



CHAPTER 9

Delivering HPV vaccine in the industrial and developing world: the role of the ob-gyn community

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KEYWORDS

HPV vaccine;
Immunization;
Developing world

Abstract The development and demonstration of the safety and effectiveness of new HPV vaccines is a major breakthrough in medical science that could prevent most cases of cervical cancer, the first or second cause of cancer death in women in most developing countries. This chapter discusses the delivery of HPV vaccine in the industrial and developing world, from the point of view of what obstetricians and gynecologists need to know to use and advocate for the use of this powerful new tool.

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1. Introduction

The development of new HPV vaccines and the demonstration of their safety and effectiveness are major breakthroughs that could prevent most cases of cervical cancer, the first or second cause of cancer death in women in most developing countries [1]. One of these new vaccines contains antigens that can also prevent genital warts, which are due to common HPV subtypes [2]. The purpose of this chapter is to discuss what obstetricians and gynecologists need to know before they deliver HPV vaccine in the industrial and developing worlds – and advocate for its use. This chapter will raise many issues that are not yet resolved because research on key scientific issues is not complete, and because policies on vaccine use have not yet been made in most countries or by the appropriate global organizations. However, this vaccine will be licensed and

available soon, and it is time for all obstetricians and gynecologists, as well as their professional organizations, to start planning for their contribution to the introduction and use of this vaccine.

Traditionally, ob-gyn practitioners have not been highly involved in immunization delivery or policy development and decision making, and the immunization community knows little about cervical cancer or HPV infection, but this will change with the advent of HPV vaccine. It is now essential to educate the ob-gyn community about immunization and the HPV vaccine, and to educate the immunization community about the importance of preventing cervical cancer and the best way to reach target groups for the vaccine. Ob-gyn practitioners may use HPV vaccine in their practice, but more importantly they should become the most powerful and effective advocates for its use, because they are the physicians who see and understand the

devastating consequences of cervical cancer firsthand.

2. How are vaccines delivered in industrial and developing countries?

Vaccines are arguably the most effective and cost-effective tools of medicine. They can be delivered to “at risk” individuals by physicians, and can also be given routinely to all children, adolescents, or adults (“universal immunization”) by the public health system. The goal of the first strategy is to protect individuals, and the intended goal of the second is to protect the community and cause significant reduction in morbidity and mortality. For example, hepatitis B vaccine is (and should be) given to health workers to protect them and their patients, but immunizing health workers did not provide a significant reduction in rates of hepatitis B-related morbidity and mortality in the community [3]. For that reason, all children and/or adolescents are now given hepatitis B vaccine in most countries. Likewise, ob-gyn practitioners can give HPV vaccine to “at risk” patients, but this alone will not control the disease in the community. Only routine use of this vaccine to all adolescents and young women (and possibly other groups discussed below) will achieve the control and elimination of cervical cancer.

Immunization is the most successful public health program globally, and approximately 75% of the world's children receive routine basic immunizations. Poliomyelitis and measles vaccination campaigns reach more than 90% of children and adolescents in the developing world, including those in the poorest countries [4,5]. In industrial countries almost every child is immunized, but a number of the poorest developing countries still only immunize 40% to 60% of their children [6]. Every country has a national immunization program (known by a variety of names) that delivers vaccines to infants, children, and often adolescents. In some countries the program also delivers vaccines against influenza, pneumococcal infection, hepatitis B, and other diseases, as well as vaccine booster doses, to adults. Most families in both developing and industrial countries receive vaccines through the public sector, although many countries also have a significant private sector market that serves wealthier families – those covered by insurance plans or who can afford to pay for the vaccines themselves.

In developing countries, new vaccines, which are expensive relative to older ones, are usually introduced first into the private sector, and after a number of years, as prices fall, they are made avail-

able to those served by the public sector. Hepatitis B vaccine, which became available in the industrial world in 1982, was not introduced into public sector programs in many of the poorest developing countries until 2000 or even 2004. By that time the price of the vaccine had fallen from approximately \$20 per dose to \$0.25 per dose. More than 80% of the countries in the world now use hepatitis B vaccine as a routine part of their national immunization programs [7,8]. This time gap between use in the industrial and developing world often means that many cohorts of people who need vaccines do not receive them. In the case of cervical cancer, screening programs that identify disease early, when it can be effectively treated, are available to women in industrial countries (and wealthier women in the developing world), and the mortality from cervical cancer is much lower where such programs are in place and functioning. Most women in the developing world will never be screened for cervical cancer, and when the disease does present clinically, women usually do not receive adequate treatment. The public health community is exploring new ways to make adequate supplies of affordable new vaccines available to the developing world in a much shorter time than in the past [9]. It would be a tragically missed opportunity to wait for decades to pass before the benefits of HPV vaccine are made available to women in the developing world.

3. Competitive realities in the developing world

Developing countries have very limited budgets for immunization; and as underused and new vaccines are made available, governments and the donors that support them will have difficult choices to make regarding which new vaccines, if any, to introduce. HPV vaccine will compete with vaccines against major killers of children such as pneumococcal pneumonia and meningitis, *Haemophilus influenzae* type b, meningococcal meningitis, and rotaviral diarrhea. The impact of these vaccines will be seen more quickly than that of HPV vaccine because of the long incubation between HPV infection and cervical cancer. Pediatric vaccines will also be favored in many countries, because pediatricians have major input into immunization programs and policies as they seek to prevent the diseases they treat. In addition, delivering pediatric vaccines utilizes an existing system that routinely reaches 75% of the world's children. Giving vaccine to adolescents (except through campaigns) and adults (except tetanus toxoid [TT]) to pregnant women to protect the newborn is not part of the immunization

system in many developing countries, and would require the costly development of additional infrastructure.

4. Target groups for the HPV vaccine

The target groups for the optimal use of HPV vaccine have not yet been fully determined. HPV vaccines have been designed as pre-exposure vaccines and have been shown to be effective in preventing HPV infection. We do not yet know if this vaccine will have any benefit after infection occurs. For this reason, many HPV experts believe that the initial target groups for the vaccine are adolescent girls and young women [10]. Some countries have licensed the vaccine for both males and females. It is optimal to reach women before the onset of sexual activity because HPV infection occurs rapidly thereafter. Most industrial countries have successful programs that deliver hepatitis B vaccine to adolescents, but most developing countries do not. School-based immunization is one way to reach large numbers of girls, but in many developing countries many girls do not go to school or leave after a few years of primary education. Nevertheless, countries that cannot currently deliver vaccines effectively to adolescents will need to develop that capability if they decide to deliver HPV vaccine. An infrastructure will be needed to deliver vaccines against HPV, and, when they are developed, against other sexually transmitted diseases as well. Cultural issues related to immunizing women for a sexually transmitted infection will be discussed below.

The possibility of designing a routine health visit for adolescents has been discussed for many years in industrial and some developing countries [11]. However, adolescent care seems to fall between the cracks of pediatric and ob-gyn care in many countries. An adolescent visit could deliver hepatitis B vaccine and booster doses of other vaccines, and counseling could be provided for such crucial issues as reproductive choices and family planning, sexually transmitted disease (STD) and HIV prevention, nutrition, smoking, drug prevention, and psychological health. If this visit were to become routine it would also provide an excellent venue to deliver HPV vaccine.

Approximately 70% of women worldwide receive antenatal care, and it is estimated that 50% of women receive TT or tetanus toxoid and diphtheria (Td) vaccine during antenatal visits [12]. Since all of these women are sexually active, the issue for researchers is to determine what proportion is already infected with HPV types 16 and 18, and to model the impact and cost-effectiveness of programs to reach

these women with HPV vaccine. In developing countries where neonatal tetanus is still a problem, campaigns to deliver TT or Td to women of child-bearing age have been ongoing for many years with variable results. It is conceivable that campaigns of this type could be extended to reach adolescent girls (or girls and boys), and that the campaigns could be undertaken in countries that do not currently conduct TT campaigns. The cost-effectiveness of this approach needs to be modeled by health economists.

Vaccination of men is a more controversial issue. Morbidity and mortality from HPV-16 and HPV-18 occur from anal, penile, and oral/pharyngeal cancers among men, but these cancers are less common than cervical cancer [13]. The efficacy of HPV vaccine in preventing these diseases has not yet been established. Of course, HPV vaccines that also provide protection against genital warts will be attractive to health care systems as well as to men and women, as genital warts are very costly and significantly reduce the quality of life. The strongest argument for immunizing men is that, with high immunization coverage of both men and women, transmission of the virus may be significantly reduced or even eliminated, thus protecting women who have not been immunized. A great reduction in the transmission of hepatitis B, or its virtual elimination, has been documented in populations with high immunization coverage of infants and adolescents, e.g., in Europe and North America (including Alaska natives), The Gambia, American Samoa, and many sites in Asia, although there are still carriers of the virus in these populations [14]. Vaccinating only women against HPV would protect immunized individuals, but many men would continue to be sources of infection to unimmunized women and, possibly, immunized women in whom immunity wanes. The duration of protection from HPV vaccine is not yet known. Research is ongoing on the effectiveness of the vaccine in preventing infection in men and the duration of immunity in men and women.

The effectiveness and cost-effectiveness of routine immunization of infants and/or younger children is also under discussion. Infants and younger children would be reached through the highly effective vaccine delivery system already implemented for them, and they may need lower and thus less expensive doses. Even if a single booster dose was needed in adolescence to insure immunity during the period of risk, the total cost and effectiveness of the program might look favorable. Modeling to examine these questions should be undertaken, but data on immunogenicity and safety in young children is not yet available.

A question of primary concern to ob-gyn practi-

tioners is whom they will vaccinate or recommend for vaccination in their practice and/or the hospitals and clinics where they work. Various professional groups and government agencies will be issuing recommendations to guide practitioners, and national health systems, health maintenance organizations, and insurance programs will identify which patients they will cover financially. Physicians will also want to know whether serologic or HPV testing (if available) prior to immunization is indicated and cost-effective. Routine testing before or after immunization is not routinely done for any vaccine in public health practice.

5. Who decides on the best use of the vaccine?

Because the burden of disease, socioeconomic level of the populations targeted, and realities of vaccine delivery programs differ from country to country, each country will ultimately decide whether to use HPV vaccine and determine the target groups that receive it. Each country has a national control authority (separate from the national immunization program) that must license the vaccine after determining that it is safe and effective. Developing countries usually license vaccines that have been "prequalified" by the World Health Organization (WHO) and approved by national licensing authorities in industrial countries such as the United States, Australia, Canada, and the United Kingdom, or the European Agency for the Evaluation of Medicinal Products (EMA) in Europe. However, each country is legally responsible for licensing the vaccine itself.

Most countries also have an expert advisory body on immunization that advises their national immunization program on which vaccines to use and how to use them. This expert group is usually composed of academic experts, health economists, and representatives of relevant professional societies and civil society. Decisions on the use of HPV vaccine should include input from organizations that represent obstetricians and gynecologists as well as pediatricians and family practitioners. Ob-gyn professional societies should be among the most powerful advocates for the use of HPV vaccine.

6. Cultural issues and concerns

HPV vaccine is designed to prevent a sexually transmitted infection, and this fact raises a number of cultural issues and concerns that must be understood and dealt with as we plan to introduce this

vaccine. The HIV/AIDS epidemic and the responses it elicited at every level of society stand as evidence of the complexity of cultural issues relating to sexuality. Various groups of the "religious right" in the United States are already preparing to oppose the use of HPV vaccine should its use become mandatory for school entry. It is very likely that certain religious groups in other countries will take a similar position, and it is certain that the very active anti-immunization groups around the world will raise many objections to the vaccine. It should be kept in mind that immunization is highly successful in the world despite anti-immunization ideas, but effective advocacy for a vaccine requires an understanding of these issues and planning and training to deal with them effectively.

Religious fundamentalists opposing the use of HPV vaccine argue that it would give young people "permission" to have sex before marriage, that the vaccine would not protect them from other STDs, and that "their" children will not have premarital sex and therefore do not need the vaccine. When hepatitis B vaccine was introduced these objections were raised but never became a major hindrance. There were other modes of transmission of the hepatitis B virus to justify its use, and the "religious right" was not as powerful in the United States as it is now.

The position of conservative religious groups can perhaps be predicted from their rhetoric and behavior regarding HIV/AIDS issues. It is likely that a number of countries will not support the use of this vaccine. However, it is important for the international community to educate physicians and public health officials in these countries about HPV and the burden of cervical cancer, and about the fact that cervical cancer can be prevented by a vaccine. With this knowledge, using or not using the vaccine will be their choice.

Worldwide, antivaccine voices are as varied as their impact in various countries [15]. There are many examples of serious damage to immunization programs caused by antivaccine activities, and antivaccine groups are very active on the internet, where some adopt official-sounding names and develop Web sites designed to mislead the public into thinking they are official government sites. In every country, advocates for HPV immunization must understand how anti-immunization groups work in their country, and receive training in the communication skills needed to counter these groups [16]. Since the content of the attacks tends to be similar in most countries, a Web site developed by FIGO and other advocacy organizations could be a very helpful source of facts for those who need to deal with these issues.

A very serious problem that has had a major impact on immunization programs in Africa, Asia, India, and Latin America are rumors that immunization is a plot to sterilize girls and women, or to use them as “guinea pigs” to test antifertility vaccines. Rumors of this type have circulated for many years and have negative effects on immunization programs in Mexico, Tanzania, the Philippines, India, Nigeria, and a number of other countries. The impact on the Polio Eradication program was so severe that immunization in Northern Nigeria stopped for almost a year and the virus spread to more than 20 other countries that were formerly free of polio, as far away as Yemen and Indonesia [17]. For many years, such rumors spreading through northern India have been among the major factors preventing India from becoming polio free. There is concern that a vaccine given exclusively to adolescent girls and young women to prevent a sexually transmitted infection will exacerbate these rumors in susceptible populations. There is also a political dimension to these rumors. In Nigeria and northern India, as minority populations have been urged to take vaccines by distrusted majority governments, opposition politicians have sometimes denounced immunization as a political tool.

7. Advocacy, communications, and training

Although most physicians in the ob-gyn community understand the impact of cervical cancer, and know that is caused by HPV infection and that a safe and effective vaccine will soon be available, most health workers, medical decision makers, the media, and the public do not have this information. Ob-gyn practitioners and their national and international professional societies must play a primary role in educating these groups. Presentations about the vaccine should be on the agenda of appropriate ob-gyn meetings at national, regional, and global levels, and on the agendas of appropriate meetings of the immunization community as well as at general medical meetings. It will be important to build a bridge between the immunization and ob-gyn communities because each has skills and knowledge needed to effectively introduce the HPV vaccine.

At the country level, the national professional ob-gyn societies can and should issue their own guidelines for use of the vaccine, ideally in line with the expert advisory group and government guidelines. The national societies should also develop educational materials for their members and the public, and undertake educational and advocacy programs aimed at promoting the use of the vaccine in their

countries. FIGO could prepare model guidelines and educational and training materials to help national societies with this task. These model guidelines and materials could be used where national societies are unable to prepare their own materials, but ideally each country or regional group should translate the materials into appropriate languages and add country-specific content based on local data, recommendations, and the like.

At the global level, international agencies such as WHO have a major role to play in the introduction of HPV vaccine [18]. WHO needs to develop policies and recommendations for the use of HPV vaccine as well as develop educational materials. WHO is headquartered in Geneva but operates through 6 regional offices and has staff in most developing countries. These regional and country offices have considerable autonomy and it is possible that the different regions will have different policies on the use of HPV vaccine. The United Nations Children's Fund (UNICEF) is very important in facilitating immunization at the country level, especially the procurement of vaccines, but this organization typically has limited interest in vaccines that do not immediately lead to increases in child survival.

FIGO should develop a clear policy on the use of HPV vaccine. At the global level it should become one of the major advocates for vaccine use, and should interact with international agencies, bilateral donors, foundations, and other partners towards this end.

8. Conclusion

Cervical cancer is the number one cancer killer of women in the developing world, and safe and effective vaccines to prevent its cause, HPV infection, will be available soon. The development of these vaccines is among the great recent accomplishments in preventive medicine, and it is up to the ob-gyn practitioners and their national and international societies to lead the way in the advocacy, communications, and training needed to put this tool into medical and public health practice. The ob-gyn community has not been highly involved in immunization, and the immunization community knows little about cervical cancer, HPV, or the importance and availability of HPV vaccine. Therefore, a major effort must be undertaken to build a bridge between these communities, and to educate the larger health care community, decision makers, the media, and the public. In the past, it has taken decades for a new vaccine used in industrial countries to become available and affordable to most people in the developing world, so we must develop

new ways to allow all women to benefit from this vaccine as soon as possible.

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