and lessons learned has demonstrated the acceptability and feasibility of HPV vaccinations in LLMICs. Four areas require dedicated action to overcome remaining challenges to national scaling-up: maintaining momentum politically, planning successfully, securing financing, and fostering sustainability. Advances in policy, programming, and science may help accelerate reaching 30 million girls in LLMICs with HPV vaccine by 2020.

KEYWORDS

Delivery; Global; Human papillomavirus; Low- and lower-middle income countries; Vaccine

1 | INTRODUCTION

Human papillomavirus (HPV) vaccines have been available since 2006. Numerous clinical trials of quadrivalent (HPV types 6, 11, 16, 18) and bivalent (HPV types 16, 18) HPV vaccines demonstrated nearly 100% prophylactic efficacy against vaccine type persistent infections and cervical intraepithelial neoplasia (CIN), the necessary precursors to cervical cancer,¹⁻³ leading to approval and commercial availability. These vaccines have proven to be long-lasting against both infection and disease clinical endpoints,^{4,5} eliciting very high antibody levels and avidity suggestive of enduring protection.⁶⁻⁸ Longitudinal studies of the bivalent HPV vaccine suggest it confers high levels of cross-protection against HPV types not targeted by the vaccine.⁹ In addition to primary safety assessments conducted as a part of the original efficacy trials,¹⁰ expert agencies have maintained vigilant post-licensure monitoring of the safety

of HPV vaccines, with recent reviews conducted in 2015 by the European Medicines Agency and by the Global Advisory Committee on Vaccine Safety of the WHO, confirming the continued safety of their use.^{11,12}

Since April 2009, the WHO has recommended that HPV vaccination be included in national immunization programs, provided that in each country preventing cervical cancer constitutes a public health priority, introduction is programmatically feasible, sustainable financing can be secured, and the cost-effectiveness of HPV vaccination strategies are considered.¹³ In 2014 the WHO Strategic Advisory Group of Experts on immunization reviewed new research and recommended revisions to the WHO position paper to reduce the previously required three-dose schedule to a two-dose schedule (0 and 6–15 months afterwards for the second dose) for HPV vaccination for girls aged 9–14 years,¹⁴ based on compelling evidence of the non-inferiority of the immunogenicity of two doses in adolescent girls to

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that of three doses in young adult women for whom efficacy had been demonstrated.^{8,15}

Since 2013, Gavi, the Vaccine Alliance (Gavi), has made HPV vaccines available to eligible countries at subsidized prices ranging from US \$0.20 per dose to 20% of the Gavi purchase price (currently around \$4.50 per dose),¹⁶ depending upon income level. All low-income countries (n=31) and nearly half of lower-middle income countries (n=23) are currently eligible to access vaccines at these discounted prices through Gavi. Countries can apply for national introduction of HPV vaccine through Gavi, to receive subsidized vaccine and a one-time vaccine introduction grant at \$2.40 per eligible girl as partial support for start-up expenses for national rollout.¹⁶ Until December 2016, countries were eligible to apply to the Gavi HPV demonstration program (now discontinued), which provided free HPV vaccine and a small operational grant to pilot delivery in one or more representative districts in the country.¹⁷ Gavi has a goal of achieving vaccination of at least 30 million girls by 2020 through Gavi support.¹⁸

This supplement paper draws on recent summaries of global HPV vaccine delivery experiences in the published literature and from technical and policy documents of key international organizations. The focus is on 43 of the total 83 World Bank-classified low- and lower-middle-income countries (LLMICs) that had at least 6 months of experience delivering HPV vaccines by May 2016 (Supplementary material Table S1). We review their progress with HPV vaccine introduction, remaining challenges, and actions needed to achieve the Gavi goal for 2020. The experience of Senegal is summarized as an illustrative country case study.

2 | PROGRESS TO DATE IN LLMICs

Initial national introductions of HPV vaccine occurred in high-income countries and focused on adolescent girls aged 12–14 years through school-based programs.^{19,20} Some early adopter countries implemented time-limited catch-up campaigns for young women up to age 18 years or older. National introductions of HPV vaccine expanded in high-resource countries from 2008–2012, with a few countries, such as Denmark, opting for clinic-based delivery.²⁰ Most countries provide the vaccine free-of-charge or fully reimbursable through their national immunization programs. In early reports, population-based three-dose coverage in these countries has ranged from 32% (USA) to 98% (Malaysia), with most (29 of 54 countries reporting recent data) averaging over 70% coverage in the target population.²⁰

2.1 | Early pilots and national introductions

At the time of the initial introductions in high-income countries, there was uncertainty as to whether and how HPV vaccines could be delivered in low-resource settings.^{21,22} To study these questions, PATH partnered with ministries of health in four low- and middle-income countries—India, Peru, Uganda, and Vietnam—to carry out demonstration programs.²³ Conducted from 2007–2010 and reaching from 4000 to 25 000 young adolescent girls, these programs resulted in 56%–99%

three-dose vaccine coverage, illustrated the acceptability and feasibility of such programs, estimated the costs of HPV vaccine delivery in low-resource settings,^{23–31} and provided a guide for the implementation of such programs in other countries.³² In addition, Merck & Co established the Gardasil Access Program (GAP) in 2009.³³ Initial pilot programs in 2009 and 2010 were conducted by civil society organizations, universities, nongovernmental organizations, and a few governments in 10 countries.³⁴ Both the approaches and eligible populations varied widely. By the end of 2014, all 31 of the GAP pilot programs had been completed in 21 LLMICs, with the majority reporting that they reached more than 70% of their HPV vaccine uptake goal.^{33,35}

Two countries—Bhutan and Rwanda—introduced HPV vaccine nationally with donations from Merck & Co. In 2010, Bhutan rolled out a school-based national program for all girls aged 12 years, plus catch-up vaccinations for the 13–18-year-old female population.³⁶ Coverage in the first year was 99% among 12-year-olds and 89% in the catch-up population. The country switched to routine delivery in health facilities from 2011–2013 for several reasons, including concerns about sustaining financing for delivery, and during this period coverage ranged from 67 to 69%.³⁶ In 2014, the government reverted to a primarily school-based delivery, facilitated by a switch to the two-dose schedule, after which coverage increased to greater than 90%.^{20,36}

Rwanda launched its national HPV vaccination program in 2011, delivering vaccine in schools to all girls in primary grade six. Reported coverage was 93% in the first year and 98% in 2014.^{20,37} The country credits the public–private partnership with Merck, high level political commitment and champions such as the First Lady, the strong foundation of the Rwandan health system, and comprehensive community sensitization prior to national introduction as keys to the success of its HPV vaccination program.³⁷

2.2 | Expanding access

Access to HPV vaccination in LLMICs has been facilitated by financial assistance, scientific advances, and program tools. In late 2012, assistance for LLMICs increased with the announcement by Gavi of a purchase price of \$4.50–\$4.60 per dose of HPV vaccine from Merck & Co or GlaxoSmithKline.¹⁶ Since 2013, most financial support for LLMICs to introduce HPV vaccines has been through Gavi, which has approved support for 21 demonstration programs and four national programs.^{18,38} In 2016 Gavi made a one-time offer of catalytic support to 13 countries (of which seven have been approved) that “graduated” from eligibility for Gavi support prior to 2013. By and large, countries are targeting vaccinations to a younger age, frequently aged 9 or 10 years, and choosing to use primary schools as a location for vaccination given that the largest proportion of the eligible population is attending school.^{39–42} These programs have been able to achieve levels of vaccine coverage comparable with those observed in high-income countries—predominantly 70% or greater.^{18,39}

Access also has been expanded by evidence for the efficacy and effectiveness of HPV vaccines given on the two-dose schedule, with countries switching their Gavi programs to the newly recommended schedule. With one less contact between vaccinators and the target

population, cost declined and feasibility of delivery increased.³⁹ The revised recommendation also opened up new delivery options for dose spacing—up to 15 months between first and second dose—allowing for annual schedules, as in Chile.^{14,43} Several countries that have completed their 2-year Gavi HPV demonstration programs have indicated that they are considering implementation of an annual schedule (0 and 12 months) as their national introduction strategy (Vivien Tsu, personal written communication, December 2016).⁴⁴

In addition to the financial and vaccine support provided to LLMICs through Gavi, tools and resources for planning and implementing effective HPV vaccine delivery programs are available in multiple languages.^{32,45–50} The London School of Hygiene and Tropical Medicine and PATH conducted a recent comprehensive review of experiences in HPV vaccine delivery in more than 40 low- and middle-income countries and generated materials in multiple languages for countries to learn about the global experience to date.^{39,50} Gavi also supports a variety of partners to provide countries with technical assistance for the planning, implementation, and evaluation of HPV vaccine delivery.

2.3 | Country example: Senegal

From 2014 to 2016, Senegal conducted a Gavi-supported HPV demonstration program introducing the quadrivalent HPV vaccine in two districts (Dakar Ouest and Meckhe—urban and rural districts, respectively).⁵¹ Vaccines were delivered by the routine national immunization program through schools and community outreach to girls aged 9 years, both in school and out of school. To assess the performance of this program, a coverage survey, a modified post-introduction evaluation (PIE), and a costing analysis (using standardized methods employed in all Gavi-supported HPV demonstration programs) were conducted after the first year of implementation.

Vaccination coverage was 74.8% in the urban district and 91.8% in the rural district, even though 37.0% of girls in the rural district were out of school.⁵¹ The three primary reasons for acceptability by parents were belief in the value of vaccination (68.7%), belief in preventing diseases (66.2%), and desire to protect against cervical cancer (59.1%). The main reason for non-vaccination was families not being aware of the HPV vaccination program (45.3%). The PIE revealed key lessons learned, such as the importance of counting target girls in advance for better planning of vaccine and human resources needs, coordinating with schools for vaccination days, engaging health personnel for vaccine delivery, and supervising regularly to help correct deficiencies during the program.⁵² Advanced community sensitization by community health workers regarding HPV vaccines and the demonstration program increased community acceptability and aided in finding girls who had received the first dose for administration of dose two. Finally, the costing exercise showed the feasibility of a larger introduction at an affordable price, with a financial cost of \$13.94 for a fully vaccinated girl (vaccine cost included).

Because of the high disease burden, the encouraging results of the three evaluations of this program, and the funding opportunities offered by Gavi, Senegal decided to introduce the vaccine at the national level. With broad involvement from the Ministry of Health, Ministry of Education, Ministry of Finance, civil society

representatives, and international partners; the country developed a scale-up plan for HPV vaccinations. Senegal was approved for support by Gavi in December 2016, and the country will launch HPV vaccine nationally in the latter part of 2017.

2.4 | Summary

In the past 10 years, we have seen remarkable progress in the global scale-up of HPV vaccinations: more than 100 countries now have experience with HPV-vaccine delivery (Fig. 1A–D). Half of the LLMICs with programs (16/32) have taken these steps just in the last 3 years (Supplementary material Table S1). In high-income countries, adoption of HPV vaccine at scale progressed over a period of 4–6 years. While the pace of national introduction in LLMICs is slower, the appetite for gaining HPV vaccine delivery experience on a small scale has been unexpectedly robust. There is now a critical mass of experience accumulated (Supplementary material Table S1), and more than 20 LLMICs are poised to introduce HPV vaccines in the next 4 years.

3 | REMAINING CHALLENGES

With eight LLMICs having now introduced HPV vaccine nationally and at least seven more projected in the next 4 years, we are at a critical juncture. The success of national introduction, measured by high coverage sustained over time, will depend largely upon whether countries can apply the knowledge, experience, and evidence now available. Access to numerous tools and resources, the availability of competent technical assistance from experienced partners, and fostering of country-to-country learning could be catalytic over the coming years.

Four areas require concrete, dedicated action to help countries grow from small pilot and demonstration programs to sustainable and effective national HPV vaccine introduction: maintaining momentum, planning successfully, securing financing, and fostering sustainability.

3.1 | Maintaining momentum

As Rwanda found, political will is paramount for successful introduction of HPV vaccination.^{37,39} Support from national decision makers assists in securing funding from government agencies for vaccine procurement and delivery. It is incumbent upon national immunization programs and partners to continue to engage with key stakeholders, advocates, and civil society organizations throughout the decision-making process to maintain attention on cervical cancer prevention as a priority.

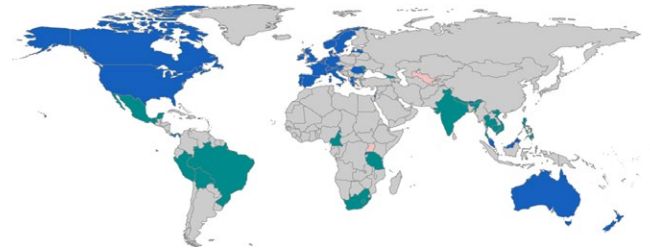
International advocacy groups can also play an important role in keeping momentum. Several agencies and initiatives provide timely information on the global burden of disease and the disproportionate impact cervical cancer has in LLMICs.^{53,54} The First Ladies Initiative and the Cervical Cancer Prevention Initiative are examples of forums that are used to build political engagement and commitment from country decision makers.^{55,56}

Momentum for action also can be supported by new scientific evidence. The evidence is becoming more robust for the tremendous



(A) Accumulation of global HPV vaccine experience, 2007

(B) Accumulation of global HPV vaccine experience, 2010



(C) Accumulation of global HPV vaccine experience, 2013

(D) Accumulation of global HPV vaccine experience, October 2016

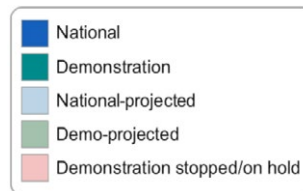
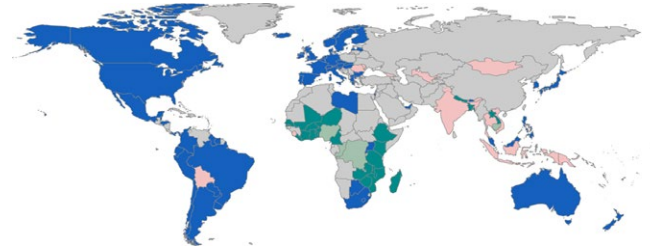
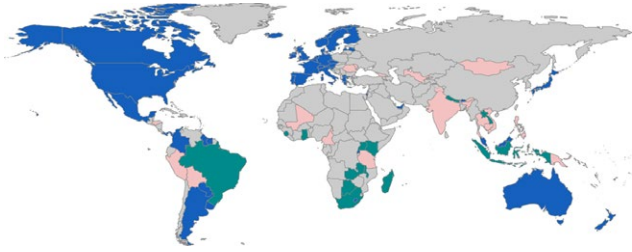


FIGURE 1 (A) Accumulation of global HPV vaccine experience, 2007. (B) Accumulation of global HPV vaccine experience, 2010. (C) Accumulation of global HPV vaccine experience, 2013. (D) Accumulation of global HPV vaccine experience, October 2016. [Colour figure can be viewed at wileyonlinelibrary.com]

impact that HPV vaccines are having on infection and disease outcomes. To date, more than 40 studies of incident, persistent or prevalent infections, genital warts, and CIN across many countries have demonstrated significant reductions in vaccinated populations.^{57–61} Further evidence of herd protection in unvaccinated populations due to protection provided by HPV vaccine programs,^{57,61} even in places with low coverage,^{57,59} is particularly encouraging for stakeholders who worry that high coverage is too difficult to achieve. These advances need to be brought to the attention of decision makers and partners to maintain political will and momentum for HPV vaccine introduction.

3.2 | Planning successfully

A consistent learning from the past 10 years of HPV vaccine delivery in LLMICs is that poor planning negatively impacts programs. Examples of poor groundwork include not coordinating with the education sector for school-based vaccinations^{39–41}; not allowing sufficient time for the planning process itself; and not adequately sensitizing national level stakeholders, community leaders, and parents of eligible girls.^{39,62} Confusion in the eligibility criteria and application of those criteria during vaccinations was also noted as a challenge.³⁹ Guidance

from WHO suggests countries need to consider 6–9 months as the minimal time to plan a quality HPV vaccination program.⁴⁵

3.3 | Securing financing

Despite numerous studies of the cost-effectiveness of HPV vaccine introduction in LLMICs,^{63–65} there are few published data on documented costs of delivery and the components of those costs.^{31,66–68} Microcosting studies done with the early demonstration programs and GAP pilot programs estimated that the incremental financial costs for HPV vaccine delivery ranged from \$1.11 to \$2.74 per dose (based on the three-dose schedule implemented at the time).^{31,69} However, costing analyses from five initial Gavi HPV demonstration programs resulted in estimated financial costs of delivery between \$3.10 and \$9.21 per dose (three-dose schedule).³⁹ For comparison, the two LLMIC national programs that conducted detailed costing analyses after vaccinations determined that it cost \$2.40 per dose delivered in Bhutan's school-based program in 2010 and \$3.37 per dose delivered in Rwanda's initial school-based program from 2011.^{36,70}

The cost per dose in HPV demonstration programs masks two important dynamics—first, the proportion attributable to startup expenses versus that for recurrent costs; and second, the components



or drivers of these costs (both startup and recurrent).^{31,66} Unpacking the cost-per-dose data reveals that for most demonstration programs, approximately 50% of the cost per dose was for expenses incurred to start the program; e.g. training, microplanning, and social mobilization.^{31,66} Demonstration programs did not benefit from economies of scale observed for other new vaccine introductions that launched nationally from the start.⁷¹ Both the total costs and the proportions spent on different program components varied widely across countries, for both demonstration programs and national introductions, illustrating that it may be unrealistic to assume the cost of HPV vaccine delivery across LLMICs will be uniform.⁷¹

To secure adequate financing for national scale-up, countries will need to understand the drivers of costs and estimate introduction startup and recurrent costs for delivery—including the costs for vaccine procurement—regardless of co-financing arrangements for countries eligible for Gavi support. Interviews from 24 LLMICs indicated concerns about financial sustainability that were hindering decisions to scale-up from demonstration programs to national introduction. Four factors were mentioned: vaccine price; co-financing of vaccines and the increasing country share of this responsibility over time; startup and delivery costs; and securing adequate budget from government and/or donors.³⁹

Programs that leverage existing structures, processes, and activities conducted routinely by national immunization programs will be more likely to gain cost efficiencies for HPV vaccine introduction. For example, adding HPV vaccination training and microplanning to existing training and planning activities could reduce startup costs. Delivery costs for conducting vaccinations in schools may be reduced if countries use routine outreaches (largely conducted at schools already) instead of stand-alone outreaches requiring separate transport and payments to health workers.

To secure finances, countries may require support to review their program activities carefully, understand the costs of different components (including vaccine costs), and make prudent choices to build efficiencies in program design. National immunization programs that make a request for funding based on solid, empirical data, with a strong justification of how costs were reduced through efficient planning, will be better placed when negotiating funding from ministries of health, ministries of finance, and international donors.

3.4 | Fostering sustainability

Political, programmatic, and financial sustainability follow directly from overcoming the challenges outlined above. Maintaining momentum among policy makers, government officials, key stakeholders, and those who influence them requires concerted and repeated efforts to foster the enabling environment needed for political sustainability. Using existing health system infrastructure such as training sessions, outreach programs, and community education programs can boost efficiency. Recent data suggest that the manufacturing cost of producing quadrivalent HPV vaccine is between \$0.48 and \$0.59 a dose, significantly lower than Gavi purchase price of \$4.50 negotiated with the manufacturer.⁷² This

suggests there could be room to negotiate a further reduction in the Gavi purchase price.

4 | GOAL FOR 2020: REACHING 30 MILLION GIRLS

A global analysis of HPV vaccination coverage suggested that only 1% of young women aged 10–20 years in LLMICs had been fully vaccinated by the end of 2014.⁷³ While the pace has picked up since then, the reach of HPV vaccines in countries with the highest rates of cervical cancer is still lagging. As LLMICs navigate this crucial juncture in the evolution of their HPV programs, developments in policy, programming, and science have the potential to amplify current efforts by LLMICs to convert their small-scale HPV demonstration programs to full national implementation.

In regard to policy changes, the Gavi Board announced significant changes for HPV vaccines in December 2016.⁷⁴ The Board approved the discontinuation of the HPV demonstration program and recommended that countries be allowed to provide HPV vaccine to all girls 9–14 years of age in the first year of their national program. This should result in a higher number of girls receiving HPV vaccines sooner. To assist countries in implementing these policy changes, Gavi increased the financial support available to LLMICs for HPV vaccines, recognizing that the first year of HPV vaccine introduction may require one-time investment for activities such as intense social mobilization or additional training for healthcare workers.^{31,39,66,67,71}

With regard to programmatic advances, vaccinating a multiage cohort (or “catch-up”) may have advantages compared with gradual vaccination over time of an equal number of girls. In addition to the potential reduction in delivery costs as vaccination services reach more girls more quickly, vaccinating a larger proportion of the population at once can interrupt HPV transmission more significantly, resulting in population-level benefits and faster appearance of herd protection.^{57,75,76} The well-documented lessons learned from LLMICs’ experience preparing for and implementing HPV vaccination programs—along with a range of available tools and resources^{45–50} and numerous individuals and agencies able to provide technical support to countries—can be mobilized to advance effective programming in more countries.⁷⁷

Scientific advances in vaccine development also offer promise. A nonavalent vaccine, which is similar in constitution to the quadrivalent HPV vaccine but protects against five additional oncogenic HPV types (31, 33, 45, 52, 58), has been shown in clinical trials to be as efficacious against infection and cervical disease and as immunogenic against types 6/11/16/18 as the quadrivalent vaccine, even with a two-dose schedule.^{78,79} The nonavalent vaccine is now in routine use in the USA, and other high-income countries are analyzing the cost-effectiveness of two-dose nonavalent HPV vaccine programs compared with their current programs. While the incremental benefit of the nonavalent vaccine over the quadrivalent vaccine or bivalent vaccine is modest,⁸⁰ if the nonavalent HPV vaccine price is comparable to current prices for existing HPV vaccines, it may become an option



for many countries. As of 2016 this vaccine was under review for pre-qualification by WHO.

Other new HPV vaccines that may become more available globally by 2020 include two being developed by Chinese companies (Innovax and Walvax).^{81–83} Technology transfers of existing vaccines to middle-income country manufacturers have occurred in Brazil and Argentina (for supplying the local market) and are ongoing with the Serum Institute of India (both for supplying the local market and for export).^{84–86} New HPV vaccines in the marketplace, especially those prequalified by WHO, could increase competition among manufacturers and reduce prices.

Another exciting advance in the science of HPV vaccines is the possibility that one dose of HPV vaccine could provide enough protection to significantly reduce the burden of cervical cancer.⁸⁷ Delivery of one dose of HPV vaccine would be immensely easier for LLMICs and could radically change the vaccine introduction paradigm. While early studies show promise, additional evidence for the efficacy and duration of protection of one-dose schedules is needed.^{88,89} Tradeoffs between achieving low or moderate coverage with more doses versus high coverage with a single dose will be important considerations for countries from financial, programmatic, and equity perspectives.

Renewed commitment, collaboration, and coordination by all partners can make the goal of reaching 30 million girls in LLMICs with HPV vaccine by 2020 a reality. We know what it takes. Now, more than ever, is the time to move from knowledge to action.

AUTHOR CONTRIBUTIONS

DSL drafted the manuscript and all co-authors made substantive review and contributions thereafter. There was no formal research, original data collection, or data analysis conducted as a part of this review paper.

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CONFLICTS OF INTEREST

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

Table S1. HPV vaccination experience in low- and lower-middle-income countries, as of December 2016.