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Commentary

HPV vaccination strategies targeting hard-to-reach populations: Out-of-school girls in LMICs

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1. The potential to reduce the morbidity and mortality caused by HPV-associated cancers

Human papillomavirus (HPV) is the primary cause of cervical cancer (CC) and is also associated with cancers of the oropharynx, rectum, anus, penis, vulva and vagina as well as genital warts [1]. More than 500,000 new cases of CC occur worldwide annually; an estimated 238,600 women died of CC in 2015. CC is a leading cause of death among women in many settings, and it disproportionately affects women in low and middle income countries (LMICs) where access to screening and prompt treatment is limited [1,2]. To address this disparity, efforts to increase access to HPV vaccines to prevent CC are urgently needed. The World Health Organization (WHO) recommends two doses of HPV vaccine spaced six months apart for girls aged 9–14 years [3] and three doses for immunocompromised girls or girls aged 15 years and older [3].

2. HPV vaccine introduction and challenges

Despite the broad recognition that HPV vaccination is a key component of comprehensive CC prevention strategies, vaccine coverage remains low. Only 7.2% of women aged 10–20 years in upper-middle income countries, 0.1% in lower-middle income countries, and 1.0% in low income countries were fully vaccinated, as per national guidelines, in 2014 [4]. The particularly low coverage in low and lower-middle income countries has been driven by delayed or deferred national vaccine introduction and challenges associated with implementing multi-dose adolescent vaccination programs. Attaining and maintaining high HPV vaccination coverage, particularly in LMICs, is central to reducing the suffering caused by HPV-associated cancers.

By June 2017, at least 91 countries had introduced HPV vaccines, and 46 LMICs had undertaken demonstration projects to evaluate delivery strategies prior to national introduction [5,6]. At least 42 LMICs delivered HPV vaccination through school-based programs as a primary strategy or paired with health facility or outreach vaccination [5].

School-based vaccination programs have been shown to be effective because they provide a venue for healthcare workers to

vaccinate a large proportion of those eligible for vaccination in a centralized location [7,8]. However, school-based programs are not designed to reach out-of-school adolescents and may also miss those who are frequently absent. In Sub-Saharan Africa alone, an estimated 18.6 million primary school-aged girls are not enrolled in school, accounting for approximately 23.3% of all primary school-aged girls in 2014, and an additional 5 million were not regularly attending school [9]. Out-of-school girls, on average, come from families with fewer resources and from more rural areas, which coincides with the risk factors for missed childhood vaccinations, early marriage, age-discordant relationships, and sexually transmitted infections including HPV [10–12]. In light of these concerns, the WHO has highlighted the need for the development of complementary HPV vaccination strategies to identify, communicate with, and access out-of-school girls [13,14]. However, ensuring equitable access to HPV vaccine for out-of-school girls will require context-specific strategies that can be efficiently and effectively delivered alongside school-based HPV vaccination programs. Addressing this need and developing complementary programs for out-of-school girls presents unique challenges.

3. Targeting out-of-school girls for HPV vaccination

Here, we outline several key considerations to take into account when designing programs to ensure high HPV vaccine coverage among out-of-school girls in settings where school-based programs are the primary strategy for delivering HPV vaccine. Specifically, we aim to generate discussion by highlighting methods and approaches that can be used to (1) identify and quantify out-of-school adolescents eligible for HPV vaccination, (2) understand barriers to HPV vaccine access and acceptance, (3) communicate effectively with communities and eligible girls about HPV and HPV vaccine, and (4) increase HPV vaccine access by creating opportunities for follow-up, outreach, and integrated health services. We summarize these recommendations to address the need, identified by the WHO, to integrate strategies that reach marginalized populations into the ongoing efforts to deliver the HPV vaccine through school-based programs [13,14]. The following strategies are presented as evidence-based examples that will need to be tailored to the local context and considered in light of available resources if they are to have the greatest likelihood of success.

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1. Identifying and quantifying out-of-school adolescents eligible for HPV vaccination

The first step in developing complementary HPV vaccination programs that target out-of-school girls is to quantify how many vaccine-eligible out-of-school girls live in a given community. While this quantification may occur at national level using census and household survey data, local quantification is also needed to ascertain the population of out-of-school girls, thereby enabling more accurate coverage targets and ensuring that sufficient resources and vaccine supplies will be locally available to reach this population [5]. Thus, community health workers (CHWs) and health facility staff responsible for delivering vaccinations at the local level should make plans to determine the number of adolescents eligible for vaccination, including those who are out-of-school [5]. To achieve this goal, health facility staff could liaise with school administrators or local civil or religious leaders to identify and quantify the number of vaccine-eligible out-of-school girls in their communities [15].

To improve the identification of out-of-school girls, methods such as snowball sampling could be used, whereby each girl not attending school identifies other peers not attending school [16,17]. Respondent-driven sampling techniques, pairing snowball sampling methodology with estimation procedures, could also be used to correct for the nonrandom sample [16,17]. Though resource-intensive, these sampling techniques have been effectively undertaken to identify HIV-positive individuals in hidden populations in low-resource areas and could be used to identify out-of-school girls [18].

2. Understanding barriers to HPV vaccine access and acceptance

Barriers to HPV vaccination among out-of-school girls are poorly understood. Further research is needed to understand their awareness and perceptions of HPV risk and HPV vaccination and to identify physical barriers to accessing HPV vaccine. The same snowball sampling or respondent-driven sampling techniques that quantify the number of out-of-school girls could also be utilized to invite out-of-school girls to participate in research that identifies barriers to HPV vaccine access and acceptance. Other qualitative methods, such as Focus Group Discussions have been successfully implemented in Kenya among hard-to-reach populations prior to national HPV introduction to ascertain attitudes towards HPV vaccination [19]. As the barriers to HPV vaccination may vary by country and local context, multi-site research studies could provide a greater understanding of the complexity of barriers to HPV vaccination. An understanding of the barriers to HPV vaccination for out-of-school girls is central to developing evidence-based, tailored intervention programs to address them.

3. Effective communication with communities and adolescents about HPV and HPV vaccination

Communication messages about HPV and HPV vaccination that reach out-of-school girls, their parents, and their communities that address real or perceived concerns have the potential to dramatically improve HPV vaccination coverage in this population. In an HPV vaccination uptake case-control study in Tanzania, insufficient information and misperceptions were listed as the major causes of non-vaccination [20].

In order to increase vaccine confidence, eligible adolescents, their parents, and communities need access to information about HPV, cervical cancer, and HPV vaccine, as well as logistical information about where to access vaccination. In an assessment of HPV vaccination social mobilization strategies in LMICs, interactive communication strategies such as home visits by health workers

achieved over 90% coverage in the eligible population in 50% of projects as compared to non-interactive (e.g. radio announcement) mobilization strategies, which achieved over 90% coverage in only 17% of projects [21].

Community involvement is also key; a systematic review of strategies to address vaccine hesitancy found that the involvement of traditional and religious leaders was associated with a fourfold increase in polio vaccine uptake in low coverage areas [22]. Communication strategies targeting out-of-school girls might utilize community leaders, CHWs, school administrators or peers to identify and invite out-of-school girls to attend schools on the day of vaccination to receive HPV vaccine alongside their enrolled peers, for example. This approach could leverage the knowledge of adolescents themselves who may be well-positioned to reach out to their peers who are out-of-school or not regularly attending school.

Short message services (SMS) reminders have also increased completion rates for infant vaccination in LMICs and could be used by HPV vaccination programs in certain contexts where cell phone ownership is high among students or their parents [23].

4. Increasing HPV vaccine access by identifying opportunities for follow-up, outreach, and integrated health services

Although 31 out of 43 LMICs implementing demonstration and/or pilot HPV vaccination projects noted that they had a strategy for reaching out-of-school girls, few have been evaluated [5]. In national HPV vaccination programs in Rwanda, Colombia, Malaysia and Mexico, strategies to reach out-of-school girls at scale have utilized active tracing by CHWs and vaccination campaigns at local health centers [24–26]. Some countries also reported ‘mop-up’ vaccination campaigns where girls could access missed doses at schools, and CHWs in Rwanda went to the houses of girls who were absent on the day of vaccination to inform them that they could access HPV vaccine at the local health facility [5,25,26]. To improve HPV completion rates, peer tracking has also been successfully implemented, where vaccination teams identify girls who have not completed the HPV vaccination series and, after vaccinating them, request that they help locate peers who have not completed the vaccination schedule. The authors noted that this strategy required substantial time, human resources, and finances [27], again highlighting the need for health authorities to plan in advance to ensure that the strategies adopted are feasible and sustainable in a given context.

HPV vaccine planning and outreach can be incorporated into locally-directed routine vaccination outreach utilizing the Reach Every District (RED) strategy [28]. Additionally, the quadrivalent Gardasil vaccine’s licensed temperature stability up to 42 °C for up to 72 h could expand systematic outreach opportunities from last mile facilities in areas where vaccine availability is an issue [29].

Integrating HPV vaccination into other preventive health measures offers an opportunity to boost vaccination coverage and increase access to other health interventions. Providing the dual benefits of HPV vaccination to girls and a screen-and-treat program for their female parent or guardian at the same location concurrently could increase both motivation to access HPV vaccination opportunities for out-of-school girls and screening for their female parent or guardian. This strategy was implemented in 13 of the 23 (56.5%) institutions participating in the Gardasil Access Program [27]. In an integrated program implemented in ten schools in South Africa, three-dose HPV vaccine completion rates were 82.6% among adolescent girls who initiated vaccination and screening rates for female caretakers increased by 14.1% compared to baseline [30,31]. Intergenerational CC prevention programs could increase access to both vaccination and screening and provide opportunities to educate girls and their parent or guardian

about HPV, cervical cancer, and effectiveness of vaccines. Integrated approaches require coordination between vaccination and screening programs to ensure that they are implemented concurrently.

4. Conclusions

The need to reach out-of-school adolescent girls in LMIC eligible for HPV vaccination is clear, thus, we highlight four considerations to consider to achieve this goal: (1) quantification, (2) identifying barriers, (3) effective communication and (4) targeted vaccination strategies to overcome barriers and increase access. Opportunities exist for local health authorities and partners to design, implement, and evaluate these strategies in various combinations relevant to local contexts in future demonstration projects or pilot studies to assess which modalities are most effective in vaccinating out-of-school girls. As additional countries consider implementing school-based HPV vaccination programs, efforts should also be undertaken to identify best practices for ensuring that out-of-school girls also benefit from national HPV vaccination programs. Recent estimates suggest that global HPV vaccination of adolescent girls could prevent 690,000 cases of CC and 420,000 deaths during their lifetime [32]. HPV vaccine introduction in LMICs presents an exciting opportunity to ensure that the full benefits of HPV vaccines, in terms of CC cases and deaths averted, can be achieved. Given that Gavi-eligible countries are required to incorporate strategies to reach marginalized populations, which include out-of-school girls, into their HPV vaccine introduction plans, the steps we have outlined can contribute to these discussions [24]. Comprehensive plans are needed to ensure that eligible out-of-school adolescents, who may be at even higher risk of HPV infection, are not forgotten in the global effort to prevent CC. The success of HPV programs—and the health of many millions of girls—depend upon it.

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Conflict of interest

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