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Status of HPV vaccine introduction and barriers to country uptake

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ABSTRACT

During the last 12 years, over 80 countries have introduced national HPV vaccination programs. The majority of these countries are high or upper-middle income countries. The barriers to HPV vaccine introduction remain greatest in those countries with the highest burden of cervical cancer and the most need for vaccination. Innovation and global leadership is required to increase and sustain introductions in low income and lower-middle income countries.

1. The status of HPV vaccine introduction

Since first licensure of human papillomavirus (HPV) vaccines in 2006, the HPV vaccines (bivalent, quadrivalent and 9-valent) have proven to be safe, highly immunogenic and to induce strong direct and indirect protection against HPV and its sequelae [1–5]. National programs with just 50% coverage (or more) of 2 or 3 dose schedules have demonstrated a dramatic impact on population level HPV prevalence, persistent HPV infection, genital warts, and cervical intraepithelial neoplasia [5].

By the end of 2008, a quarter of high-income and upper-middle-income countries (HIC/UMIC) had introduced national HPV vaccination programs but there had been no national introductions in low- and lower-middle-income countries (LIC/LMIC). A recent study estimated that by 2014, just 1.1% of girls aged 10–20 years old in all 84 LIC/LMIC had been vaccinated with 1 or more doses of HPV vaccine, and more than two-thirds (70%) of cervical cancer cases occurred in countries without a national HPV vaccination program [6]. By October 2016, 86 countries (40% of the global total using World Bank definitions) had included HPV vaccines as a part of their national vaccination schedule, but again introductions were primarily in HIC/UMIC with 74 (55%) having national programs compared to only 12 LIC/LMIC (14%; Fig. 1) [7]. Worldwide, approximately 24% of girls aged 9–14 years are were living in a country with a national HPV program in October 2016 (World Bank population figures).

Although the proportion of LIC/LMIC with national HPV vaccination programs is still low, six new introductions took place between 2015 [8] and 2016 [9]. This doubled the number of LIC/LMIC with HPV vaccine programs, setting a new pace for national introductions in the countries who need it most (Fig. 2). In addition, a further 15 LMIC and 16 LIC had delivered HPV vaccine in at least one small scale pilot or demonstration project by May 2016 but had not yet 'scaled-up' to a national program (Fig. 1) [7].

Until October 2016, national introductions in low- and middle-income countries were facilitated through pharmaceutical companies' adhoc donations (e.g. Rwanda's introduction in 2011/12) [9], partner organization funding (e.g. Bhutan and Vanuatu who were supported by the Australian Cervical Cancer Foundation [ACCF] in 2010 and 2013 respectively) [9] and the pooled procurement mechanism of the PAHO revolving fund for governments of countries in Central and South America [7,11]. The PAHO revolving fund has secured vaccine supply at a low price for its members (2017 list price at $8.50 per dose for bivalent and $9.80 for quadrivalent) and therefore bridged the affordability gap for middle-income countries who were ineligible for other vaccine funding. With this funding support, by the end of 2016, 17 of 53 countries and territories in Central and South America had introduced the vaccine, giving theoretical access to 87% of girls aged 9–14 years living there [11].

More recently, LIC/LMIC were able to receive support through Gavi, the Vaccine Alliance (e.g. Uganda in 2015). Between 2013 and 2016, Gavi provided support to over 20 eligible countries (those with GNI per capita $\leq$ $1580 US) for 2-year HPV vaccine demonstration projects [9,12]. Gavi covered the entire cost of vaccines and injection consumables and partially financed delivery

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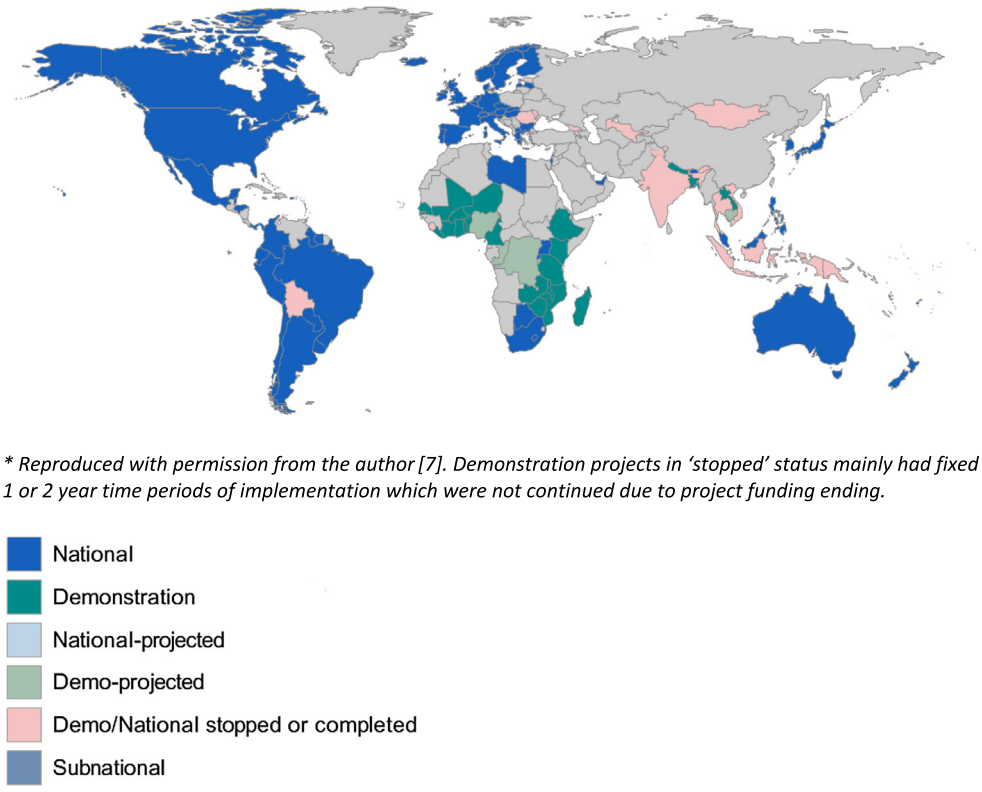

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Fig. 1. Accumulation of global HPV vaccine experience, October 2016[*7]. [*]Reproduced with permission from the author [7]. Demonstration projects in 'stopped' status mainly had fixed 1 or 2 year time periods of implementation which were not continued due to project funding ending.

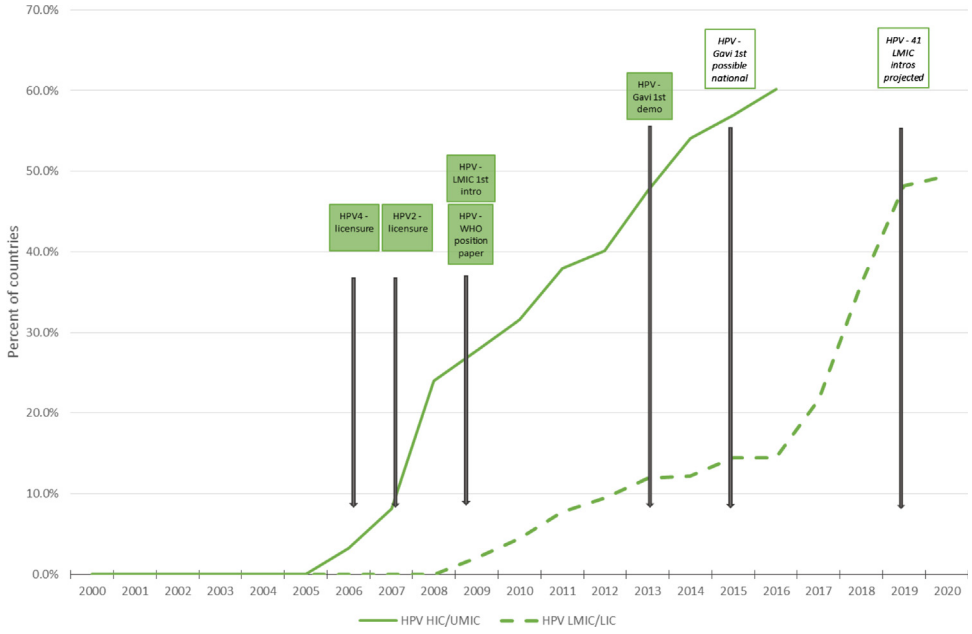

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Fig. 2. Percentage of countries that have included HPV vaccines as a part of their national vaccination schedule by country income group, 2000–2016, and projections for the future[*] [10]. [*]Adapted and reproduced with permission from the author [10].

costs for two years ($4.80 US per girl or $50,000 US, whichever amount was greater in the first year of support, and $2.40 US per girl or $25,000 US, whichever amount was greater in the second year of support). Countries were only eligible to apply for support for national programs if they had experience of delivering a multi-dose vaccine to adolescents, otherwise they could apply for national programs in the second year of their demonstration project funding [12]. Given Gavi's eligibility criteria, funding for national introduction in most LIC/LMIC only practically became available in 2015 [10]. At the end of 2017, 47 countries remained

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eligible for full support from Gavi for HPV vaccine introduction, this included all 31 LIC plus 16 LMIC (30% of 53 LMIC using WB definitions). A further 11 LMIC were in the 'accelerated transition' phase of Gavi support and eligible for some co-financing support for HPV vaccine costs. Although the pace of introductions in LIC/LMIC since licensure has been slow, the pace since vaccine became accessible to these countries, given the barriers to introduction outlined later in this article, is encouraging [10].

Within countries, the coverage achieved by national programs has been highly variable [8]. Among HIC, successful programs such as those in Scotland and Australia have reached >80% of targeted girls with the full schedule [8,13,14]. However, simultaneously, some HIC have struggled to achieve even 50% coverage (e.g. France, USA, Japan, Denmark) due to perceived health concerns fueled by media coverage and/or lack of endorsement from healthcare providers [8,15,16]. Rumors about the vaccine causing disorders such as Postural Tachycardia syndrome (POTS) or isolated episodes of mass psychogenic illness related to receiving the vaccine have created significant problems [16]. In the USA coverage of approximately 30% has been attributed to reliance on health facility based delivery alongside provider reluctance to recommend the vaccine [17,18].

Although fewer LIC/LMIC than HIC/UMIC have introduced national programs and their target population is narrower (often restricted to 9 year-olds only or a single school grade [8] in contrast to the 12–26 year olds targeted in some HIC), the coverage achieved in their national programs has been high [9]. Administrative coverage estimates (number of doses delivered over the estimated target population) available in mid-2016 from 4 national programs in LIC/LMIC indicate that 80–90% of the girls targeted received at least one dose [9] (Table 1). There have been some rumors [19] and issues around acceptability and/or low coverage in some LIC/LMIC but these have generally not been the reason for the lack of national introductions in LIC/LMIC to date [9].

When estimating global HPV vaccine coverage, doses delivered in over 66 small-scale pilots and demonstration projects in LIC/LMIC/UMIC should be taken into account, alongside provision through the private sector and non-government health care providers. Small scale pilots or demonstration projects were generally funded by external donors which restricted the size and scope of these projects to one or two districts of a country (the geographic administrative boundary for health services), targeting between 5,000 and 25,000 girls within preset eligibility criteria (often a single age or single grade cohort) [7,9]. Most small-scale pilots and demonstration projects in LIC/LMIC have achieved 70–90% coverage with the 2 or 3 dose schedule. Data from 56 distinct delivery strategies in 33 LIC/LMIC that implemented demonstration projects indicate median coverage with at least one dose was as high as 93% [9]. Taking just the most recent estimates across the 34 LIC/LMIC with coverage data from national programs or demonstration projects up to May 2016 indicates median coverage with at least one dose is 88% (Table 1). These coverage estimates are supported by a small number of coverage surveys conducted after small demonstration projects in LIC/LMIC (N = 17, median 88%; range 72–99%) [9].

It is important to recognise that the program support from Gavi prior to 2017 for vaccine delivery in LIC/LMIC was targeted to a single year of age cohort from among 9–14 year olds or a single grade [12] at school unless countries could obtain external funding or vaccine donations from other sources. Thus, most LIC/LMICs have had significant financial barriers to vaccinating more than a single year of age cohort each year. Although coverage has generally been high in these specific target populations, the numbers vaccinated as a proportion of the total female population above the age of 9 years may always be lower than in HIC where delivery has often been given to an wider age range through catch-up campaigns that may include vaccinating girls aged up to 26 years (e.g. Australia) [13].

Since the end of 2014, when an estimated 1.2% of 10–14 year-olds in LIC/LMIC had received at least one dose of the vaccine, a large number of girls have been vaccinated [6]. The aforementioned 66 demonstration projects and pilots run by key stakeholders have demonstrated political will and a recognition of the need to introduce the vaccine for cervical cancer prevention. Additionally, some countries have implemented a third 'bridging year' of HPV vaccine delivery to their demonstration project district while the country gains approval for its national HPV program. Changes in Gavi policy to provide HPV vaccine support for national programs, without requiring a demonstration project first, and to deliver to a multi-year cohort of 9–14 year-old girls in the first year of national introduction will enable an acceleration of national programs in LIC/LMIC from 2017 onwards. A further 11 LIC/LMIC have been approved for national programs, scheduled to launch in 2018 and 2019. All but one of these programs are targeting girls aged 9–14 years during the first year of national scale-up and then routinely vaccinating all new cohorts of 9 year old girls in the subsequent years. Projections by Gavi and other partners indicate a further 15 countries will apply for support for national introductions of HPV vaccine over the next few years (Fig. 2).

2. The importance of HPV vaccine introduction in LIC/LMIC

It will be important to continue to expand vaccination availability since the other main intervention to prevent cervical cancer, cervical screening, remains challenging to implement in many LIC/LMIC where more than 85% of cervical cancer cases occur. The impact that cytology-based screening has had on cervical cancer rates in HIC has not been replicable in low-resource settings [20]. Cytology-based screening methods require substantial logistical and human resources and necessitate women to return at regular intervals for re-screening due to the low sensitivity of cytological screening [20].

Although globally, 25 countries have introduced national VIA-based screening programs, among LIC/LMICs services are generally

Table 1
Coverage of at least one dose in 34 distinct LIC/LMIC (taking the most recent data available by May 2016 [9].

Countries classified by Income group and most recent program/project	Number of countries with data	Coverage with at least 1 dose of HPV vaccine				
		≥90%	80–89%	70–79%	60–69%	Median
National program						
LIC	1	1 (100%)				NA
LMIC	3	1 (33%)	1 (33%)	1 (33%)		84%
Demonstration project						
LIC	14	7 (50%)	4 (29%)	2 (14%)	1 (7%)	89.5%
LMIC	16	7 (44%)	5 (31%)	4 (25%)		88%
Total	34	16 (47%)	10 (29%)	7 (21%)	1 (3%)	88.5%

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restricted to small scale pilots [21] or heterogeneous coverage via ad-hoc service provision from non-governmental organizations. Even in countries with national programs, coverage is often low, at around 10–20% of adult women in the poorest countries [22].

HPV testing using self-collected samples has the potential to increase coverage of screening services significantly, especially in hard to reach populations [22]. In Uganda, HPV testing using self-collected samples achieved 95% uptake, compared with 48% coverage using VIA [22]. However, until low-cost point of care tests become widely available, HPV testing remains expensive to establish and maintain as a primary screening test. Additionally, the specificity of HPV testing may favor treatment algorithms that include a second diagnostic test but this is not ideal in countries where currently the only chance of achieving good coverage is with a single visit algorithm [20]. The most cost-effective methods to triage and treat HPV-infected women in LIC/LMIC are yet to be determined [22,23]. HPV testing as a screening method has only been in the form of small scale demonstration projects to date, with no known national introductions in LIC/LMIC [20].

Despite innovations in screening and self-collection of samples, the estimated percentage of women who are accessed by at least one screening test in their lifetime and treated for precancers is still very low in LIC/LMIC [22]. More than 85% of all cervical cancer cancers and deaths are in LIC/LMICs (Table 2). The increased burden of cervical cancer among HIV-infected women increases the potential impact of vaccination in some LIC/LMIC. However, given the target age group for vaccination, 9–13 year-old girls in most LIC/LMIC, it is projected to take decades for the current coverage of vaccination and screening services to impact cervical cancer rates [24].

3. Challenges in implementing HPV vaccination programs in LIC/LMIC

There are multiple factors affecting HPV vaccine introduction in LIC/LMIC; historical, programmatic, and residual barriers to HPV vaccine introduction are highlighted below.

3.1. Historical/structural

Despite vaccine licensure in 2006 and rapid uptake by some HIC, funding and support for introductions in LIC/LMIC only became available to the poorest countries in 2013 through Gavi and even then it was in practice restricted to demonstration projects until countries accrued some experience in delivering a new vaccine to young adolescents. For most countries, this meant that funding for national introductions was available from 2015, after the first two-year demonstration projects were completed. Prior to price negotiations through Gavi, the vaccine was prohibitively expensive for LIC at >$100 US per dose. Gavi negotiated supply at $4.50–4.60 US per dose. The only national programs in LIC before 2015 were through donations from pharmaceutical companies or NGO support (e.g. Rwanda, Lesotho, Bhutan, Vanuatu). In this context, the 12 national introductions among LIC/LMIC within two years from funding and affordable vaccine really being available (2015–2016) are encouraging [10].

3.2. Programmatic

Gavi supported HPV vaccine delivery in over 20 demonstration projects between 2013 and 2016. By the July 2017, nine of these countries had made national decisions to scale up and received approval from Gavi for vaccine support and financing. A further two had approval to conduct Gavi national programs without conducting a demonstration project. However, for many LMICs, there are still significant programmatic and financial barriers to implementing HPV vaccine nationally. Pneumococcal conjugate vaccine (PCV), rotavirus and inactivated polio vaccines, which are more easily integrated into the existing infant EPI schedule than HPV vaccine and are accompanied by influential access models, e.g. the Accelerated Development and Introduction Plans (ADIPs) [10] and The Polio Endgame [26][2], may compete with HPV vaccine for the limited financial and human resources required for new vaccine introduction [27,28].

Despite co-financing of vaccine supply for Gavi eligible countries, co-financing commitments have been unaffordable for some countries with large populations and multiple new vaccine introductions in the past year, e.g. PCV and rotavirus vaccines [29]. Competing priorities have led to some of the earlier introductions of infant vaccines to be continued (for now) at the expense of plans to scale-up HPV vaccination. Countries approaching the threshold Gavi eligibility threshold (GNI per capita rises >$1580 US) must plan to enter a 5-year transition phase with a year-to-year increase of co-financing commitments each year, until the country is fully financing their EPI program. During the period 2014–2016 some Gavi countries only funded 15–30% of their routine immunization programs [29]. Even the cost of a two-dose schedule to girls is seen as too expensive at the current Gavi vaccine price of $4.50 US per dose. Imminent 'transition' out of Gavi support understandably has led to reluctance among policy makers and ministries of finance to commit to another new vaccine introduction.

There is evidence from a number of demonstration projects and studies, e.g. Vietnam, Uganda, and Rwanda, that vaccine delivery does not have to be expensive [30,31]. If supported by Gavi for demonstration projects, countries received substantial funds to cover the delivery cost of the vaccine. Most countries used these funds to conduct a specific HPV vaccination campaign with little integration into existing services or routine immunization programs since the demonstration project was usually implemented in a small area of the country. The older age of the target group also made integration into the routine immunization system more challenging than for infant vaccinations. Generally, the demonstration projects used all of the available funds from Gavi and therefore cost analyses indicated a high cost of delivery per dose. The mean cost of delivery in a five country analyses was $6.00 US per dose for a campaign style delivery including mobilization, training, delivery and some evaluation [9]. The largest proportions of delivery costs were allocated to transportation and per diem costs for health

Table 2
the proportion of countries with national HPV vaccination programs and their cervical cancer burden.

Income group	Number of national HPV vaccine programs	Number of cervical cancer cases in women estimated 2012[a]	Cervical cancer incidence rate/100,000 women years[b]	Cervical Cancer mortality rate/100,000 women years[b]
HIC/UMIC	74/134 (55%)	83,078 (14%)	9.9	3.3
LIC/LMIC	12/84 (14%)	444,546 (86%)	15.7	8.3

[a] Data in HIC/UMIC are strongly influenced by the large population of China (UMIC) with an estimated 61,691 active cases in 2012, incidence rate of 7.5/100,000 and a mortality rate of 3.4/100,000. Data in LIC/LMIC are heavily influenced by the large population of India (LMIC), with an estimated 122,824 cases of cervical cancer in 2012, an incidence rate of 22.0 and a mortality rate of 12.4/100,000 women.
[b] Age-standardized rates from 2012 [25].

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workers and supervisors to travel to schools but social mobilization activities also accounted for a large proportion of funds in cost analyses [32]. Policy makers perceived that delivery of HPV vaccine was expensive and unsustainable. For national vaccination programs, including HPV vaccine programs, Gavi does not provide support for delivery costs and this was a factor contributing to a number of LIC deciding not to scale-up immediately after their demonstration projects [9,27].

At the end of 2017 it remained unclear as to whether the 26 (49%) LMIC not eligible for full or partial support from Gavi would introduce HPV vaccination (21 countries) or sustain their programs (5 countries). These countries constitute the 'missing middle', unable to afford the vaccine at negotiated prices with the manufacturers but equally ineligible for donor support. India is an important country among the 21 LMIC yet to introduce and ineligible for full Gavi support. The number of 9–14 year old girls living in a country with a national program would increase by approximately 71.9 million if introduction occurred nationally across India and bring the proportion of 9–14 year old girls living in a country with a national program to approximately 44%.

3.3. Residual barriers to delivery now

In countries that have not yet introduced HPV vaccine, new Gavi guidelines indicate that countries applying for HPV vaccine support in 2017 onwards should do so for a national program. Funding will be supplied through a vaccine introduction grant (VIG) of $2.40 US per girl in a single age cohort, e.g. girls aged 9 years, to support the startup of the national program in the first year, e.g. training and social mobilization, as per Gavi policy for other vaccine introductions. Additionally in the first year, a multi-age cohort can be targeted and vaccine will be supplied at no cost for the estimated target population between 10 and 14 years of age for the first year only. Operational support for the costs of delivery to the additional multi-age cohort of girls will be commensurate with the amount given for other campaigns at $0.65 US per eligible girl [33]. For countries with no HPV vaccine experience but confidence that they can deliver a national program, this is likely to reduce the barriers to introduce and increase coverage in LIC/LMIC. However, issues of competing priorities are likely to remain, as well as the reluctance to commit to another new vaccine introduction if graduation from Gavi support is imminent. The required political will and commitment to take on a national program is greater than that needed to apply for a demonstration project that was almost fully funded by Gavi.

In-school delivery strategies with some strategy to reach out of schoolgirls are to date the predominant delivery strategy chosen to achieve high coverage and delivery is still perceived as expensive, although there have been experiences that have proved the contrary [34,35]. The HPV demonstration program in Bangladesh documented 87% coverage with school-based delivery at a financial cost of delivery per dose of just $0.57 US (vaccine provided by Gavi at no cost), which was achieved by including HPV vaccine delivery into health worker's expected job duties with no additional compensation [36,37], [pers. Communication D.S. LaMontagne]. Experience with routine, non-campaign style delivery on a national scale is limited and needs to be expanded to assess the achievable coverage and the cost of such using this strategy in different settings. Vaccine delivery is not necessarily expensive when integrated more fully into the regular EPI program structure and processes and high coverage can be achieved [38,39].

Supply of HPV vaccines needs to be maintained and needs to have the capacity to increase as and when demand increases globally. Limited competition in the current market may be keeping vaccine procurement prices high. It is unclear how the new nonavalent vaccine will be priced or whether it would be procured by either Gavi or the PAHO revolving fund.

Acceptability among the community and prompt address of rumors needs to be maintained as these can derail vaccine programs. Given the experiences in Japan [16], India [40], and Denmark [41], the global community needs to remain vigilant and share lessons to prevent rumors or episodes of psychogenic illness affecting delivery in LIC/LMIC.

The focus on attaining 100% coverage can be unhelpful. Significant impact of vaccination on disease could be achieved with coverage even lower than 40% [5,24,42]. Introduction should be encouraged, alongside experimentation with delivery strategies and intervals between doses to enable countries to design their own sustainable programs, even if this means a few years of lower coverage than could be achieved with a campaign. Although dropout rates in small scale demonstration projects and national programs in LIC/LMIC to date have been very low, with the majority achieving $\leq$10% dropout [9], the ability to track girls and maintain adherence in multi-year cohorts targeting 9–14 year-old girls needs to be monitored.

4. Catalysing national scale up in LIC/LMICs

The change in Gavi guidelines for support of HPV vaccination programs may mean broader target populations in first year and more national introductions. Forward projections indicate that by 2020, 48% of LIC/LMIC may have introduced the vaccine [10].

New programs could be designed more efficiently, which may encourage some of the countries that have become hesitant since their demonstration projects to introduce HPV vaccines imminently. Larger multi-year cohorts could be vaccinated with less frequent campaigns. For example, the current two-dose schedule could be delivered as one dose every 12 months rather than every 6 months.

There is some evidence that one dose of HPV vaccine may be enough to stimulate a protective immune response [4,43]; however, the duration of vaccine-induced protection and the applicability of reduced schedules for HIV-positive girls remain unclear. Randomised controlled trials to assess immunogenicity and efficacy of a one-dose regimen are ongoing [44,45]; if successful, HPV vaccine schedules may reduce even further. A one-dose regimen may help to overcome a number of the barriers to national introduction described previously and accelerate the currently projected fast pace of national introductions in LIC/LMIC in the next few years:

- Vaccine supply costs would halve if a one-dose schedule proves effective. At $4.50 US per dose, HPV vaccine would remain an expensive per unit cost in comparison with other vaccines; however, delivery to girls only would keep the cost of the program lower than other multi-dose regimens to entire birth cohorts (for female and male infants), e.g. three-dose pneumococcal conjugate vaccination programs.
- The schedule may be logistically easier to deliver and easier to integrate into routine delivery by specifying delivery on a certain birthday or when a child reaches a certain grade in school or be easier to combine with annual vaccination events such as national immunization weeks, tetanus toxoid campaigns, or annual school health days. One-dose may allow wider age cohorts to be vaccinated within the same funding envelope for delivery, especially if vaccine is delivered to all ages in a mass national campaign like activities implemented during the Africa Vaccination Week [46].
- Recurrent costs related to delivery of the vaccine may fall, although many start-up costs, e.g., training, microplanning, social mobilization, will remain.

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- The perceived challenges of delivering a multi-dose schedule to adolescents and concerns over the capacity of the workforce to achieve good coverage in this target population may decrease, making HPV vaccine seem more like a relatively 'easy win'.
- Perceived delivery costs (both opportunity costs and financial costs) among policy-makers may fall and this may aid policy makers to prioritise the vaccine over other expenditures in the health program.
- Metrics of the success of the program, e.g. coverage, would be easier to track with the use of a simple register or card and no loss-to-follow-up.
- A one-dose regimen may extend existing vaccine supply for a longer period and/or for more individuals.
- Countries with sufficient funds and supply may be able to decide whether to vaccinate a broader age cohort of young women or extend vaccination to cohorts of young men also.

5. Conclusion

Substantial progress has been made; over 80 countries worldwide now have HPV vaccination programs; the barriers to HPV vaccine introduction remain greatest in those countries with the highest burden of cervical cancer and the most need for vaccination. Funding for eligible LIC/LMIC is available through Gavi to vaccinate 40 million girls by 2020; however, international commitment is needed to maintain current HPV vaccine programs and extend support after 2020. In the long-term, work is needed to ensure a sustainable structure of international funding and support and to strengthen health systems and immunization programs in order for HPV vaccine to become just one of a platform of services delivered to young men and women. In the short-term, if one-dose HPV vaccination became viable, some of the significant barriers to scale-up and sustained use in LIC/LMIC may be overcome.

Conflicts of interest

The authors have no conflict of interests to declare.

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