Important Safety Information for several GlaxoSmithKline Inc. vaccines: Potential Risk of Underdosing

2018/05/01

Audience
Healthcare professionals including family physicians, pediatricians, pharmacists, nurses, nurse practitioners, physicians' assistants, and those working in travel clinics.

Key messages

- **This information is applicable to the following vaccines: BOOSTRIX, BOOSTRIX-POLIO, ENGERIX-B, HAVRIX, HAVRIX Junior, INFANRIX-IPV, INFANRIX-IPV/HIB, INFANRIX-hexa, TWINRIX and TWINRIX Junior (see section "Products affected*").**
- **Leakages have occurred from ceramic coated tip (CCT) syringes used for several GlaxoSmithKline Inc. vaccines in Canada. The leakages occurred at the connection of the syringe tip and the needle hub during vaccine preparation or administration at an approximate rate of 3 per 100,000 syringes distributed. The integrity of the syringe and sterility of the contents were not compromised.**
- **Administration of vaccines from leaking syringes can result in a potential risk of underdosing, that may leave patients inadequately protected from disease after vaccination (see section "Information for healthcare professionals").**
- **Healthcare professionals are advised:**
    - **not to use the syringe when the leakage occurs during reconstitution of lyophilized vaccines.**
    - **when the leakage occurs during vaccine injection and the individual received less than the standard dose, the decision to revaccinate should take into account both the potential benefits and risks associated with administering a repeated dose (see section "Information for healthcare professionals").**
- **GlaxoSmithKline Inc. has been working with Health Canada to provide information regarding the leaking syringes for vaccines and the corrective actions implemented. The introduction of improved CCT syringes on the Canadian market is anticipated in 2018. However, both improved and affected CCT syringes are expected to be on the market until the end of 2019, the estimated time for using up the potentially affected syringes.**

What is the issue?
There have been reports of leakage from CCT syringes used for several GlaxoSmithKline Inc. vaccines during vaccine preparation or administration. Although the leakage does not pose a concern for the vaccine sterility, there is a potential risk of underdosing associated with administration of a vaccine from a leaking syringe that may leave patients inadequately protected from disease after vaccination.

Products affected*

Product (medicinal ingredient(s))	**DIN#**
BOOSTRIX (combined diphtheria, tetanus, acellular pertussis (adsorbed) vaccine)	02247600
BOOSTRIX-POLIO (combined diphtheria, tetanus, acellular pertussis (adsorbed) and inactivated poliomyelitis vaccine)	02312557
HAVRIX (hepatitis A vaccine, inactivated)	02187078
HAVRIX Junior (hepatitis A vaccine, inactivated)	02231056
INFANRIX-IPV (combined diphtheria, tetanus, acellular pertussis and inactivated poliomyelitis vaccine)	02241284
INFANRIX-IPV/HIB (combined diphtheria, tetanus, acellular pertussis, inactivated poliomyelitis, *Haemophilus influenzae* type b vaccine	02257122
INFANRIX-hexa (combined diphtheria and tetanus toxoids, acellular pertussis, hepatitis B (recombinant), inactivated poliomyelitis and adsorbed conjugated *Haemophilus influenzae* type b vaccine)	02253852
TWINRIX (combined hepatitis A (inactivated) and hepatitis B (recombinant) vaccine)	02230578
TWINRIX Junior (combined hepatitis A (inactivated) and hepatitis B (recombinant) vaccine)	02237548

*__Note:__ In addition to the above-noted products, 1 lot of ENGERIX-B (Adult), which was released in Canada for shortage mitigation, provided in a syringe format (**Lot AHBVC650AV, Expiry Date: March 2020**) may also be affected.

Background information
Beginning in July 2015, GlaxoSmithKline Biologicals SA identified an increase in the reporting rate of leakages in CCT syringes at the connection of the syringe tip and the needle hub during vaccine preparation and administration (see Figure 1). The integrity of the leaking syringe and sterility of the contents were not compromised.

Figure 1: Examples of different volume losses (blue area)

Picture A	Picture B
	

A review of GlaxoSmithKline Biologicals SA pharmacovigilance data as of December 14, 2017 did not find evidence that the observed leakage has resulted in vaccination failure (lack of efficacy) or any other patient safety concern. In Canada, the syringe leakage rate is 3 per 100,000 syringes distributed, although the precise frequency of leakage is not known and may be higher.

GlaxoSmithKline Inc. has implemented corrective actions with its syringe suppliers and has introduced improved syringes in its filling operations as of January 2018. However, both the improved and current CCT syringes will be on the market during 2019, with the proportion of potentially affected syringes progressively decreasing towards the end of 2019 by when the current syringes are expected to have been used up.

Data relevant to the administration of lower antigen content are available for HAVRIX and ENGERIX-B [1-2]. These data suggest that the administration of half the required antigen dose of HAVRIX or ENGERIX-B will not affect seroprotection or seropositivity. As the probability of a leakage resulting in patients receiving half the required dose is very low, leakage is not expected to impact seroprotection/seropositivity following vaccination.

No dose-range studies are available for TWINRIX, but the immune response to the two antigens in the TWINRIX vaccine was demonstrated to be at least as good as that after vaccination with the monovalent vaccines, HAVRIX and ENGERIX-B [3], for which data on administration of lower antigen content are available.

For the other vaccines potentially impacted by leakages, it is not possible to assess the likely impact of underdosing on seroprotection/seropositivity. However, for vaccines given in a multi-dose schedule (2-3 priming doses plus booster), it is highly unlikely that each dose will be administered with a leaking syringe.

Regarding the potential risk of overdosing in case of revaccination, the reported adverse events after overdosage with vaccines, including INFANRIX-IPV and INFANRIX-IPV/Hib, BOOSTRIX, BOOSTRIX-POLIO and TWINRIX [4-7], were similar to those reported with the standard dose administration.

Information for healthcare professionals

If the leakage occurs **during reconstitution** of lyophilized vaccines, healthcare professionals should not use the syringe.

If the leakage occurs **during vaccine injection,** the healthcare professional can decide whether to revaccinate individuals who have been given less than the standard dose. (see Additional information on recommendations in the event of underdosing)

Additional information on recommendations in the event of underdosing
Since no local recommendations are in place, the following US Centers for Disease Control and Prevention (CDC) and the UK Public Health England (PHE) recommendations may be considered.

- According to the CDC guidelines, it is recommended that "Any vaccination using less than the standard dose should not be counted, and the person should be revaccinated according to age unless serologic testing indicates that an adequate response has developed. If a partial dose of a parenteral vaccine is administered because of syringe or needle leakage, the dose should be repeated" [8].

- According to United Kingdom Public Health England, it is recommended that "Where vaccines are administered to patients at less than the recommended dose, vaccination will need to be repeated because the doses that patients received may not be sufficient to evoke a full immune response. Vaccination should ideally be repeated on the same day. If it is not possible to repeat the vaccine on the same day, live vaccines should be repeated following a minimum interval of four weeks since the incorrect dose. Inactivated vaccines should be repeated as soon as possible" [9].

Information for consumers
Vaccines work by helping the body to produce its own protection (antibodies) against certain infectious diseases such as:

- diphtheria, tetanus (lockjaw)
- pertussis (whooping cough)
- poliomyelitis (polio)

- bacterial meningitis (inflammation of the membranes surrounding the brain)
- hepatitis A and B (inflammation of the liver)

Vaccines are sold directly to healthcare professionals and are intended strictly for professional use. Patients and caregivers should contact their healthcare professionals to discuss what this new information means to them.

Action taken by Health Canada
Health Canada is communicating this important safety information to healthcare professionals and Canadians via the Recalls and Safety Alerts Database on the Healthy Canadians Web Site (www.healthycanadians.gc.ca/recall-alert-rappel-avis/index-eng.php) and through the MedEffect™ e-Notice email notification system.

Report health or safety concerns
Managing marketed health product-related side effects depends on healthcare professionals and consumers reporting them. Any case of leaking syringes or any other serious or unexpected side effects in patients receiving BOOSTRIX, BOOSTRIX-POLIO, ENGERIX-B, HAVRIX, HAVRIX Junior, INFANRIX-IPV, INFANRIX-IPV/HIB, INFANRIX-hexa, TWINRIX and TWINRIX Junior should be reported to GlaxoSmithKline Inc. or Health Canada.

GlaxoSmithKline Inc.
7333 Mississauga Road
Mississauga Ontario
Canada L5N 6L4
Tel: 1-800-387-7374

To correct your mailing address or fax number, contact GlaxoSmithKline Inc.

You can report any suspected adverse reactions associated with the use of health products to Health Canada by:

- Calling toll-free at 1-866-234-2345; or
- Visiting MedEffect Canada's Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax.

For other health product inquiries related to this communication, contact Health Canada at:

Regulatory Operations and Regions Branch
E-mail: dcviu_uvcem@hc-sc.gc.ca
Telephone: 1-800-267-9675

Original signed by

Dr. Susie Barnes MRCGP FFPM
Vice President and Country Medical Director
GlaxoSmithKline Inc.

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2. Innis B, Snitbhan R, Kunasol P et al., J. Protection against hepatitis A by an inactivated vaccine. JAMA. 1994;271(17):1328-34.
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4. INFANRIX-IPV/Hib Product Monograph, dated May 29, 2017.
5. BOOSTRIX Product Monograph, dated March 05, 2018.
6. BOOSTRIX-IPV Summary of Product Characteristics https://www.medicines.org.uk/emc/medicine/28679
7. TWINRIX Product Monograph, dated August 11, 2016.
8. CDC, accessible at: http://www.cdc.gov/vaccines/pubs/pinkbook/vac-admin.html#nonstandard Last accessed: 06/Feb/2017.
9. UK Public Health England: Vaccine Incident guidance: Actions to take in response to vaccine errors. March 2012. Accessible at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/326417/Vaccine_Incident_Guidance.pdf Last accessed: 06/Feb/2017.