

## Safety of HPV vaccination: A FIGO STATEMENT

July, 2013

Human papillomavirus vaccines are used in many countries; globally, more than 175 million doses have been distributed. Extensive pre- and post-licensure data on the safety of the vaccines are available. Sources of information to evaluate the safety of the HPV vaccines have included:

1. Randomised controlled clinical trials
  2. The US Vaccine Adverse Event Reporting System (VAERS)
  3. Surveillance of Adverse Events Following Vaccination in the community (SAEFVIC), Victoria, Australia established in 2007
  4. European Medicines Agency, 2010
  5. Post licensure experience
    - a. Passive surveillance
    - b. Passive and active surveillance
    - c. Population based Epidemiologic surveillance
- **Randomised controlled trials performed prior to licensure** in a number of countries, to which new trials in countries such as Korea, China, Japan and Vietnam have been added
    - Safety endpoints have included local and systemic adverse events (AEs), serious AEs, deaths, new onset medical conditions, including chronic and/or autoimmune diseases, as well as pregnancy outcomes
  - **Safety Findings of clinical trials of the quadrivalent vaccine:**
    - Pooled analyses of trials involving more than 20 000 females aged 9 – 26 years and 1350 males aged 9 – 16 years from Europe, North and South America, showed that injection site reactions such as pain, erythema and swelling were more common in vaccine recipients than in those who received adjuvant or placebo vaccinations. In almost all cases, symptoms were self-limiting and resolved within 48 hours
    - There was no difference in common adverse experiences such as headache, fever and nausea
    - There was also no difference in the frequency of SAEs overall or by organ system over a median follow up of just under 4 years
    - Deaths occurred in 0.1% in both the vaccine and placebo groups, with no deaths deemed vaccine related
    - The overall proportion of participants reporting new onset autoimmune conditions was not different in each group (2.4% in both) over the 4 year follow up period
  - **Safety findings of clinical trials of the bivalent vaccine**
    - The safety profile from clinical studies of the bivalent vaccine is consistent with that of the quadrivalent vaccine with pain at the injection site being the most common finding (up to 97% of those vaccinated in data pooled from 11 studies involving over 30 000 females older than 10 years), and erythema and swelling
    - There were no significant differences in SAEs, unsolicited symptoms and medically significant conditions in the vaccinated compared to the control groups

- 5 deaths were reported (only one of whom received vaccine), and none were considered vaccine related
- In follow up studies over 4 year periods, rate of vaccine-related SAEs, new onset chronic disease and new onset autoimmune disease was no different between the two groups
- **In summary:**
  - All randomised clinical trials of both the bivalent and quadrivalent vaccines provide evidence of an excellent safety profile. The most common complaint was pain at the injection site which was largely self-limiting and resolved spontaneously

### Special circumstances

- **Safety in Pregnancy**
  - HPV vaccinations are not recommended for use in pregnant women, however some participants did become pregnant during the clinical trials
  - Pregnancy registries have been established for both commercially available vaccines
  - Pregnancy outcomes were the same in the bivalent and quadrivalent vaccines compared to control recipients and the general population.
  - There is no evidence from either clinical trials nor post licensure data that there is an increase in congenital anomalies or obstetric complications in women receiving vaccine
- **Post licensure data**
  - Data from passive, active and population based epidemiologic surveillance studies conducted since 2006, have not shown any difference in conditions such as Guillain Barre Syndrome, stroke, appendicitis, seizures, allergic reactions, anaphylaxis and venous thromboembolism – these data were obtained from the Vaccine Safety Datalink cohort in which a total of 600 558 doses of the quadrivalent vaccine were recorded. A medical record review of all 8 vaccinated potential venous thromboembolism cases in the age group 9 – 17 years, 5 cases complied with the standard definition of VTE and all five had known risk factors for VTE (oral contraception use, coagulation disorders, smoking, obesity or prolonged hospitalisation)

### Specific conditions

- **Syncope**
  - Disproportionately higher rates of syncope after HPV Vaccination compared with pre-licensure RCTs were reported from post-licensure surveillance in the Netherlands, Australia, and Italy.
  - Considering that injection site pain is common in HPV vaccination, syncope is considered an uncommon side effect rather than an adverse event to vaccination, and the recommendation is to take precautions (such as sitting

- after injection) to prevent falling if dizziness or fainting occurs, stressing the necessity for close observation for 15 – 30 minutes post vaccination
- Syncope in women vaccinated against HPV does not appear to be more common than that reported with other types of vaccination. The Center for Disease Control and Prevention evaluated syncope after the licensure of three vaccines: the HPV quadrivalent vaccine, the quadrivalent meningococcal conjugate vaccine in a single dose and the tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine in a single dose and found that the incidence of syncope was similar and advised that in all cases of administering vaccination, patients should be observed for at least 15 minutes after vaccination (as is recommended by the Advisory Committee on Immunization Practices) in order to prevent injuries related to syncope.
- **Anaphylaxis**
    - Although rare, anaphylaxis can occur after any vaccination either due to the antigen and/or vaccine adjuvant
    - Reporting rates of anaphylaxis following HPV vaccination have been consistent in both national passive surveillance and population-based studies and found to be in the estimated range of 1 – 10 cases per million doses, which compares favourably with other vaccines such as tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccines.
  - **Guillain Barre Syndrome (GBS)**
    - A review of GBS cases reported to the US VAERS suggested a potentially 2.5 – 10 time greater rate of GBS within 6 weeks after vaccination with the quadrivalent vaccine compared to that expected in the general population. After extensive investigation, it was concluded that the temporal relationship to vaccination and lack of a control group meant further investigation was required. Subsequent population based studies using extensive case finding have not provided evidence of a rate that is significantly greater than that expected in the adolescent and young female population.
  - **Venous Thromboembolism (VTE)**
    - VTE post vaccination has only been rarely reported and all cases had other risk factors for VTE such as oral contraceptive use. In addition, the temporal relationship to vaccination was highly variable making this unlikely to be a vaccine related complication.
  - **Complex Regional Pain Syndrome (CRPS)**
    - AE following immunisation commonly include local pain at the injection site, but the development of CRPS, has only been described in children immunised with rubella and hepatitis B vaccines. CRPS is a clinical syndrome

that affects one or more extremities and is characterised by persistent pain disproportionate to the initiating event, which is often minor trauma

- 4 cases were reported to the Surveillance of Adverse Events following Vaccination in the Community after it was initiated in Victoria, Australia 2007, and one case from the UK
- 4 of the 5 cases met the criteria for CPRS and all resolved within 5 days to 7 months without recurrence or consequence
- It is important to be aware of this syndrome which can be triggered by any injury to the extremity, including intra-muscular injection.
- Cases of chronic pain in the extremities have been reported in Japan where over 8 million doses of HPV vaccine have been distributed – the issue is being intensively investigated but data received to date does not convincingly implicate HPV vaccination, as opposed to any other type of vaccination

Conclusions

- The Global Advisory Committee on Vaccine Safety (GACVS) of the World Health Organisation (WHO), reviewed the safety of HPV vaccination on June 13, 2013, the Committee's last review having taken place in 2009.
- The Committee considered all available evidence on HPV vaccination and have concluded that both commercially available vaccines are safe.
- Having reviewed all available data, the FIGO Gynecologic Oncology Committee and the FIGO sub-committee for Cervical Cancer Prevention supports the continued administration of the HPV vaccines in appropriate populations.
- This recommendation has been approved by the FIGO Executive Board

**Signed by:**

**Professor Sabaratnam Arulkumaran: President FIGO**

**Professor Lynette Denny: Chair, FIGO Gynecologic Oncology Committee**

**Professor Joanna Cain: Chair: Sub-Committee for Cervical Cancer Prevention**

**Date:**

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