BC Centre for Disease Control
AN AGENCY OF THE PROVINCIAL HEALTH SERVICES AUTHORITY

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INFANRIX hexa™ Question and Answer Document

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1.0 INFANRIX hexa™ VACCINE

1.1 What is INFANRIX hexa™ vaccine?

- A hexavalent vaccine that protects against six diseases: diphtheria, tetanus, pertussis, hepatitis B, polio, and *Haemophilus influenzae* type b (Hib).
- INFANRIX hexa™ will replace Pediacel® and hepatitis B vaccines in the routine infant primary immunization series at 2, 4 and 6 months of age.

1.2 When will INFANRIX hexa™ be introduced?

- February 1, 2009.
- All infants born on or after December 1, 2008 will be offered INFANRIX hexa™ at 2, 4, and 6 months of age. Infants born before that date *who have not yet started their primary immunization series* may also receive this vaccine.
- Pediacel® will continue to be used for the 18 month booster.

1.3 What is the difference between INFANRIX hexa™ and Pediacel®?

- Infanrix hexa™ has six components, including hepatitis B.
- Pediacel® has five components (diphtheria, tetanus, acellular pertussis, polio, Hib).
- Infanrix hexa™ and Pediacel® are ***not*** considered interchangeable in the primary series of three doses given at 2, 4 and 6 months. This is because clinical trials demonstrating interchangeability have not been conducted. The primary series should be completed with the same product whenever possible.

1.4 Why are we switching to INFANRIX hexa™ vaccine?

- One less injection at each of the 2, 4, and 6 month immunizations, while providing similar protection.
- Expected increase in vaccine coverage levels.
- Improved security of vaccine supply by providing a market in Canada to a second vaccine supplier.

1.5 How is INFANRIX hexa™ supplied?

- As a single dose pre-filled syringe containing Pediarix™ (DTaP – HBV – IPV) (suspension for injection) and a single dose vial of adsorbed Hib (lyophilized powder for reconstitution and injection).

- No needles will be supplied with the vaccine.

1.6 What are the steps involved in administering INFANRIX hexa™?

- Remove one Pediarix™ syringe and one vial of Hib vaccine from the box.

- Attach a safety needle to the syringe and agitate thoroughly until there is a homogeneous white turbid suspension.

- Inject the Pediarix™ into the vial containing the freeze-dried Hib to **reconstitute**. After the addition of the Pediarix™ to the Hib vial, the mixture should be well shaken until the Hib pellet is dissolved. The reconstituted vaccine presents as a slightly more cloudy suspension than the liquid component alone.

- Withdraw all of the reconstituted vaccine from the vial.

1.7 The product monograph states "the vial should be kept at room temperature for at least 5 minutes before connecting the syringe and reconstituting the vaccine." Should we do this?

- No. Further communications from GlaxoSmithKline (GSK) Canada indicate that the instruction to allow vaccine to reach room temperature is not necessary.

1.8 When was INFANRIX hexa™ approved for use in Canada by Health Canada?

- Infanrix hexa™ was first approved for use in Canada in 2004. The first approved formulation contained trace thimerosal in the Engerix-B (hepatitis B) component. The formulation being used in BC is the thimerosal-free formulation, which was approved by Health Canada in November 2007.

- Infanrix hexa™ was first approved internationally in October 2000 with close to 14 million doses distributed between October 2000 and April 2008.

1.9 Where else in the world is INFANRIX hexa™ used?

- Infanrix hexa™ is administered in 69 countries, including Australia, Germany, Austria, Switzerland, Belgium, the Netherlands, France, Italy, Spain, Mexico, Argentina, and Brazil.

2.0 COMPONENTS OF INFANRIX hexa™ VACCINE

2.1 What is the polio component of the vaccine?

- The three polioviruses are cultivated on a continuous VERO cell line, purified and inactivated with formaldehyde. VERO is a continuous cell line developed in 1962, initiated from kidney cells of an adult African green monkey. This is the same process used to manufacture the polio component of Pediacel® vaccine.

2.2 Are there trace amounts of thimerosal in INFANRIX hexa™ vaccine?

- No. The most recent product monograph dated July 18, 2008 lists all the components of INFANRIX hexa™ vaccine and is available at: http://www.gsk.ca/english/index.html under Products, Vaccines.

- Other vaccine components are aluminum hydroxyphosphate sulfate, L-histidine, polysorbate 80, trace amounts of polymyxin B and neomycin, and there is latex in the syringe plunger and cap.

3.0 CONTRAINDICATIONS TO INFANRIX hexa™ VACCINE

3.1 What are the contraindications?

- History of anaphylactic reaction to a previous dose of DPT, DTaP, IPV, Hib or Hepatitis B containing vaccine or to any INFANRIX hexa™ vaccine component.

- History of Guillain-Barré Syndrome (GBS) within 8 weeks of receipt of a tetanus-containing vaccine.

- INFANRIX hexa™ is not indicated for children ≥ 7 years of age.

3.2 The product monograph states the vaccine should not be administered to an infant who has experienced encephalopathy of unknown etiology, occurring within 7 days following previous vaccination with a pertussis containing vaccine. Does this mean a change in practice?

- No, this is not a change in practice. The product monograph for Pediacel® contains a similar statement.

- The 2006 Canadian Immunization Guide, 7th ed. states “People with encephalopathy or encephalitis that develops within 7 days after immunization should be investigated. Those who have an alternative etiology for the encephalopathy (e.g., viral infection) or who recover fully by the next scheduled

vaccination may be immunized without deferral. People with encephalopathy that persists or who have no alternative etiology should be referred to a specialist for further consultation and may be immunized if their condition is stable and found not to relate to immunization."

4.0 EFFICACY OF INFANRIX hexa™ VACCINE

4.1 Pediacel® is a 5 component pertussis vaccine and INFANRIX hexa™ is a 3 component pertussis vaccine. Will this affect the efficacy and immunogenicity of the pertussis component of INFANRIX hexa™ vaccine?

- The pertussis component of Pediacel® vaccine contains 5 antigens: pertussis toxoid (PT), filamentous hemagglutinin (FHA), pertactin (PRN), and fimbrial proteins 2 and 3 (FIM2 and FIM3). INFANRIX hexa™ vaccine contains 3 pertussis antigens: PT, PRN, and FHA. The concentration of each of these antigens is 5 µg greater than in Pediacel® vaccine.

- A consistently high response to all pertussis vaccine antigens was observed after the booster vaccination during the second year of life regardless of the vaccine used during primary series or booster administration.

- INFANRIX™ vaccines have remained unchanged for 10 years and are associated with excellent and consistent clinical vaccine efficacy (84-89% against laboratory-confirmed "typical" pertussis).

4.2 Is there any concern regarding decreased Hib antibody?

- No. In population surveillance studies, combination vaccines were highly protective against invasive Hib infection. Specifically hexavalent vaccines such as INFANRIX hexa™ show high effectiveness against invasive Hib disease and the booster vaccination provides additional benefit to the high protection already provided by the primary series.

4.3 How does the protection against hepatitis B compare (between RecombivaxHB® and INFANRIX hexa™ vaccines)?

- In studies of seroprotection rates achieved after immunization with either pentavalent vaccines in which hepatitis B vaccine was administered concurrently at a separate site, or with INFANRIX hexa™ vaccine, it was found that seroprotection levels varied between 95% and 100%, regardless of the type of vaccine used.

4.4 What about the efficacy of the other components?

- Diphtheria – one month after completion of the three-dose primary series, ≥ 97% of vaccinees in all studies achieved a protective level of antibodies, regardless of the type of vaccine used.

- Tetanus – one month after completion of the three-dose primary series, ≥ 99% of vaccinees had a protective antibody level, regardless of the type of vaccine used.

- Poliovirus – when antibodies were measured one month after completion of the three-dose primary series, ≥ 95% of vaccinees had a seroprotective level of antibodies against all three types of poliovirus.

4.5 The NACI statement indicates that trials comparing Pediacel® and INFANRIX hexa™ have not been conducted in selected populations, such as the Canadian Aboriginal population and that further data are needed. What is being done about this?

- The Vaccine Evaluation Center (VEC) is conducting a post licensure study using INFANRIX hexa™ in aboriginal infants compared to non-aboriginal infants in British Columbia.

- This study is examining immunogenicity. There are 224 participants in the study, 112 per arm. Each infant will receive 3 injections of INFANRIX hexa™ vaccine (at 2, 4, and 6 months of age) and have a blood sample drawn at 7 months of age.

5.0 SCHEDULING OF INFANRIX Hexa™ VACCINE

5.1 Why are INFANRIX hexa™ and Pediacel® not interchangeable in the primary series?

- There are insufficient data to document the safety, immunogenicity, and efficacy of using DTaP vaccines from different manufacturers in a mixed sequence in the primary series given at 2, 4 and 6 months of age.

- Whenever possible, the same DTaP-containing vaccine product should be used for all doses of the primary vaccine series.

- When not possible, such as for infants or young children arriving in Canada from other countries where different products are used, the primary series should be completed with the available product(s) in BC. Vaccination should not be

deferred because the product used for previous doses is not available or unknown.

- There are no data documenting adverse consequences of switching from one product to another during the primary series.

5.2 What is the minimum age for first dose and what are the minimum intervals between doses for INFANRIX hexa™?

- The minimum age for a first dose is 6 weeks of age.
- The minimum intervals between subsequent doses of INFANRIX hexa™ are based on those recommended for hepatitis B vaccine. A minimum of 4 weeks must pass between dose 1 and 2. Dose 3 must be given at least 16 weeks after the 1st **and** 8 weeks after the 2nd dose.

5.3 Can INFANRIX hexa™ be administered with other vaccines?

- Yes. Infanrix hexa™ can be safely administered at the same time or at any time before or after any other vaccine. As for other vaccines, it should be administered in a separate injection site, by separate needle and syringe.

6.0 SPECIAL SITUATIONS

6.1 What about infants at high risk of hepatitis B or those less likely to respond to hepatitis B vaccine?

- Infants who are at high risk of hepatitis B infection at birth will continue to receive hepatitis B vaccine at birth, along with hepatitis B immune globulin if their mother is HBsAg positive or is at high risk for hepatitis B infection. **Administer INFANRIX hexa™ at 2, 4, and 6 months of age to these infants.** These infants will receive a total of four doses of Hepatitis B vaccine. This is a change from the 0, 1 and 6 month doses of Hepatitis B that has been used with these infants. The HBIg and/or hepatitis B vaccine administered at birth will provide protection for the infant until the next dose is administered at 2 months of age.

  As it may take some time for the dissemination of information regarding this schedule change, infants born in December 2008 may still receive hepatitis B vaccine at birth, 1 month of age, and 6 months of age. When an infant presents at 2 months of age for immunization, assess for previous hepatitis B immunization before administering INFANRIX hexa™. For those infants who have received a dose of hepatitis B vaccine at birth **and** at 1 month of age, administer Pediacel® at 2, 4, and 6 months of age, and hepatitis B vaccine at 6 months of age.

- Ensure the birth dose of hepatitis B vaccine is entered into iPHIS as dose 1 of hepatitis B vaccine. Enter first INFANRIX hexa™ dose as DTaP/HB/IPV/Hib dose 1.

- Infants and children who are immunocompromised (solid organ transplant, chronic kidney disease, HIV, immunosuppression, and HSCT) require double µg doses of Hepatitis B vaccine. These children will require Pediacel® and RecombivaxHB® vaccines.

6.2 What if a child has already started their primary immunization series with Pediacel® and Hepatitis B vaccine?

- Complete the primary series with Pediacel® and RecombivaxHB® vaccines.

6.3 What if a parent tells the health care provider that their family is moving to another province or another country before completion of the primary vaccine series?

- As of early 2009, British Columbia is the only Canadian jurisdiction using INFANRIX hexa™ in its publicly funded program. This may change over time. INFANRIX hexa™ will be available for purchase from GSK throughout Canada.

- If a parent indicates that the family will be moving within Canada but outside of BC before completion of the primary series, offer to start a Pediacel® and RecombivaxHB® immunization series.

- If one or two doses of INFANRIX hexa™ are administered before the parent informs the health care provider of a pending move out of province, inform the parents that, based on current evidence, the best practice is to complete the primary series using the same type of DTaP–containing vaccine.

- When INFANRIX hexa™ is unavailable in another jurisdiction, the series can be completed using any approved product(s) to provide protection against the six diseases, e.g., Pediacel® and either RecombivaxHB® or Engerix-B™.

6.4 What about those infants born at less than 2000gm AND who receive a birth dose of hepatitis B vaccine?

- Immunize with the complete INFANRIX hexa™ series. These infants will no longer require an additional dose of hepatitis B vaccine at 8 months of age as they will have received 4 doses of vaccine at completion of the INFANRIX hexa™ series.

6.5 What if a parent refuses hepatitis B vaccine?

- Pediacel® will be available and can be offered according to the routine schedule.

6.6 What if a child presents on or after 12 months of age and has not received any vaccines yet?

- A new SCHEDULE B: CHILDREN ≥ 1 YEAR BUT < 7 YEARS WHEN STARTING IMMUNIZATION will be added to Section II of the Immunization Program Manual.

- Immunize the child with the INFANRIX hexa™ series (as per Schedule B) ensuring that the last dose is given before the seventh birthday. Administer other vaccines as appropriate for child's age.

- Individuals between the ages of 2 and 7 years will benefit from the protection without the extra injections necessary for separate administration of hepatitis B vaccine and Pediacel®.

- Although only one dose of Hib vaccine is required for protection after 15 months of age, there is no harm in receiving additional doses of Hib conjugate vaccine.

6.7 What if a child receives INFANRIX hexa™ for dose 1 and dose 2 at appropriate ages but then has immunization delayed until after 2 years of age?

- Administer one dose of INFANRIX hexa™ when the child re-presents, provided the child is under 7 years of age at the time. In six months, administer one dose of Quadracel® vaccine (using minimum spacing guidelines and noting that the child has now received one dose of Hib vaccine at >15 months of age).

6.8 Is there any concern with giving more than the recommended number of doses of Hib vaccine when administering INFANRIX hexa™ to a child who is delayed in starting immunization?

- No, there is no increase in adverse events associated with additional doses of Hib vaccine. While it is recognized that the child doesn't require the extra doses of Hib vaccine for protection, the parent and health care provider can consider the benefit of fewer injections with INFANRIX hexa™ vaccine.

6.9 I forgot to reconstitute the Hib component of the vaccine and gave only the Pediarix™ in the syringe. How do I immunize the infant against Hib?

- Administer a dose of Hib (Act-HIB®) vaccine separately as soon as possible. (Note the minimum spacing between doses one and two and between doses two and three of Hib vaccine is 4 weeks.) Continue using INFANRIX hexa™ to complete the primary series.

6.10 What if Pediacel® and separate hepatitis B vaccines are administered instead of INFANRIX hexa™ vaccine?

There is a lack of data regarding the interchangeability of Pediacel® and INFANRIX hexa™ vaccines for the primary series of doses given at 2, 4 and 6 months. The best practice is to complete the primary series with the same vaccine(s). However, based on expert opinion, the following guidelines may be followed:

- If the Pediacel® and separate hepatitis B vaccines are given at the first immunization appointment, the infant should continue to receive separate Pediacel® and hepatitis B vaccines to complete their primary series. Note this on the infant's record to ensure the series is completed with the same products.
- If Pediacel® and separate hepatitis B vaccines are given as the second dose of the primary series in an infant who received INFANRIX hexa™ for their first dose, administer INFANRIX hexa™ at the next (third) immunization appointment. Follow worksite protocol regarding informing parents and recording vaccine error. Administer Pediacel® for the 18 month booster as per the routine schedule.
- If Pediacel® and separate hepatitis B vaccines are given as the third dose of the primary series in an infant who received INFANRIX hexa™ for their first two doses, follow worksite protocol regarding informing parents and recording vaccine error. Administer Pediacel® for the 18 month booster as per routine schedule.
- There is no need to repeat the vaccine dose that was administered using the alternate product(s) in the primary series.
- There is no need to have the parent/representative re-consent for the vaccine series as consent is given for protection against the specific diseases, not for the administration of the particular vaccine.

7.0 ADVERSE EVENTS ASSOCIATED WITH INFANRIX hexa™ VACCINE

7.1 How do the rates of adverse events compare between Pediacel® and INFANRIX hexa™?

- There have been no head to head trials for direct comparison between Pediacel® and INFANRIX™ vaccines.

- The potential difference between the two vaccines is the higher incidence of fever ≥ 38°C reported with INFANRIX™ vaccines. However, the studies reporting this were conducted using 2, 3, and 4 month or 3, 5, and 11 month schedules. The incidence of fever ≥ 39.5°C was not significantly different between the two vaccines (0% - 1.2% with Pediacel®/Pentacel® and 0% - 1.4% with INFANRIX™ vaccines).

- The incidence of other local and systemic reactions was comparable following immunization with either of the vaccine families.

- In studies examining concurrent immunization with Prevnar™ vaccine and INFANRIX hexa™ vaccine, a higher incidence of fever (including ≥ 39.5°C) was reported in infants receiving INFANRIX hexa™ and Prevnar™ compared to infants receiving the hexavalent vaccine alone. However, the incidence of fever following administration of the two vaccines in the primary series was lower than that observed after the booster vaccination.

7.2 Will there be a change in our pre or post immunization care recommendations?

- No, the recommendations following administration of INFANRIX hexa™ vaccine will remain the same as with the administration of Pediacel® and Hepatitis B vaccines.

7.3 What will the temporal criteria be for adverse events following INFANRIX hexa™ immunization?

- Refer to the temporal criteria for pentavalent (DTaP/IPV/Hib) and separate hepatitis B vaccines. Refer to BC Communicable Disease Manual, Chapter 2, Section X at http://www.bccdc.org/content.php?item=193. When there is a discrepancy between the temporal criteria for these two vaccines, use the longer of the two intervals.

8.0 REFERENCES

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