Governing Council

ISSUE BRIEF

HPV Vaccine Safety

Introduction

Since their early availability in 2006 in the US and Europe, HPV vaccines have been received with great interest and optimism. Pre-dating their availability for public use, the safety profile, clinical effectiveness and public health potential of HPV vaccines have been carefully scrutinized by the World Health Organization and national regulatory agencies in the US, Europe, Australia and many other countries. Sophisticated monitoring systems continue to track the safety of the vaccines as their use expands globally.

In both pre-marketing and post-marketing surveillance, HPV vaccines have proven to be as safe or more safe than other commonly used vaccines. This brief is designed to provide a summary of the most recent data and dispel any misunderstandings that might have emerged from inaccurate or inadequate coverage of HPV vaccines in the media over the past several years.

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Cervical cancer and HPV vaccines

Every year, nearly 500,000 women are diagnosed with cervical cancer and over 270,000 die from this disease. More than 80% of deaths occur in developing countries. Virtually all cases of cervical cancer are caused by oncogenic types of human papillomavirus (HPV). Women often become infected with HPV soon after sexual debut. While most women naturally clear the virus, those who do not are at risk for developing cervical cancer.

Widespread HPV vaccination offers a groundbreaking new tool, particularly for developing countries where effective screening systems have been difficult to put in

place. Currently two HPV vaccines are approved and available for use in over 100 countries.

Both vaccines are preventive, not curative for HPV infection or HPV-related diseases. Therefore, HPV vaccine is most useful when given to girls and women prior to infection. The vaccines are made from non-infectious particles and contain no live virus or viral DNA, so they cannot cause new infections. Neither vaccine contains thiomersal, a mercury compound that has been used as a preservative in some vaccines.

HPV vaccine safety

Led by the Global Advisory Committee on Vaccine Safety (GACVS) at the World Health Organization (WHO), all agencies reviewing and monitoring HPV vaccine safety continue to conclude that HPV vaccines are safe and effective and that the benefits far outweigh the risks.[1,2]

Global and national safety review and monitoring systems for new vaccines are complex. Before a new vaccine is approved for use by the WHO or a national licensing agency, objective experts review efficacy, safety and adverse events records from large-scale clinical trials. If these data are sufficiently sound, the product is licensed for use. A second phase of monitoring begins once a product is introduced to the public.

Pre-licensure safety data for HPV vaccines came from clinical trials that included well over 10,000 girls and young women for each of the two vaccines.[3,4,5] Between licensure in June 2006 and May 2009, 24 million doses of Gardasil® have been distributed in the United States[6] and over 40 million doses have been distributed worldwide. As of May 2009, seven million doses of Cervarix® have been distributed worldwide.[7]

Since the introduction of HPV vaccines in the US, Australia, Europe and an increasing number of middle-income countries, many national and international agencies have been monitoring HPV vaccine safety rigorously. These agencies follow up on any adverse event reports to determine if the problem was caused by vaccination, or not. They also work together to ensure that recommendations around HPV vaccine use are informed by the latest safety outcomes.

HPV 16 and 18 are responsible for 70% of cervical cancer. HPV 6 and 11 are responsible for genital warts.

Gardasil® manufactured by Merck protects against HPV types 6,11,16,18.

Cervarix® manufactured by GlaxoSmithKline protects against HPV types 16 and 18.

Agencies monitoring HPV vaccine safety

- Vaccine Adverse Event Reporting System (VAERS) within the US Food and Drug Administration
- The European Medicines Agency (EMEA)
- The Medicines and Healthcare Products Regulatory Agency (MHRA) in the United Kingdom
- The Therapeutic Goods Administration (TGA) in Australia
- The Global Advisory Committee on Vaccine Safety (GACVS) at the World Health Organization

How is safety monitored?

Agencies in individual countries and at WHO rigorously monitor reports of adverse events that occur after vaccination. Such reports usually come from health professionals, people who have been vaccinated, parents, vaccine manufacturers, or third parties. In the United States anyone can use the internet to make a report, so it is important to remember that an initial report of a problem does not mean that the vaccine caused the problem or increased the risk of that event, only that the event occurred after vaccination. If scientists monitoring the reports begin to see a potential pattern of problems following vaccination, they initiate an intensive investigation to determine if the event was merely coincidental with immunization, or if the vaccine could have caused the problem.

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Limitations of such monitoring systems (called "passive surveillance") include underreporting, reporting bias, and the absence of denominator data or base rate of each event within the general population. In spite of these limitations, monitoring systems can and do provide early alerts about rare safety issues that only become evident when millions of people are using a vaccine or drug.

News stories linking HPV vaccination to deaths or serious issues often fail to explain how the reporting system works, and they confuse reports of events following immunization (there can be many such reports) with confirmed causal links between the vaccine and the health problem (very few). Misleading headlines have caused a lot of confusion and unnecessary anxiety.

Latest information on HPV vaccine safety

Common minor side effects

Common side effects are minor and can include pain, swelling, or redness at the injection site. Fever and nausea also are common but not more so in girls who received an HPV vaccine compared to girls who received a placebo injection. Such side effects generally pass within a day or two.

Fainting after HPV vaccination was found to be more common among teens than among young children or adults. However, fainting among teens is most often a response to the injection process rather than a side effect of the vaccine. A US study showed that fainting was not more common after HPV vaccination compared to other vaccines given to teenagers and young women. Therefore, as with other vaccines, a standard fifteen-minute resting period is recommended post-vaccination to prevent any injury associated with fainting.[8]

These less serious events are similar to those associated with other adolescent vaccines and are less common when compared to all vaccines. These events make up 7% of US Vaccine Adverse Event Reporting System (VAERS) reports, with about 54 events per 100,000 individuals vaccinated.[9,10] This is less than the average of 10%-15% across all vaccines.

Serious adverse events

Serious adverse events for both vaccines are extremely rare and are no more common than for other vaccines. Events involving hospitalization, death, disability, life threatening illness, or other medically important conditions account for

approximately 3 per 100,000 events reported to the US VAERS for Gardasil® in the US. There does not appear to be any significant difference in number or severity of adverse events between the two HPV vaccines.[7]

Other potential vaccine related adverse effects include Guillain Barre Syndrome (GBS), venous thromboembolic events (VTEs) and serious allergic reactions. HPV vaccines have not been shown to increase risk of these events among women with no known risk factors.

Guillain Barre Syndrome (GBS) is an autoimmune disease of unknown cause that affects the nervous system and may lead to paralysis (though this usually is temporary). Severe cases are life-threatening but most patients recover. In extremely rare circumstances, surgery or vaccinations can trigger GBS. A recent study of girls and young women who received more than 375,000 doses of HPV vaccine showed no increased risk of GBS.[11] The reporting rate to VAERS is 2 per 1,000,000 individuals vaccinated with Gardasil® in the US.[10]

The relative risk of venous thromboembolic events (VTEs) such as deep vein blood clots is 2 per 1,000,000 individuals vaccinated with Gardasil® in the US. Ninety percent of cases (28 of 31 VAERS reports, all in women ages 15-39) had a known risk factor for VTEs including use of oral contraceptives and family history.[10]

HPV vaccines continue to show very good safety profiles, with no causal links to any deaths and with very low rates of serious side effects.

Serious allergic reactions are a rare side effect of most vaccines. The rate of anaphylaxis, the most serious kind of allergic reaction, is not higher after HPV vaccination compared to other vaccines.

Despite early confusion propagated by the media, not a single death following HPV vaccination appears to have been caused by the vaccine. In the US, where autopsy and medical records were available for 20 of the 32 deaths reported sometime after HPV vaccination, 80% of fatalities were found to have occurred for reasons other than vaccination while 20% (4 cases) had unknown causes.[6,10] There was no common pattern that would suggest that any of the deaths were caused by vaccination with Gardasil®. The one reported death after vaccination with Cervarix® also was found not to have been caused by the vaccine.[7]

HPV vaccine safety in special populations

Pregnant women

HPV vaccines are not recommended for pregnant women. If a woman learns that she is pregnant after she has started the three dose series, she should wait until after her pregnancy to complete the series. That said, no statistically significant increase in spontaneous abortion rates or congenital abnormalities has been observed for either HPV vaccine, though data are limited.

HIV-positive women

As HPV vaccines are not live vaccines, they can be safely administered to HIV positive individuals. However, it is not clear how effective the vaccines can be in triggering an immune response in HIV-infected or otherwise immuno-compromised individuals.

Other safety and efficacy issues

People who have had a serious allergic reaction following a specific vaccine or are seriously allergic to anything in a vaccine should discontinue vaccination.

Vaccination is ineffective in women who have already been exposed to HPV, so is less likely to be protective in older women, although there are no known safety issues specific to this group.

Cervical Cancer Action

Cervical Cancer Action: A Global Coalition to Stop Cervical Cancer (CCA) was founded in 2007 to expedite the global availability, affordability, and accessibility of new and improved cervical cancer prevention technologies to women in developing countries.

For more information:
Cervical Cancer Action
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1 World Health Organization. Weekly Epidemiological Record, Nos. 28/29, 20 July 2007, 82:255-256. http://www.who.int/wer/2007/wer8228_29.pdf

2 World Health Organization. Weekly Epidemiological Record, No. 5, 30 January 2009, 84:37-40. http://www.who.int/wer/2009/wer8405.pdf

3 FUTURE II Study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. N Engl J Med 2007; 356:1915-27.

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7 http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/VaccinesandRelatedBiologicalProductsAdvisoryCommittee/UCM181371.pdf

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10 Slade, BA, Leidel, L, Vellozzi, C, et. al. Postlicensure safety surveillance for quadrivalent human papillomavirus recombinant vaccine. JAMA 2009;302:750-757.

11 http://www.cdc.gov/vaccines/recs/acip/downloads/mtg-slides-oct08/14-5-hpv.pdf