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IPVS statement on "Temporary HPV vaccine shortage: Implications globally to achieve equity"

1. Key points

1. Cervical cancer elimination as a public health problem has become a worldwide goal led by WHO, with HPV vaccination a central and essential part of the strategy to achieve this l.
2. The increased vaccine demand this has produced has resulted in vaccine shortages predicted to last another 3–5 years (to 2023–5).
3. Strategies to manage during this time of vaccine shortage have been proposed by the SAGE Committee including temporarily suspending gender neutral and multi-birth cohort vaccination programs and an off label protocol of delaying the second dose of vaccine 2–3 years.
4. Many countries have multi-year contracts for vaccine for gender neutral and multiple birth cohort vaccination that in the short term are likely to be difficult to alter.
5. Due to complex regulatory rules, moving vaccine supplies from one country to another may not be possible in the short term, reducing the desired impact of the recent SAGE recommendations.
6. Interrupting existing multiple birth cohort and gender neutral HPV vaccine programs (in developed countries) may be detrimental to vaccine confidence and equity.
7. Existing HPV vaccine manufacturers are rapidly scaling up vaccine production and new manufacturers (e.g., China and India) are preparing to enter the market place.

2. Call to action for elimination of cervical cancer as a public health problem

We have the tools including vaccination, cervical cancer screening and treatment of women with disease to reduce significantly cervical cancer incidence and mortality. The tools were the basis for the Director-General of the WHO, Dr Tedros's call-to-action in May 2018 to eliminate cervical cancer as a public health problem and to foresee cervical cancer as a "rare" disease [1]. To achieve this, WHO has set targets for 2030, which include 90% of girls vaccinated against HPV before the age of 15 years, 70% of women will have been screened for cervical cancer by ages 35 and 45 years, and 90% of those with cervical precancer or cancer will have been treated worldwide [2].

As of June 2019, 96 countries have introduced the HPV vaccine into their national immunisation programs; however, most of those countries are high-income. In contrast, 94% of Gavi-eligible countries have yet to introduce HPV vaccination. Of the Gavi eligible countries that have commenced a program, Rwanda has been very successful, achieving > 90% coverage [3]. In addition, countries transitioning out of Gavi such as Bhutan have also achieved very high vaccine coverage, well over 90% with excellent vaccine efficacy [4]. Globally though only approximately 6% of vaccine age eligible girls are fully vaccinated, underscoring the challenges faced to achieve the goal of 90% vaccination coverage by 2030 [5]. In most countries, the cohorts for immunisation are adolescent girls 9–14 years of age receiving 2 doses of vaccine at a 0–6 or 0–12 months, with or without catch up immunisation.

Since the Call to Action, more and more countries have considered or initiated implementation of new HPV vaccination programs or expanded existing programs. In particular, the demand among Gavi-eligible countries has increased dramatically because demonstration projects are no longer required and vaccination of multiple age cohorts has been recommended [6]. Accordingly, there has been an unprecedented increase in demand for HPV vaccines. In 2018, the demand for HPV vaccines more than doubled compared to 2017, whereas the demand prior to this had remained relatively stable. For example, in 2011, there were approximately 40 publicly funded programs and this has more than doubled in 2019 to over 80. In addition, 40 countries to date have already implemented or announced a gender-neutral vaccine program [7].

This huge increase in demand has outstripped current manufacturing capacity resulting in a worldwide shortage of HPV vaccines expected to last for at least 4–5 years (i.e. to 2024/5).

3. WHO SAGE recommendations [8]

WHO SAGE recommends in this period of supply constraint that the primary target population for HPV vaccination should continue to be girls aged 9–14 years, prior to becoming sexually active, with a two-dose schedule. IPVS endorses this recommendation [9,10]. SAGE has also made recommendations to temporarily pause implementation of gender-neutral, older age (> 15 years), and multi-age cohort vaccination until sufficient supplies are available, to equitably address demands worldwide. The argument here is to allow these vaccine doses to be used in countries seeking to start an HPV vaccine program for girls or countries with limited vaccine supply. However, vaccine procured through government contracts for national immunisation programs cannot readily be transferred from one country to another, due to differing regulatory requirements across countries. As such, this recommendation may not lead to the desired vaccine re-distribution SAGE envisions in the short term.

WHO SAGE recommendations are advisory guidelines. For countries with established gender-neutral programs, temporarily ceasing them could have negative consequences for vaccine confidence, as well as issues around equity and significant challenges in restarting a public health program.

Another potential "off-label" strategy for those countries seeking to initiate new HPV vaccine programs is to consider use of an extended second dose strategy. That is, offering a single dose now to young girls with an extended interval of 3–5 years for the second dose. This strategy does presuppose that resources and commitment exists to identify girls who need a second dose and to actually reach the girls and vaccinate with the second dose several years after the first dose, which may be challenging.

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Currently there are encouraging observational data from India [11], Costa Rica [12], Australia [13], Denmark [14] and USA [15] that suggest one dose may provide protection against infection and disease. However, we await RCT data before a single vaccine dose can be recommended for young girls. Ongoing trials should produce results to this respect within the 4/5 year period of expected vaccine shortage.

4. HPV vaccine manufacturing scale up to meet demand

The inherent complexities of vaccine manufacturing require long lead times of up to four years for manufacturing product from start to finish. Both manufacturers (Merck and GSK) are investing in new manufacturing facilities and/or expansion of existing facilities, but will require substantial time to build these facilities and obtain the necessary regulatory approvals, as well as develop the critical infrastructure needed to produce vaccine. Merck, the primary manufacturer of HPV vaccine, has committed to expand significantly its manufacturing capacity to meet the growing global demand in three ways. First, they have expanded and maximized existing facilities to achieve increased levels of output and nearly doubled the number of HPV vaccine doses produced in these existing facilities. Second, they have collaborated with qualified contract manufacturers to increase capacity. Thirdly, they have invested ~$1.7 billion in expansion of vaccine production, including HPV, at several new sites in the US. Thus, the number of doses manufactured will continue to increase each year and delay is expected to be short-term. However, the supply of HPV vaccines is predicted to remain constrained for the next three to five years.

Vaccine manufacturers have limited flexibility to reallocate doses from one country to another due to differing regulatory requirements across countries. For example, vaccines may have to meet country specific requirements in different ways including testing, quality control, packaging, and/or language requirements. Therefore, simple transfer of vaccine from one country to another may not be possible in the short term.

IPVS has been advised that currently ~60% of Merck HPV vaccine doses go to low- and middle-income countries (Merck, personal communication).

Other potential vaccine candidates, which should contribute to the global vaccine supply, are those being developed by China and India [16]. These have been or currently being trialled for efficacy, immunogenicity and ultimately submission to government for licensure [17]: they include two that are bivalent and one quadrivalent.

5. Conclusion

IPVS fully supports the SAGE concerns and recommendations of prioritising vaccination of sexually naive girls and meeting the WHO target of 90% vaccine coverage of girls before age 15 by 2030. IPVS also supports the delaying of new programs for gender neutral or mature age women to focus on adolescents. Trust and confidence in HPV vaccines is central to successful HPV vaccine implementation and coverage and caution should be taken in changing HPV vaccination dissemination in countries with existing programs. Careful consideration of whether freed up vaccine doses can be transferred to another country needs evaluation and what the long-term effects of vaccine policy changes will have on overall vaccine confidence must be evaluated.

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