Many low- and middle-income countries are moving to introduce HPV vaccine into their national immunization programs. To improve coverage, equity, and sustainability, public health officials and practitioners can use planning and implementation lessons learned, including successful school-based delivery strategies, innovative approaches to reach out-of-school girls, best practices for communication and social mobilization, and integration of services to reduce delivery cost. Policy makers, donors, and global partners should continue to consider ways to drive down costs of vaccine procurement.

CERVICAL CANCER BURDEN AND HPV VACCINE RECOMMENDATIONS

As countries move to add primary prevention to their strategies to combat death and morbidity associated with cervical cancer, many practitioners in immunization as well as experts in non-communicable and communicable diseases will benefit from keeping up-to-date with recent developments in practice and implementation regarding human papillomavirus (HPV) vaccine delivery.

Persistent infection of cervical epithelial cells with “high-risk” carcinogenic types of HPV causes 99% of the estimated 530,000 global cases of cervical cancer each year—the majority of which occur in low- and lower-middle-income countries, where screening and treatment programs are not typically robust. HPV types 16 and 18 cause 70% of cancer globally; the contribution of 5 more high-risk HPV types accounts for 90% of the global cervical cancer burden.

Three HPV vaccines are currently on the global market: a bivalent product (protecting against HPV types 16 and 18), a quadrivalent product (protecting against HPV types 6, 11, 16, 18), and a nonavalent product (protecting against HPV types 6, 11, 16, 18, 31, 33, 45, 52, 58). These vaccines are close to 100% efficacious at preventing HPV infection from the HPV types they target directly, with additional cross-protection against other HPV types. Multiple clinical trials, particularly of the bivalent and quadrivalent products (the first market entrants), have also demonstrated close to 100% efficacy in protecting against cervical intraepithelial neoplasia caused by HPV types covered by these vaccines. All 3 vaccines offer a similar, positive safety profile.

The World Health Organization (WHO) recommends all countries include HPV vaccine in their national immunization schedule. WHO recommends 2 doses of HPV vaccine for girls ages 9–14 years, separated by a minimum interval of 6 months, and 3 doses of HPV vaccine for girls ages 15 years and over. Vaccination during pregnancy is not recommended; however, accumulating safety evidence suggests no increased risk of adverse pregnancy outcomes. Immunocompromised youth, including anyone with HIV, should be vaccinated with 3 doses. Of note, neither HIV nor pregnancy testing are indicated as a prerequisite for receiving the vaccine.

WHO recommends that, if feasible, countries vaccinate multiple age cohorts (e.g., 9–14 year-olds) in the first year of introduction. The existence of a cervical cancer screening or treatment program is not a prerequisite for vaccine introduction.

We offer this commentary in the hope of focusing dialogue between and among public health practitioners and public health officials on key recent developments in the planning and implementation of HPV vaccination programs.

SUPPORT FOR HPV VACCINE INTRODUCTION

Gavi, the Vaccine Alliance provides support for vaccine introduction and immunization programs in eligible countries; country eligibility for support from Gavi is chiefly determined by the gross national income (GNI) per capita, which determines the level of co-financing and nature of vaccine program support available. Between 2012 and 2016, both Gavi and vaccine...
Achieving high vaccination coverage through a routine immunization program among adolescent girls necessitates innovative delivery strategies and communication efforts. Among 45 low- and middle-income countries surveyed in 2016 after having completed HPV vaccine demonstration programs or national introduction, most (87%) used primarily a school-based delivery strategy. While the majority (96%) of programs reporting data successfully achieved first-dose vaccination coverage of at least 70% among the target age group, only 83% of programs reporting data attained the same milestone for complete series coverage. The use of a school-based delivery strategy for other relevant vaccines has been successfully implemented in some countries, for example, for second-dose measles vaccine at school entry and vaccines against tetanus, diphtheria, and pertussis. The use of school health programs to deliver other health services, such as vitamin A supplementation and deworming medications, is a well-established practice. However, while teachers can feasibly be trained to distribute tablets or medications, an injectable vaccine requires additional health worker involvement that can be disruptive or resource-intensive for national immunization programs to provide in the school setting.

Using a school-based vaccine delivery platform has effectively achieved high coverage for girls in school but poses an equity challenge for out-of-school youth, many of whom have poor access to health services and screening later in life. Despite the use of fixed-site and targeted outreach strategies to reach out-of-school girls in demonstration projects, few data-driven strategies to deliver HPV vaccines to out-of-school-girls have been designed and implemented, and fewer rigorously tested. Even in populations with high primary school enrollment, there may be poor school attendance among 9–14 year-olds. Unless social mobilization efforts are undertaken to ensure enrolled girls attend school on vaccination days, vaccination coverage will likely be low.

To continue to build successful HPV vaccination programs, several types of stakeholders must be engaged in the program planning process. Regardless of how and where the vaccine is delivered, education stakeholders need to be involved in program planning and communication, as the adolescent age group is largely enrolled in primary school. Other key stakeholders include adolescent and youth service providers, community service organizations, local women’s groups, family planning and reproductive health advocates, cervical cancer specialists, gynecology organizations, and HIV prevention and treatment groups. Vaccine delivery may also be a promising service for integration with other development or health services for girls, such as nutrition, economic empowerment, menstrual hygiene, and disease prevention, so stakeholders who are experts in those programs may be involved.

While at least 11 countries around the world, including Australia and the United States of America, routinely vaccinate boys with HPV vaccine, achieving high coverage among girls is a more cost-effective vaccination strategy in low- and middle-income countries than a “gender-neutral” vaccination strategy that immunizes both girls and boys. Countries can certainly choose to also vaccinate boys if this strategy is...
deemed financially and politically feasible; however, Gavi is currently only providing donor funding for vaccination of girls ages 9–14 years.

The current context of most countries focusing on vaccinating girls illuminates the importance of having a clear communication and social messaging campaign in place, with a realistic and nimble crisis communication strategy that can be activated quickly if rumors emerge. Vaccinating only girls can lead to rumors about the vaccine impacting fertility. Many countries have found that best practice is to have media, and well-trained media spokespersons, involved early in the planning, well ahead of vaccine introduction activities.

Although delivering vaccines to girls nationwide requires a different scale of resource commitment than a demonstration program, a number of potentially generalizable communication lessons can be drawn from studying programs that have implemented HPV vaccination to date. Program evaluations have shown how important it is for vaccination programs to be jointly “owned” by both the immunization program as well as educational institutions, for consent, social mobilization, logistics, and monitoring. Data from prior evaluations demonstrate that opt-out consent processes are generally acceptable and follow the consent format of other routine immunizations. Using an opt-in consent process can lead to rumors and misconceptions, but this may be mitigated by face-to-face communication with parents and communities. Experience responding to rumors and negative stories in the media has shown program implementers that social mobilization should happen well ahead of vaccine introduction.

Our understanding of best practices continues to evolve, highlighted by some best-case examples from Rwanda and Bhutan. In 2011, Rwanda became the first low-income country in the world to introduce HPV vaccine into its national program, and with strong leadership from its First Lady, partnership with industry, and effective, evidence-based mobilization efforts, has consistently reported between 93% and 96% full-course coverage. Bhutan, a lower-middle-income country and another early adopter, introduced HPV vaccine into its national immunization program in 2010, and with country ownership, a strong public-private partnership, an evidence-based and flexible delivery strategy, leadership from schools, and a proactive approach to media engagement, thereafter achieved consistent complete series coverage of over 90% among targeted 12-year-old girl cohorts, using a school-based delivery strategy.

Although adolescence is arguably one of the healthiest periods of the life course, investment in this population, and inquiry into which services can be successfully and cost-effectively bundled with HPV vaccination, offers significant opportunity for impact.

## ECONOMIC CONSIDERATIONS FOR LOW- AND MIDDLE-INCOME COUNTRY INTRODUCTIONS

### Cost-Effectiveness

Overall, validated and relatively sophisticated economic models predict that HPV vaccination is very cost-effective in most countries, particularly in lower-income countries. Introducing an expensive new vaccine constitutes a significant investment on behalf of a government, with vaccine cost accounting for approximately half of the total cost of procurement and delivery. Delivery costs reported across demonstration programs and delivery strategies ranged from US$1.11 to $9.21 per dose. Bhutan spent US$2.40 to deliver each HPV vaccine dose in a well-documented 2010 evaluation of its national program. In Tanzania, a 2012 analysis estimated a delivery cost using a periodic school-based campaign delivery strategy of US$3.09 per dose; this cost estimate was in addition to the cost of vaccine, and the program was categorized as a very cost-effective intervention.

### Resources to Support New Vaccines for Low- and Middle-Income Countries

All 3 HPV vaccine products on the global market are currently WHO-prequalified; as of August 2018, the quadrivalent and bivalent products are approved for Gavi funding support to eligible countries. Gavi provides a vaccine introduction grant as part of its initial start-up package to a country to cover operational costs and social mobilization efforts. Gavi-eligible countries can also procure the prequalified HPV vaccines for US$4.60 per dose (bivalent product) and US$4.50 per dose (quadrivalent product). However, as country economic indicators (i.e., GNI) improve to the point that they are no longer eligible for Gavi funding, countries must budget an incrementally larger share of the costs each year until they entirely self-fund both vaccine procurement and delivery costs. For countries whose economic indicators (i.e., GNI) improve to the point that they are no longer eligible for Gavi funding, as well as for middle-income
countries that were never Gavi-eligible, these recurring programmatic and procurement costs represent a significant portion of national immunization budgets. Depending upon the vaccine, manufacturers may agree to continue offering Gavi-negotiated prices to countries for a selected number of years after transition. However, we note the critical need for donor mechanisms to ensure that middle-income countries can introduce HPV vaccines, and that transitioning countries can sustain new introduction decisions.

Innovations and Potential Shifts in Cost
Looking forward, new developments may be able to reduce HPV vaccine procurement and delivery costs. The eventual market entry of vaccines manufactured by companies based in low- and middle-income countries and owned by local entities may create the same downward pressures on prices as we have seen with multiple other medicines and biologics. One of the key barriers to development of such low-cost second-generation HPV vaccines is the lack of standardized and widely accessible laboratory serology tests and assays to assess how new vaccines perform against the currently licensed vaccines. An initiative intended to standardize and evaluate new laboratory tests—developed by a variety of institutions—to address this gap was established at the beginning of 2017 at the U.S. National Cancer Institute.

Other factors may also play a role in reducing expected costs of program implementation. For example, an analysis by Gavi and WHO anticipates that national programs will harness economies of scale much more effectively than small demonstration programs were able to do.

Data on whether a 1-dose schedule confers adequate levels of protection show promise, but the science available does not yet provide definitive guidance for policy. The U.S. National Cancer Institute is currently conducting a large randomized controlled trial to evaluate the efficacy of a single-dose regimen in Costa Rica, with availability of results targeted for 2023.

Relationship to Cervical Cancer Screening and Treatment
As countries introduce and scale up HPV vaccination programs, cervical cancer screening remains important for women who do not get vaccinated as children and for women who may have been infected with a high-risk HPV type that is not included in the vaccine. As national stakeholders in cancer and chronic diseases come together with immunization programs and their advisory bodies to make policy on HPV vaccination, they have an important opportunity to also inform their national policies on cervical screening and surveillance programs.

Acknowledgments: The authors wish to acknowledge Terri Hyde, Kim Fox, Abigail Shefer, and Lauri Markowitz for reviewing and providing input on drafts of this commentary.

Funding: None.

Disclosure: The findings and conclusions in this report are those of the author(s) and do not necessarily represent the official position of the U.S. Centers for Disease Control and Prevention/the Agency for Toxic Substances and Disease Registry.

Competing Interests: None declared.

REFERENCES
1. de Martel C, Plummer M, Vignat J, Franceschi S. Worldwide burden of cancer attributable to HPV by site, country and HPV type. Int J Cancer. 2017;141(4):664–670. CrossRef Medline
2. Walboomers JM, Jacobs MV, Manos MM, et al. Human papillomavirus—virus is a necessary cause of invasive cervical cancer worldwide. J Pathol. 1999;189(1):12–19. CrossRef Medline
3. Globocan 2012. Cervical cancer. Estimated incidence, mortality and prevalence worldwide in 2012. Lyon, France: International Agency for Research on Cancer, 2013. http://globocan.iarc.fr/old/FactSheets/cancers/cervix-new.asp. Accessed October 4, 2018.
4. Human papillomavirus vaccines: WHO position paper, May 2017. Wkly Epidemiol Rec. 2017;92(19):241–268. Medline
5. Serrano B, de Sanjosé S, Tous S, et al. Human papillomavirus genotype attribution for HPVs 6, 11, 16, 18, 31, 33, 45, 52 and 58 in female anogenital lesions. Eur J Cancer. 2015;51(13):1732–1741. CrossRef Medline
6. Iversen OE, Miranda MJ, Ulied A, et al. Immunogenicity of the HPV-16/18 AS04-adjuvanted vaccine: a combined analysis of four randomised controlled clinical trials. Clin Vaccine Immunol. 2013;20(5):775–783. CrossRef Medline
7. Bissett SL, Gadi A, Lit M, Reddows S. Seropositivity to non-vaccine incorporated genotypes induced by the bivalent and quadrivalent HPV vaccines: a systematic review and meta-analysis. Vaccine. 2017;35(32):3922–3929. CrossRef Medline
8. De Vincenzo R, Ricci C, Conte C, Scambia G. HPV vaccine cross-protection: highlights on additional clinical benefit. Gynecol Oncol. 2013;130(3):642–651. CrossRef Medline
9. Future II Study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. N Engl J Med. 2007;356(19):1915–1927. CrossRef Medline
10. Agter D, Wheeler CM, Paavonen J, et al; HPV PATRICIA Study Group. Efficacy of human papillomavirus 16 and 18 (HPV-16/18) AS04-adjuvanted vaccine against cervical infection and precercar in young women: final event-driven analysis of the randomized, double-blind PATRICIA trial. Clin Vaccine Immunol. 2015;22(4):361–373. CrossRef Medline
11. Ault KA; Future II Study Group. Effect of prophylactic human papillomavirus L1 virus-like-particle vaccine on risk of cervical intraepithelial neoplasia grade 2, grade 3, and adenocarcinoma in situ: a combined analysis of four randomised clinical trials. Lancet. 2007;369(9576):1861–1868. CrossRef Medline
12. Naud PS, Roteli-Martins CM, De Carvalho NS, et al. Sustained efficacy, immunogenicity, and safety of the HPV-16/18 AS04-
adjuvanted vaccine: final analysis of a long-term follow-up study up to 9.4 years post-vaccination. Hum Vaccin Immunother. 2014;10 (8):2147–2162. CrossRef. Medline

13. Scheller NM, Pasternak B, Melgaard-Nielsen D, Svanstrøm H, Hvidv A. Quadrivalent HPV vaccination and the risk of adverse pregnancy outcomes. N Engl J Med. 2017;376(13):1223–1233. CrossRef. Medline

14. Eligibility and transition policy. Gavi, the Vaccine Alliance website. http://www.gavi.org/about/programmes/policies/eligibility-and-transition/. Accessed January 5, 2018.

15. Human papillomavirus vaccine support. Gavi, the Vaccine Alliance website. Available from: http://www.gavi.org/support/nv/ human-papillomavirus/. Accessed January 5, 2018.

16. Gallagher KE, Howard N, Kabakama S, et al. Lessons learnt from human papillomavirus (HPV) vaccination in 45 low- and middle-income countries. PLoS One. 2017;12(6):e0177773. CrossRef. Medline

17. Dorji T, Tsombo U, Phuntsom T, et al. Introduction of a national HPV vaccination program into Bhutan. Vaccine. 2015;33(31):3726–3730. CrossRef. Medline

18. School-based immunization. World Health Organization website. http://www.who.int/immunization/programmes_systems/policies_strategies/school_based_immunization/en/. Last updated November 21, 2017. Accessed August 31, 2018.

19. World Health Organization. Measles vaccines: WHO position paper, April 2017 - Recommendations. Vaccine. 2017; pii:50264-410X(17)30974-X. CrossRef. Medline

20. Quinn H, McIntyre P. The impact of adolescent pertussis immunization, 2004–2009: lessons from Australia. Bull World Health Organ. 2011;89(9):666–674. CrossRef. Medline

21. Federico SG, Abrams L, Everhart RM, Melinkovich P, Hambidge SJ. Addressing adolescent immunization disparities: a retrospective analysis of school-based health center immunization delivery. Am J Public Health. 2010;100(10):1630–1634. CrossRef. Medline

22. Hall A, Adjei S, Khamia C. School health programmes. Afr Health. 1996;18(6):22–23. Medline

23. Prakash R, Beattie T, Javalkar P, et al. Correlates of school dropout and absenteeism among adolescent girls from marginalized community in north Karnataka, south India. J Adolesc. 2017;61:64–78. CrossRef. Medline

24. Muyamboza KP, Mwagomba BM, Valle M, Chiumia H, Phiri T. Implementation of a human papillomavirus vaccination demonstration project in Malawi: successes and challenges. BMC Public Health. 2017;17(1):599. CrossRef. Medline

25. Howard N, Gallagher KE, Mourrier-Jack S, et al. What works for human papillomavirus vaccine introduction in low and middle-income countries? Papillomavirus Res. 2017;4:22–25. CrossRef. Medline

26. LaMontagne DS, Barge S, Le NT, et al. Human papillomavirus vaccine delivery strategies that achieved high coverage in low- and middle-income countries. Bull World Health Organ. 2011;89(11):821–8308. CrossRef. Medline

27. Watson-Jones D, LaMontagne D. HPV vaccine lessons learnt project overview. London and Seattle, WA: London School of Hygiene & Tropical Medicine and PATH; 2016. http://www.rho.org/files/PATH-LSTM_HPVacCL_overview_2016.pdf. Accessed October 4, 2018.

28. Bruni L, Barrionuevo-Rosas L, Albergo G, et al. Human Papillomavirus and Related Diseases Report: Rwanda. Barcelona, Spain: ICO/IARC Information Centre on HPV and Cancer (HPV Information Centre); 2017. http://www.hpvcentre.net/statistics/reports/RWA.pdf. Accessed October 4, 2018.

29. Gatema M, Bhatt S, Ngabo F, et al. Successful introduction of four new vaccines in Rwanda: high coverage and rapid scale up of Rwanda’s expanded immunization program from 2009 to 2013. Vaccine. 2016;34(29):3420–3426. CrossRef. Medline

30. Jit M, Brissin M, Portnoy A, Hutubessy R. Cost-effectiveness of female human papillomavirus vaccination in 179 countries: a PRIME modelling study. Lancet Glob Health. 2014;2(7):e406–e414. CrossRef. Medline

31. Bohwright S, Holroyd T, Nanda S, et al. Experiences of operational costs of HPV vaccine delivery strategies in Gavi-supported demonstration projects. PLoS One. 2017;12(10):e0182663. CrossRef. Medline

32. Quentin W, Terris-Prestholt F, Changalucha J, et al. Costs of delivering human papillomavirus vaccination to schoolgirls in Mwanza Region, Tanzania. BMC Med. 2012;10(1):137. CrossRef. Medline

33. Campos NG, Kim JJ, Castle PE, et al. Health and economic impact of HPV 16/18 vaccination and cervical cancer screening in Eastern Africa. Int J Cancer. 2012;130(1):2672–2684. CrossRef. Medline

34. Monson K, Schoenstadt A. Generic HPV Vaccine. eMedTV website. http://hpv.emedtv.com/hpv-vaccine/generic-hpv-vaccine.html. Last updated/reviewed January 9, 2017. Accessed January 14, 2018.

35. Clendinnen C, Zhang Y, Burwarran RH, Light DW. Manufacturing costs of HPV vaccines for developing countries. Vaccine. 2016;34(48):5984–5989. CrossRef. Medline

36. Cole M. New HPV serology laboratory aims to standardize assays and contribute to vaccine implementation and access. Frederick National Laboratory for Cancer Research website. https://frederick.cancer.gov/news/new-hpv-serology-laboratory-aims-standardize-assays-and-contribute-vaccine-implementation-and. Published July 28, 2017. Accessed January 14, 2018.

37. Kreimer AR, Rodriguez AC, Hildesheim A, et al; CVT Vaccine Group. Proof-of-principle evaluation of the efficacy of fewer than three doses of a bivalent HPV16/18 vaccine. J Natl Cancer Inst. 2011;103(19):1444–1451. CrossRef. Medline

38. Safaeian M, Porcas C, Pan Y, et al; CVT Vaccine Group. Durable antibody responses following one dose of the bivalent human papillomavirus L1 virus-like particle vaccine in the Costa Rica Vaccine Trial. Cancer Prev Res (Phila). 2013;6(11):1242–1250. CrossRef. Medline

39. Sankaranarayanan R, Prabhu PR, Pavlina M, et al; Indian HPV Vaccine Study Group. Immunogenicity and HPV infection after one, two, and three doses of quadrivalent HPV vaccine in girls in India: a multicentre prospective cohort study. Lancet Oncol. 2016;17(1):67–77. CrossRef. Medline

40. Kreimer AR, Struyf F, Del Rosario-Raymundo MR, et al; Costa Rica Vaccine Trial Study Group Authors; PATRICIA Study Group Authors; HPV PATRICIA Principal Investigators/Co-Principal Investigator Collaborators; GSK Vaccines Clinical Study Support Group. Efficacy of fewer than three doses of an HPV-16/18 AS04-adjuvanted vaccine: combined analysis of data from the Costa Rica Vaccine and PATRICIA trials. Lancet Oncol. 2015;16(7):775–786. CrossRef. Medline

41. Zeybek B, Rodriguez A. Comparison of long term impact and clinical outcomes of reduced dose vs standard dose quadrivalent human papillomavirus vaccine in the United States: a database study. Gynecol Oncol. 2017;145(suppl 1):3–4. CrossRef

42. Kreimer AR, Sherman ME, Sasaharuddhe VV, Safaeian M. The case for conducting a randomized clinical trial to assess the efficacy of a single dose of prophylactic HPV vaccines among adolescents. J Natl Cancer Inst. 2015;107(3):1–4. CrossRef. Medline

43. Kreimer AR. Will a single dose of prophylactic HPV vaccines provide durable protection against cervical cancer? National Cancer Institute website. https://deainfo.nci.nih.gov/advisory/joint/1215/1130Kreimer.pdf. Accessed January 5, 2018.
44. Peirson L, Fitzpatrick-Lewis D, Ciliska D, Warren R. Screening for cervical cancer: a systematic review and meta-analysis. Syst Rev. 2013;2:35. CrossRef. Medline

45. Australian Government, Department of Health. National Cervical Cancer Screening Program website. http://www.health.gov.au/internet/screening/publishing.nsf/Content/cervical-screening-1. Accessed January 22, 2018.

46. Gibb RK, Martens MG. The impact of liquid-based cytology in decreasing the incidence of cervical cancer. Rev Obstet Gynecol. 2011;4(suppl 1):S2–S11. Medline

Peer Reviewed

Received: June 21, 2018; Accepted: September 26, 2018; First Published Online: November 20, 2018

Cite this article as: Jennings MC, Loharikar A. A vaccine against cervical cancer: context for the global public health practitioner. Glob Health Sci Pract. 2018;6(4):629-634. https://doi.org/10.9745/GHSP-D-18-00222

© Jennings and Loharikar. This is an open-access article distributed under the terms of the Creative Commons Attribution 4.0 International License (CC BY 4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are properly cited. To view a copy of the license, visit http://creativecommons.org/licenses/by/4.0/. When linking to this article, please use the following permanent link: https://doi.org/10.9745/GHSP-D-18-00222