CERVARIX® CLINICAL QUESTION AND ANSWER DOCUMENT

July 2013

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This document is intended to answer clinical questions regarding the administration of CERVARIX® vaccine. For programmatic questions, refer to the "HPV Vaccine One-Time Program for Young Women Questions and Answers for Immunization Service Providers" dated July 2013.

1.0 CERVARIX® VACCINE

1.1 What is CERVARIX® vaccine?

- A vaccine produced by GlaxoSmithKline (GSK) that protects against Human Papillomavirus (HPV) types 16 and 18.
- It is a recombinant, AS04-adjuvanted vaccine.

1.2 Who is CERVARIX® vaccine for?

- In this one-time program, CERVARIX® is being provided **free** for young women ≤ 26 years of age and born before 1994 at the time of series commencement. This one-time program started in April 2012 and will continue until available vaccine supply is depleted or the vaccine has expired (August 2015). A limited supply of CERVARIX® vaccine has been purchased for the province. This is a "one time" program rather than an ongoing program. When the provincial supply has been administered, there is currently no plan to purchase more HPV vaccine for this population.
- It has been approved in Canada for females 9 through 45 years of age (inclusive).

1.3 What is the difference between Gardasil® and CERVARIX®?

- CERVARIX® is a bivalent vaccine that protects against oncogenic (cancer causing) HPV types 16 and 18.
- Gardasil® vaccine is a quadrivalent vaccine that protects against HPV types 16 and18 as well as HPV types 6 and 11; the latter two are important causes of genital warts. Gardasil® is the vaccine which is used in the school based (grade 6) program.

1.4 Is there any overlap between the population of females eligible for Gardasil® and those eligible for CERVARIX® vaccine?

- No. Publicly-funded CERVARIX® vaccine is for young women ≤ 26 years of age and born before 1994 at the time of series commencement. Gardasil® vaccine is for females born on or after January 1, 1994.

1.5 Which vaccine should I administer if a client presents who previously refused Gardasil® vaccine?

- If the client was born January 1, 1994 or later – offer publicly-funded Gardasil® vaccine (refer to nearest health unit if your facility doesn't have publicly-funded Gardasil®).

- There is a limited supply of CERVARIX® vaccine. Offer CERVARIX® vaccine only to young women ≤ 26 years of age and born before 1994 at the time of series commencement.

1.6 What if a girl presents for immunization and she previously received one or two doses of Gardasil® vaccine?

- Assess whether client is eligible for publicly-funded Gardasil® vaccine (i.e., born on or after January 1, 1994).
    - If yes, complete series with Gardasil® vaccine (refer client to nearest health unit if your facility doesn't have publicly-funded Gardasil®).

- If no, recommend client purchase Gardasil® vaccine to complete the series. If young women ≤ 26 years of age and born before 1994 at the time of series commencement and states purchasing Gardasil® is not financially feasible, offer CERVARIX® vaccine. If less than three doses of Gardasil® are administered, counsel clients that protection against HPV types 6/11 (genital warts) cannot be assured.

1.7 Are Gardasil® and CERVARIX® interchangeable?

- Whenever possible, one brand of vaccine should be used to complete a vaccine series.

- If a girl has received 1 or 2 HPV vaccine doses previously, and the brand of the previously received doses is not known, CERVARIX® may be used to complete the series. Both vaccines provide protection against HPV types 16/18 and therefore clients are likely to achieve protective antibody levels against these HPV types. If less than 3 doses of Gardasil® are administered, counsel clients that protection against HPV types 6/11 (genital warts) cannot be assured.

1.8 What if we run out of CERVARIX® before an eligible female completes the 3 dose series? Can we complete the series with Gardasil®?

- Gardasil® vaccine is only provided free for females born January 1, 1994 or later. If publicly-funded supplies of CERVARIX® have been exhausted, provide clients with information regarding how to access vaccine-for- purchase (e.g., pharmacies).

- CERVARIX® is commercially available for about $100/ dose. Patients should check with their drug plans to determine if the cost of this vaccine is covered.

- This is a one-time program and the rule “once eligible, always eligible” does not apply.

1.9 When was CERVARIX® licensed?

- CERVARIX® was first authorized for use in Canada in February 2010 for use in females 10-25 years of age. As of May 2013, it is now approved for use in females 9-45 years of age.

- It is indicated for the prevention of cervical cancer by protecting against the following dysplastic lesions caused by HPV types 16 and 18: Cervical intraepithelial neoplasia (CIN) grades 1, 2, and 3; and cervical adenocarcinoma *in situ* (AIS).

1.10 Where else in the world is CERVARIX® used?

- CERVARIX® is licensed in over 72 countries worldwide, including Australia, Brazil, South Korea, Mexico, Taiwan, England, and the United States.

- CERVARIX® has been part of the routine immunization program for 12 and 13 year old girls in England since September 2008. From September 2008 to July 2010, a catch-up program was undertaken for girls aged 14-17 and over 4 million doses of CERVARIX® vaccine were administered in the United Kingdom.

- Cervarix was approved by the US Food and Drug Administration in October 2009. The Advisory Committee on Immunization Practices (ACIP) recommends routine immunization with HPV vaccine (either CERVARIX® or Gardasil®) for all 12 and 13 year old females. Catch-up vaccination is also recommended for all females 13 through 26 years of age.

1.11 How is CERVARIX® supplied?

- As a single dose pre-filled syringe.

1.12 What is the administration schedule for CERVARIX®?

- The recommended schedule is 0, 1, and 6 months.

- The dose is 0.5 ml IM in the deltoid.

1.13 What if more than the recommended time has elapsed between doses?

- There is no need to restart the series. Administer the remaining doses according to the recommended intervals. The minimum interval between dose 1 and dose 2 is 4 weeks, the minimum interval between dose 2 and dose 3 is 12 weeks, with the third dose being given at least 20 weeks after dose 1.

- "Interruption of a recommended series does not require starting the series over again, regardless of the interval elapsed (with the exception of oral typhoid vaccine). Longer than recommended intervals between vaccine doses does not reduce final antibody concentrations, although protection might not be attained until the recommended number of doses has been administered." (BC Communicable Disease Manual, Chapter II, Immunization Program, Section IIA – Immunization Schedules, page 10: http://www.bccdc.ca/dis-cond/comm-manual/CDManualChap2.htm)

1.14 Can CERVARIX® be given at the same time as other vaccines?

- Yes. Several studies have demonstrated that there is no change in safety or immune response when CERVARIX® is administered at the same time as other vaccines such as hepatitis B, meningococcal, or tetanus/diphtheria.

- Administer all vaccines for which the client is eligible at each visit.

- Administer each vaccine in a separate syringe at a separate anatomic site.

2.0 COMPONENTS OF CERVARIX® VACCINE

2.1 What are the components of Cervarix?

- 20 µg HPV type 16 L1 protein and 20 µg HPV type 18 L1 protein

- AS04 adjuvant [3-*O*-desacyl-4'- monophosphoryl lipid A (MPL) and aluminum hydroxide]. AS04 boosts the immune response to the vaccine (see 2.2 What is AS04 adjuvant?).

- hydrated sodium chloride, sodium dihydrogen phosphate dehydrate, water for injection.

2.2 What is AS04 adjuvant?

- An adjuvant is any substance added to a vaccine to enhance the immune response by degree or duration making it possible to reduce the amount of antigen per dose or the total number of doses needed to achieve immunity.

- AS04 is composed of 3-*0*-desacyl-4'-monophosphoryl lipid A (MPL) adsorbed onto aluminum (as hydroxide salt).
    - MPL is derived from the lipopolysaccharide (LPS) molecule of the bacterial wall of *Salmonella Minnesota*. LPS is a major component of the bacterial cell wall found in many of the bacteria humans are exposed to regularly.
    - Aluminum salts (e.g., aluminum hydroxide, aluminum phosphate, or potassium aluminum sulphate) have been used as adjuvants for some time and are found in other routine vaccines such as GARDASIL®, INFANRIX hexa™, PEDIACEL®, Prevnar®, and ADACEL®.
- Recent evidence has indicated that there is a higher antibody response and titres are sustained over a longer period of time when vaccines are adjuvanted with AS04 as compared to those adjuvanted with aluminum salts alone.
- AS04 has an excellent safety profile. AS04 adjuvant is also used in a hepatitis B vaccine licensed in Europe (FENDrix™). Over 40,000 doses of AS04 adjuvanted vaccine were administered in the trials of these two vaccines. The most commonly reported reactions following immunization with an AS04 adjuvanted vaccine are local inflammatory reactions. See Section 5.0 Adverse Events Associated with CERVARIX® vaccine for more information.

3.0 CONTRAINDICATIONS TO CERVARIX® VACCINE

3.1 What are the contraindications?

- History of anaphylactic reaction to any component of CERVARIX® or to latex, found in the syringe.

3.2 Can CERVARIX® be administered to women who are pregnant or breastfeeding?

- CERVARIX® should **not** be given during pregnancy because safety of receipt of HPV vaccine during pregnancy has not been adequately studied. Women who become pregnant before series completion should defer immunization until no longer pregnant.
- In pregnant women who are inadvertently vaccinated, there is no need to consider any intervention except reassurance, as the vaccine has not been associated with teratogenicity. GSK maintains a pregnancy register to monitor fetal outcomes associated with inadvertent immunization during pregnancy.

Patients and health care providers are encouraged to report inadvertent CERVARIX® administration during pregnancy by calling GSK at 1-800-387-7374.

- Data on the safety of CERVARIX® vaccine in breastfeeding women are not available. Administer CERVARIX® vaccine to a breastfeeding woman when, in the judgement of the clinician, the risk of HPV acquisition in the mother outweighs the absence of data in this population.

3.3 Other considerations:
Women who are already sexually active:

- CERVARIX® **is** indicated for women who are already sexually active because they may not be infected with HPV and they are unlikely to be infected with both types of HPV (16/18) contained in the vaccine.
- Continue to recommend routine cervical cancer screening for sexually active females.
- HPV types 16 and 18 are responsible for approximately 70% of cervical cancer.

Women with a previous abnormal Pap test:

- CERVARIX® **is** indicated for women with a previous abnormal **Pap** test. However, it is not effective in treating abnormal cells caused by pre-existing HPV infection.

Women with a known history of HPV infection:

- CERVARIX® **is** indicated for women with a known history of HPV infection. CERVARIX® is not a treatment for existing HPV infection.
- Epidemiologic data indicate it is unlikely that the individual has been infected with both HPV types 16 and 18. One study of over 1000 women between 15 and 39 years of age undergoing prenatal testing in B.C. found that only 3.9% were infected with both HPV types 16 and 18.
- Analysis of the clinical trials regarding the efficacy of CERVARIX® vaccine revealed an efficacy of 88.2% in the prevention of cervical cancer for women who have previously been treated for HPV infection-related cervical abnormalities. Refer to Section 4.1 What is the efficacy of a complete three dose series of CERVARIX® vaccine? for more information regarding comparison of efficacy in women with a previous HPV infection and women with no previous HPV infection.

4.0 EFFECTIVENESS OF CERVARIX® VACCINE

4.1 What is the efficacy of a complete three dose series of CERVARIX® vaccine?

- Multiple studies and clinical trials of women between 15 and 25 years of age have found CERVARIX® vaccine to be 97-100% effective in preventing cervical cancer.
- In clinical trials where the Total Vaccinated Cohort (TVC) consisted of women who were negative for HPV 16/18 infection pre-immunization, the efficacy at 6.4 years follow-up was 100% against cervical cancer caused by HPV types 16/18 and 71.9% against cervical cancer caused by any HPV type.
- In clinical trials where women with a history of colposcopy were excluded, vaccine efficacy against HPV 16/18 cervical cancer in the TVC was 97.7% at 3 years follow-up and 98.9% at 4 years follow-up.
- More detailed information is available in the January 2012 NACI statement "Update on Human Papillomavirus Vaccines" available at http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/12vol38/acs-dcc-1/index-eng.php

4.2 What about immunogenicity of CERVARIX® vaccine?

- A seroconversion rate over 99% to both vaccine serotypes was found among 2200 females studied in Phase II and III protocols at seven month and 7.3 year follow-up.
- Antibody titre levels measured at 7 months were 300-fold (HPV type 16) and 200-fold (HPV type 18) higher than those induced by natural infection.
- Of the 300 women tested at 8.4 years post-immunization, 100% remained seropositive for antibodies to both HPV types 16 and 18.

4.3 What is the duration of protection from CERVARIX®?

- The duration of protection has not been established. Research done by GSK indicates the duration of protection is a minimum of 9.4 years.
- GSK studies have demonstrated continuous protective levels of antibodies to HPV types 16 and 18 up to 9.4 years following vaccination.
    - Efficacy against incident infection: 95.3% at 6.4years and 95.6% at 9.4 years;

  - Efficacy against 12-month persistent infection: 100% at 6.4 years and 9.4 years; and
  - Efficacy against cervical cancer: 100% at 6.4 years and 9.4 years.

- The NACI statement references a separate study done at 8.4 years post-vaccination:
  - 100% of participants remained seropositive; and
  - Antibody levels remained 13 fold (type 16) and 11 fold (type 18) higher than those induced by natural infection.

5.0 ADVERSE EVENTS ASSOCIATED WITH CERVARIX® VACCINE

5.1 What are the expected/most common reactions to CERVARIX®?

- Pain, swelling, and redness at the injection site are the most commonly reported local reactions. Local reactions may be more significant than those seen with Gardasil® (Merck) due to the presence of the AS03 adjuvant. Systemic reactions include fatigue, myalgia, arthralgia and headache.
- Most local and systemic reactions were transient and mild to moderate in intensity.
- In pre-licensure clinical trials, 23,713 females received either CERVARIX® vaccine or one of three control injections [hepatitis A vaccine containing either 360 or 720 ELU, or $Al(OH)_3$]. Local reactions were reported more frequently with CERVARIX® recipients than those in the control groups. More than 84% of CERVARIX® recipients reported these reactions to be mild to moderate in intensity.
- A number of studies have examined the rates of solicited adverse reactions within the 7 days following administration of CERVARIX® vaccine. In all the studies, the rate of local reactions was higher in groups receiving CERVARIX® than in those in the control groups. Control groups received a hepatitis A vaccine (320 or 720 ELU), or $Al(OH)_3$ control, or combined hepatitis A and B vaccine.
  - Pain is the most commonly reported local reaction (rates range from 71.9% to 93.4%). According to the GSK product monograph, the rate of CERVARIX® recipients reporting pain following injection decreased from dose one to dose three.

  - Redness and swelling were also reported in 22.7% to 48.0% of CERVARIX® recipients.
  - Fatigue, headache, and myalgia were the most commonly reported systemic reactions.
  - Most local and systemic reactions were reported to be mild to moderate in intensity.

- According to the UK's National Health Service website, available at http://www.nhs.uk/Conditions/vaccinations/Pages/hpv-vaccine-cervarix-gardasil-side-effects.aspx , over 4 million doses of Cervarix vaccine have been administered and the following rates of adverse events following immunization have been identified:
  - very common side effects (pain, redness, or swelling at the injection site, headaches, muscle pain, or tiredness) occurred following 10-15% of vaccine doses;
  - common side effects (nausea, vomiting, diarrhea, abdominal pain, itchy skin, red skin rash, hives, joint pain, or temperature of 38°C or greater) occurred after less than 10% of vaccine doses; and
  - uncommon side effects (upper respiratory tract infection, dizziness, or other injection site reactions such as a hard lump, tingling, or numbness) occurred after less than 1% of vaccine doses.

5.2 What other adverse events have been associated with CERVARIX®?

- In clinical trials, there were no observed differences in the rates of serious adverse events (i.e., medically significant conditions, new onset chronic diseases, new onset autoimmune diseases, and adverse pregnancy outcomes) between individuals who received CERVARIX® vaccine and those who received control vaccine.
- Additional analysis of studies of adverse events following CERVARIX® vaccine was conducted to confirm the safety of the novel adjuvant AS04.
  - The overall incidence of females who reported new onset chronic diseases was the same in the group who received CERVARIX® vaccine as in the control group.

- There were no differences in the rates of new onset autoimmune diseases between females who received CERVARIX® vaccine and those in the control group.
- Although spontaneous abortion was the most commonly reported serious adverse event, the percentage of females who reported a spontaneous abortion was the same in the group who received CERVARIX® vaccine as the control group.

5.3 How should I report Adverse Events following Immunization (AEFI) after the administration of Cervarix vaccine?

- The process for reporting AEFI is the same as the process following routinely administered vaccines. For vaccines administered outside the health unit setting, the reporting form can be found at the BCCDC website: http://www.bccdc.ca/NR/rdonlyres/0F7FC86E-924C-4232-87DD-F5859E41A7A2/0/HLTH2319pdffill_19MAR13.pdf

6.0 EPIDEMIOLOGY OF HPV INFECTION:

6.1 What is the incidence of HPV infection in BC?

- Moore et al. studied almost 5000 women between 13 and 86 years participating in the B.C. provincial cancer screening program. Results indicated:
  - Overall HPV prevalence: 16.8%;
  - prevalence of HPV types 6, 11, 16, and 18: 4.0%, 0.2%, 10.7%, and 3.5% respectively;
  - HPV positivity was most common in women under age 20.
- A separate study of 1020 B.C. women between 15 and 39 years of age found that 17.9% of the women had antibodies to HPV type 16, 9.5% had antibodies to HPV type 18, and 3.9% had antibodies to both types.
- The peak incidence of HPV infection is within the first 5 to 10 years after the first sexual experience.

6.2 What types of cancers are related to infection with HPV types 16 and 18 in women?

- There is good evidence that HPV types 16 and 18 cause cancer in a variety of anatomical sites, including cancers of the vagina, vulva, anus, oral cavity, and oropharynx.

7.0 REFERENCES

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