GACVS Safety update on HPV Vaccines
Geneva, 13 June 2013

At its meeting on 13 June 2013, GACVS reviewed updated information about the safety of HPV vaccines. The last review was conducted in June 2009. GACVS noted at the time that accumulating evidence on the safety of HPV vaccines was reassuring and that studies on HPV immunization had been initiated, along with capacity-building for adverse events monitoring. GACVS places a high priority on the ongoing collection of high-quality safety data in settings where the vaccine is being introduced.

In the past 4 years, safety data continued to accumulate as countries have initiated or expanded their immunization programs. The GAVI Alliance has also begun taking steps to make HPV vaccine available to women in developing countries where the burden of cervical cancer is considerable. To date, some 175 million doses of HPV vaccines have been distributed. A review of adverse events reported to the US Vaccine Adverse Event Reporting System following the distribution of over 23 million doses was published in 2009 (Slade 2009). Many countries were HPV is licensed now have considerable post-marketing data and no concerns have been identified.. The manufacturers of currently available vaccines have developed pregnancy registries and are maintaining long term safety studies in conjunction with efficacy.

The Committee reviewed data from the United States, Australia, Japan and the manufacturers of Cervarix® (GlaxoSmithKline) and Gardasil® (Merck). Updates from the United States included an extension of the spontaneous reports to VAERS since the published review in 2009 as well as completed and planned studies from the Vaccine Safety Datalink. In Australia a new program targeting males started in February 2013 and data are just becoming available.

Data from all sources continue to be reassuring about the safety of the two vaccines. The data from VAERS now includes over 50 million doses distributed since 2006 and the profile has not changed significantly since the review in 2009. Reported adverse events not identified at the time of the first review, namely syncope and venous thromboembolism (VTE), were further investigated. For syncope, it continues to be reported but remains an event with a plausible relationship given the population and settings under which HPV vaccine is given. Adherence to a 15-minute observation period following vaccination has thus been strengthened as a recommendation. For VTE, while a rapid cycle analysis in the VSD did not find an increased risk, this is further being investigated with appropriate control for confounders such as oral contraceptive use, smoking and other risk factors in this population. Similarly, the VSD did not find any increased risk of Guillain-Barré syndrome or stroke.

In Australia, safety surveillance has been enhanced and the expert group continues to look at reported events. To date, with almost 7 million doses distributed, the previously investigated concern regarding an increased incidence of anaphylaxis was not confirmed. Following the extension of the vaccination program in males and enhanced surveillance since February 1 2013, preliminary results show the safety profile of Gardasil as similar to the profile among females.

The experience in Australia also provides useful lessons for countries introducing new vaccines in this age group, especially when vaccines are administered in a school based vaccination settings. In May 2007, soon after the introduction of the school-based program, 26 of 720 girls vaccinated at a girls' school developed symptoms including dizziness, palpitations, syncope or collapse, weakness, and aphasia. Four were transported by ambulance to hospital where further clinical evaluation found no organic basis for the reported symptoms. This cluster of adverse events was determined to be a result of a psychogenic response to vaccination. The event generated substantial media interest and public concern in Australia. (Buttery 2008, Gold 2010). Such cases require a prompt and through medical evaluation to establish a diagnosis and then an assessment of the relationship, if any, to the vaccine or vaccination as well as a proactive approach to communication, employing risk communication principles.

Surveillance from the two manufacturers found no signals that suggest a need for revisions to product labelling. Both have maintained surveillance of pregnancy outcomes following inadvertent vaccination during pregnancy. Detailed analyses of results have not found any new adverse outcomes related to HPV vaccination. For Gardasil, long term follow-up has now extended to over 8 years in the longest cohort, and no significant increase in newly diagnosed health events have been identified among those vaccinees. Updated analyses of the pregnancy registry have also been reassuring in that no adverse pregnancy outcomes have been observed beyond background expected rates. For Cervarix, the data have been similarly reassuring regarding pregnancy outcomes and specific events of interest such as immune mediated diseases. Risk of syncope and anaphylaxis have been added to the label to warn of these potential events, the former being also possibly related to conditions around the vaccination experience itself.

Finally, cases of complex regional pain syndrome (CPRS) were reported from Japan where over 8 million doses of HPV vaccines have been distributed. CPRS is a painful condition that emerges in a limb usually following trauma. Cases have been reported following injury or surgical procedures. It remains of unknown etiology and may occur in the absence of any documented injury. CPRS following HPV vaccines has received media attention in Japan with 5 reported cases most of which seem not compatible with typical CPRS cases. Review by an expert advisory committee could not ascertain a causal relationship to vaccination given lack of sufficient case information and in many cases could not reach a definitive diagnosis. While these are under investigation, Japan has continued to provide HPV vaccine in their national program.

In summary, 4 years after the last review of HPV vaccine safety and with more than 170 million doses distributed worldwide and more countries offering the vaccine through national immunization programs, the Committee continues to be reassured by the safety profile of the available products. Anaphylaxis and syncope, outcomes previously identified as concerns, have been addressed through further studies and appropriate revisions were made to the products labeling. Serious adverse events that have been reported as potential signals have been investigated in more detail, including Guillain-Barre Syndrome, seizures, stroke, venous thromboembolism, anaphylaxis, and other allergic reactions – many using rapid cycle analysis in the VSD in the United States. Surveillance of pregnancy outcomes among women inadvertently vaccinated during pregnancy through spontaneous reports and registries have not detected any adverse outcomes above expected rates.

The cases of chronic pain being reported from Japan deserve specific mention. To date there is little reason to suspect the HPV vaccine, given its growing use worldwide in the absence of a similar signal from elsewhere. Recognizing the public concerns voiced, the Committee urges careful documentation of each case and a thorough search for a definitive diagnosis by medical specialists in order to best guide treatment. A timely clinical assessment and diagnosis of each case followed by appropriate treatment is therefore essential.

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