POLICY BRIEF

Human Papillomavirus vaccines: Call for a European change to tackle current and future shortages

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Abstract

Context

There is a global Human Papillomavirus (HPV) vaccine shortage until 2024. The World Health Organization recommended a temporary suspension of HPV vaccination for boys until all girls who need the vaccine can get it. In the European Union (EU), practices to define and monitor HPV vaccine shortages differ between the Member States. Prior policy initiatives were insufficient to address current vaccine shortages.

Policy options

Different policy options are recommended, divided into three self-developed clusters: prevention, response, and supply side. The policy options for the prevention part include decentralised surveillance and centralised surveillance. The policy options for the response part include dose sparing, EU joint procurement, postponing injection for young children, postponing vaccination for boys, and prioritisation in favour of low- and middle-income countries. The policy option for the supply side part is novel procurement agreements.

Recommendations

A traffic light system to assist policymakers has been developed. The traffic light system recommends when policymakers should implement the suggested policy options. The traffic light system describes four stages: Green light (shortage prevention); Amber light (imminent shortage prevention); Red light (shortage management); Shortage lessons. These recommendations will improve EU crisis management.

Keywords: *Healthcare Disparities; HPV; Papillomavirus Infections; Papillomavirus Vaccines.*

Introduction

The Human Papillomavirus (HPV) is a deoxyribonucleic acid (DNA) virus species that include more than 200 identified genotypes. Its transmission is skin-to-skin, mostly during sexual intercourse. Most HPV infections are asymptomatic. Some types of HPV cause benign skin and genital warts. Others are responsible for 99% of all cervical cancers but are also part of other anogenital (vulva, vagina, penis) and oropharyngeal cancers (1).

In 2020, in the 27 countries of the European Union (EU), more than 30,000 cervical cancer cases have been diagnosed, and more than 13,000 women died of this disease (2). The incidence rate (age-standardised to the European population) was 12.8 new cases per 100,000 women annually, with important disparities between countries; the two extreme rates were Malta (5.7) and Romania (32.3) (2). The mortality rate was 5.3 deaths per 100,000 women annually, with the same critical disparities between countries, from Finland (2.1) to Romania again (16.9) (2).

With the introduction of HPV vaccination, a significant decrease has been shown in terms of HPV infections and cervical neoplasia for women, along with anogenital warts for women and men (3). In Australia, the first country in the world to implement HPV vaccination in 2007, an elimination of cervical cancer (defined by four new cases per 100,000 women annually) is expected in 2028 (4).

In the European Region, the World Health Organization (WHO) published a 2022-2030 roadmap towards the elimination of cervical cancer (5). The WHO has focused on HPV vaccination (6–8) and has called for the elimination of cervical cancer (7). The triple target to meet by 2030 is the following: 90% of girls fully vaccinated by 15 years of age; 70% of women screened by 35 and 45 years of age; 90% of diagnosed women receiving treatment (5). Likewise, the goal of the Europe Beating Cancer Plans is to vaccinate at least 90% of the EU target population (8).

Context

HPV vaccination shortage

There is a global shortage of HPV vaccines (9). The shortage will have a serious impact on girls at risk of contracting

cervical cancer living in low- and middle-income countries (LMICs)(10), and is therefore risking the achievement of the elimination goal by the WHO (11). To a lesser extent, even the EU experiences the effects of this shortage, above all in its countries with the lowest income such as Romania (12,13).

According to SibiliaQuilici, executive director of Vaccines Europe, the main reason for this shortage is the increase in demand. “There has been a five-year period of stable demand with regard to HPV, and suddenly, in 2018, the demand doubled”, she said (14).

Challenges in addressing the doses shortage

To circumvent major step backs in the achievement of the 2030 elimination plan, the WHO’s Strategic Advisory Group of Experts (SAGE) recommended a temporary suspension of HPV vaccination for boys, to prioritise girls living in countries where the burden of cervical cancer is high. However, most European countries are not following this advice and are implementing a gender-neutral vaccination program (11).

Another challenge which became apparent is the lack of comparable data on HPV vaccination in the EU. Currently, the definition of coverage of HPV vaccines varies between the Member States, as does the information systems of shortages and the requirements for shortage notification (Table 1). This makes it difficult to quantify the demand for HPV vaccines and the number of vaccine shortages (15,16). Lastly, no country offers any data on stocks of HPV vaccines (Table 1). The differences in definitions, indicators, and monitoring systems result in a barrier in comparison and preclude the EU from preventing and adequately responding to vaccine shortages.

These challenges pose a problem today and set challenges for tomorrow: planning an EU strategy, setting targets and indicators when there is a lack of data and definitions change between EU countries; foreseeing shortage without comparable national or supranational surveillance; reacting to an existent shortage while aiming for the vaccination targets set out in the strategies/initiatives.

Table 1: Examples of information about HPV vaccination in five EU countries

Country	Definition of HPV vaccine coverage	Indicators or data on vaccine hesitancy	HPV vaccine stocks measures	Information on the current shortage
Finland	Proportion of boys or girls who received one dose of an HPV vaccine. It assesses how many boys or girls have received the vaccine in the specific year they were born (*e.g.* 2008, 2009, 2010…). Individuals older than 15 need three doses. However, coverage is only shown for one dose (17,18)	Charts on vaccine hesitation and underlying reasons. It also collects data on changes in vaccination coverage per region (19)	No data	Searchable database (20)
France	Two categories: "At least one dose at 15 years old" and "Complete vaccination at 16 years old" (taking into consideration two doses before 15 years old and three doses after)(21)	National and local studies. Some quantitative and qualitative data about vaccination hesitancy among specific groups, such as General Practitioners (GPs) and families (22–24)	Information available on the website of the French Medicines Agency (25)	No information about an HPV vaccine doses shortage on the French Medicines Agency website
Germany	Percentage of girls/boys aged 15/18 fully vaccinated (depending on their age, whether two or three times)(26)	No data from the government; different studies assess vaccination hesitancy (27,28)	No data	The Paul-Ehrlich Institute (PEI) provides information on current vaccine supply shortages (29)

Italy	Italy measures vaccine coverage by assessing how many people born in a specific year received the vaccine, starting from the year they were eligible until today (30)	Independent researchers conduct surveys, interviews, and questionnaires to measure vaccine hesitancy among parents. Data on vaccine hesitancy are not published by the government (31)	No data	The Italian Medicines Agency publishes a "List of medicines currently in short supply", which is periodically updated (32)
Netherlands	Vaccination coverage is determined at 14 years of age and without age limit, by birth cohort with two doses over five months apart in percentage (33)	The National Institute for Public Health and the Environment (RIVM) performs studies about both acceptance of the National Immunisation Programme and specific vaccines as well as the intention to receive vaccination (33)	No data	No data

This policy brief addresses the European Commission and the Member States and advocates for a change at the EU level to be more resilient and to tackle the current and future HPV vaccine shortages.

Policy Options

The policy options can be separated into three self-developed clusters:

I. "Prevention": What to do to prevent future vaccine shortages.
II. "Response": What to do when there is a vaccine shortage.
III. "Supply side": What changes are needed for the side of the suppliers.

Cluster I – Prevention: Surveillance and Monitoring

A common framework with standard definitions of indicators, the same for each country, is needed to, first, better monitor demand and supply and flag up mismatches leading to shortages, and, second, assess where, in times of shortages, vaccines could be temporarily suspended and redistributed. The following table (table 2) shows possible indicators. The surveillance could be performed decentralised or centralised.

Table 2. List of potential indicators for decentralised surveillance

Category	Indicator
Demography	• Composition of the population for each birth year and gender
Vaccination reserves and use	• Number of doses delivered • Number of doses administered by birth year and gender • Number of doses expired (so discarded) • Number of doses that left the territory
Vaccination coverage	By birth year and gender (from N-11 to N-25) • At least one dose (all ages) • Two doses out of three (more than 15 years only) • Complete vaccination (two or three doses, depending on the age)

Option IA – Decentralised surveillance

With a decentralised framework, the EU is setting the indicators (exemplarily, Table 2), but each Member State is responsible for surveying and monitoring themselves. The decentralised framework is mostly aimed at shortage prevention to see when the available national stocks are not sufficient to fill the demand.

Option IB – Centralised surveillance

In a centralised surveillance framework, an EU body would collect the HPV vaccine data to develop an overview of the current HPV uptake and shortages in the Member States. There are some observable developments, upon which a centralised framework for an emergency situation can be built.

In 2021, the European Cancer Organisation's HPV Action Network addressed the urgency of developing an HPV Vaccine tracker by the European Centre for Disease Prevention and Control (ECDC). This system would provide an overview of the continuous information on the HPV vaccine coverage of the EU Member States (8).

Following the Covid-19 pandemic, developments to harmonise shortage notifications can be observed. The establishment of a harmonised system of monitoring shortages of medicinal products and medical devices ("European shortages monitoring platform") at the European Medicines Agency (EMA) is being requested until 2025 (34,35). A limitation is, that the monitoring only encompasses the

medicinal products on the critical medicines list or the ones whose shortage can lead to a public health emergency (Decision 1082/2013/EU – Article 12). The Executive Steering Group on Shortages of Medical Devices (MDSSG) is responsible for the development of the list of critical medicines (Regulation (EU) 2022/123 – Article 6). We advocate for the inclusion of HPV vaccines on this list.

To fully grasp the supply situation in Europe, it would be further useful to have an extension of the monitoring system to report stocks. However, a challenge concerning exchanging information relating to production capacities, sales, or market shares is the EU competition rules, which prohibit the exchange of confidential, strategic information between competitors. This means that information on planned production, and capacity for vaccines needs to be aggregated and anonymised to prevent the identification of specific companies (36).

The centralised approach is a more urgent way of shortage management, where active redirection of vaccines is needed according to the scenario.

Cluster II – Response: the demand side

The goal for a fast response lies in the prioritisation of vaccines to the risk groups for which the burden of disease is higher. For this reason, the moral question of where should the available doses be allocated has to be raised and answered.

Four possible policy interventions can be undertaken in case of an HPV vaccine shortage, to be adopted according to the severity of the situation, from green to red.

1. HPV dose sparing and joint procurement (green)
2. Postponing vaccination for young children (yellow)
3. Postponing vaccination for boys (orange)
4. Prioritisation in favour of low- and middle-income countries (red)

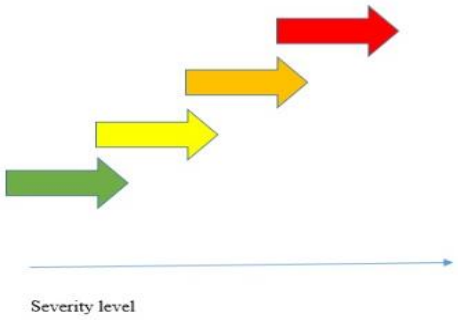

Figure 1. Severity level of shortage and corresponding intervention

Option IIA – Dose sparing

Currently, the use of a single dose does not appear in recommendations. However, evidence is culminating in considering this implementation. In Costa Rica and India, immunogenicity after a single dose could be observed, even if inferior compared to levels after two or three doses of vaccine. In Australia, Denmark, and the United States, one dose of the 4-valent recombinant HPV vaccine seems as effective as two or three doses in protecting the subject against high-grade cervical lesions. Five more randomised controlled trials and two observational studies are currently taking place in Costa Rica, Kenya, Tanzania, Gambia, South Africa and Thailand, and their preliminary results seem positive (11). Hence, dose sparing might be the solution to future HPV vaccine shortage in the future.

Option IIB – EU joint procurement

The newly established EU Health Emergency Preparedness and Response (HERA) structure can be key to managing and funding a joint procurement of HPV vaccines in the EU (37,38).

The effectiveness of EU joint procurement initiatives is scarcely researched (39). However, during the Covid-19 pandemic, the procurement initiative of the EU successfully gathered vaccines and distributed them, which prevented vaccine nationalism and gave smaller countries more substantial purchasing power associated with pooled order volumes (40).

Additionally, there is criticism of small joint procurement initiatives which consist of two to three countries and not on a supranational level (40–43). However, in specific circumstances, especially in the context of high global demand, there is no alternative to procurement organised by a coalition of governments and supranational organisations (40). Some research on joint procurement of HPV vaccines shows a significant price decrease (9,44). However, good procurement practices are essential for public procurement to be successful (40,45,46).

This policy option provides an EU-wide change in the procurement of HPV vaccines. The European Commission should enable the mechanisms of HERA to procure HPV vaccines jointly and distribute them *via* rescEU in times of high global demand.

Option IIC – Postponing injections for young children

In the case in which postponement of vaccination for certain groups has to be considered, our recommendation is to start by considering young children, both girls and boys.

In many European countries, children receive their first dose when they are very young, years before their first sexual experience could occur. For instance, in the Netherlands, from 2022 boys and girls that turn 10 will receive two doses in the same year (47). In Austria, they receive the first dose when they are nine years old, and in Portugal when they turn 10. In the vast majority of European countries, children receive the first two doses in their twelfth year of life (11). It could be argued that by delaying the vaccination of one or two years, the children would still not be a part of a risk group since, given their age, they would have not yet engaged in sexual intercourse. Another possible option would be to extend the interval between the first and the second dose, offering the second dose two or three years after the first one. This measure would be cost-effective and gain time while addressing the shortage (11).

Option IID – Postponing vaccination for boys

In the case in which postponing vaccination for the younger groups would not be enough, postponement of vaccination for boys should be considered. Although males are also affected by the burden of disease and can contract HPV-related cancers such as penile cancer or anal cancer, the main threat to the health of the individual affected by HPV is cervical cancer (48). Boys represent a risk group and deserve equal protection. Nevertheless, in terms of health benefits, a delay in vaccinations for boys would have fewer consequences than for girls (11).

Option IIE – Prioritisation in favour of low- and middle-income countries

The current shortage has sparked a debate on whether vaccination for boys should be suspended to have enough doses for girls living in LMICs. The extension of HPV vaccination to boys implied a substantial increase in demand, which, combined with the Covid-19 pandemic, led to the current shortage. Hence, until 2024, the WHO

declared that the girls living in countries with a high burden of cervical cancer would not have a sufficient amount of doses. The WHO calls for action did not lead to a European response. We call for change and want to highlight the moral obligation that the EU has to protect these girls and prioritise public health over national interests. In many LMICs, prevention and screening strategies are still insufficient, and 84% to 90% of all cervical cancers are registered in these countries. Moreover, the average individual health benefit gained from giving a dose of vaccine administered to a boy in Europe is substantially lower than the average individual health benefit gained by giving that dose to a girl living in a LMIC (11). Therefore, our policy recommendation is to prioritise LMIC girls and allocate vaccines in those countries in case we find ourselves in times of extreme global shortages.

Cluster III – Supply side: novel procurement agreements

Current procurement practices have a short-term horizon and disregard production and planning periods for manufacturers. Further, public procurement poses the threat of creating a significant shortage of vaccines, as smaller manufacturers, who have lost a public bid, will exit the vaccine market. This leads to the existence of a single manufacturer and no "backup" manufacturer in times of crisis (15).

If manufacturers know the future vaccine demand, they can decide which capacity investments they can perform (15). Long-term and accurate forecasting of vaccine demand is, therefore, crucial to sustaining the supply of vaccines, contributing to a stronger vaccine industry and enabling sustainable supply (36).

Furthermore, even though the EU Public Procurement Directive 2014/24/EU emphasises the focus on quality and innovation aspects of procured goods, many Member States are still using the lowest price as a rationale. This leads manufacturers to avoid future tenders and focus on countries with more sustainable business conditions (15).

We are recommending the following points for future procurement agreements:

- Long-term tender
- Splitting of tender awards between manufacturers
- Focus on quality and innovation aspects instead of price only

Box 1. Recommendations for procurement agreements

Recommendations

Appropriate preparation and reaction to a vaccination shortage would be a composite solution from the options proposed above. Resilience is defined as "the ability to prepare for, manage (absorb, adapt and transform) and learn from shocks" by WHO. These policy recommendations are an adaptation from the four-stage shock cycle in their 2020 policy brief about strengthening health systems resilience (49).

A traffic light colour system could help the EU and the Member States to adapt their response. This barometer could be available on the website of the EMA for transparency, following the example of the French and Italian Medicines Agencies (25,32).

Stages

Stage 1: Green light – Shortage prevention

At this baseline stage, there is no shortage. The decentralised surveillance system builds upon the information the Member States and the pharmaceutical industry provides and collects it at a regular pace set in advance. Based on the surveillance system, Member States can perform long-term and accurate demand planning. Jointly with the establishment of new procurement agreements, this would enable an adaptation of the production to suit the needs and forecast a potential shortage. No joint procurement is planned at this stage.

Stage 2: Amber light – Imminent shortage preparation

At this stage, a potential shortage is looming, as flagged by the system of sensors described above (stage 1). The information from the Member States and the pharmaceutical industry is being used to prepare for different scenarios, with a calculation of the doses concerned for each one of them, using the data available: demography composition, stocks, vaccination coverage, etc. The aim is to prepare a checklist of decisions to make in case a plan has to be activated on short notice, *i.e.* the "trigger". For instance, is dose-sparing or postponing doses relevant in the coming shortage? If so, at what intensity,

and for which groups? How many doses could be derived for the countries that need it the most?

Stage 3: Red light – Shortage management

At this crisis stage, the shortage is a reality. The list of countermeasures has already been set at the previous stage and can be "triggered" at any time. Centralised surveillance or stock management (joint procurement) could be a solution handled by health authorities. A combination of the scenarios discussed in stage 2 could participate in redirecting the correct number of doses needed.

Stage 4: Shortage lessons

At this recovery stage, the shortage is behind. Each stakeholder would estimate the impact of the measures taken: the relevance of using centralised surveillance or a joint procurement, an estimation of doses derived with the measures taken and the feedback from the pharmaceutical industry about the redirection of the vaccine production. The assessment produced at this stage could serve as a road map for the return to stage 1.

Table 3. Stages of vaccination shortage management

Summary of stages

Stage 1 Green light	**Shortage prevention** ● Prevention: Decentralised surveillance ● Response: None ● Supply side: Better procurement agreements
Stage 2 Amber light	**Imminent shortage preparation** ● Prevention: Intensification of data surveillance (more frequent) ● Response: Assess different scenarios and assessing the number of doses for each one, ready for a quick activation (preparing the "trigger")
Stage 3 Red light	**Shortage management** ● Prevention: Centralised surveillance, joint procurement (depending on scenarios) ● Response: "Trigger". Active redirection of doses where they are needed according to the different scenarios assessed
Stage 4	**Shortage lessons** ● Prevention: Evaluate the efficacy of the surveillance system ● Response: Estimate the number of doses redirected (given, spared, etc.)

	• Supply side: Feedback on the actions taken during the shortage

Limitations

The scope of this policy brief obstructs a detailed look at the issue and consequently allows a partially superficial view of the problem. Other relevant elements, especially related to the sociopolitical and cultural fields, could have been included in the research to explain the in-depth issue and its determinants. The policy brief represents the input and an overview of a broader issue that could be addressed in more detail with further research. Especially the introduction of a surveillance system on HPV, while innovative, lacks evidence in the literature. Furthermore, the implementation process could have been further elaborated by addressing barriers to the engagement of the stakeholders and limitations in their scope of action. Moreover, being HERA a new institution, it is hard to foresee the role that it could play in tackling future shortages.

Conclusion

HPV shortages have resulted in unequal access to the vaccine globally and in Europe. Moreover, definitions of HPV coverage and data collection differ between EU Member States. This makes it hard for scientists and politicians to quantify the demand for HPV vaccines and the number of vaccine shortages. Additionally, stocks of HPV vaccines are also not documented. The current policy landscape was not sufficiently designed to address the HPV shortages. That highlights the importance of a short- and long-term strategy and more decisive European leadership towards change for HPV vaccination, as theorised by John Kotter (50). This paper provides recommendations for the EU to become more resilient in times of crisis. It gives policy options according to three clusters: prevention, response, and supply. This paper then identified policy options that suit the assigned cluster's demand.

Moreover, this paper concluded when policymakers should implement these policy options with a simple traffic light colour system. Altogether, these recommendations will give the EU more resilience towards HPV vaccine shortages.

Conflicts of interest

The authors declare no conflict of interest.

Acknowledgments

The authors would like to thank Prof.Dr. Kasia Czabanowska from Maastricht University for the leadership training in the master "Governance and Leadership in European Public Health" and for the opportunity to write and publish this policy brief.

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