Hepatitis A and Hepatitis B Vaccines: Recommendations for Interrupted Schedules, Booster Doses, Repeat Doses, & Last-Minute Travellers

BOTTOM LINE

(More details in text that follows)

Interrupted Schedules: ***Early Dose:*** Ensure the minimum interval has been met; if it has not, the dose will most often need to be repeated. ***Late Dose:*** If a dose has been delayed, in almost every situation, there is no need to repeat the dose or restart the series; however, it is important the series is completed.

Interrupted Product Supply: Ideally use the same product for the entire series but if circumstances warrant, other brands can be used interchangeably.

Booster Dose Hepatitis A: There is currently no recommendation for a booster dose of the hepatitis A vaccine after a primary series has been successfully completed.

Booster Dose Hepatitis B: Routine booster doses of hepatitis B vaccine are not recommended for immunocompetent individuals after a primary series has been completed. Periodic booster doses may be recommended in some cases for individuals who are immunocompromised or who have chronic renal failure.

Booster Dose Combined Hepatitis A/ Hepatitis B: Because there is never a need to boost the hepatitis A component, routine boosters or repeating a series of the combined vaccine are unnecessary regardless of time elapsed since original series. Assess for need for Hepatitis B booster.

Repeat Doses Hepatitis B: High-risk individuals who fail to adequately respond to a series of hepatitis B vaccine may require additional doses.

Last Minute Travel: The individual's risk & immune status as well as destination and amount of time before departure will factor into the best regimen to use in those who do not have time to complete a full series. See Tables 2 & 3.

Important Note:

It is the pharmacist's responsibility **to review an individual's history prior to prescribing and/or administering vaccine (whether pursuant to a prescription written by a pharmacist or other authorized prescriber), to ensure vaccination is appropriate.**

- E.g. booster doses following successful completion of a full series are not appropriate for hepatitis A vaccine and not appropriate for *most* individuals for hepatitis B vaccine. See text for details.
- E.g. Most SK residents born since 1984 would have received routine hepatitis B vaccine in Grade 6. If records are unavailable and the client does not recall receiving HB series, proceed with HB vaccine as per indication.[1]

Contents

Completion of Interrupted Hepatitis A (HA) and Hepatitis B (HB) Vaccine Schedules

Refer to product monographs or the Canadian Immunization Guide (CIG) for established schedules of monovalent Hepatitis A vaccine (HAV) and monovalent Hepatitis B vaccine (HBV) schedules. The most common schedules for *pre-exposure* immunization in those 5 years and older as well as their minimum intervals are presented in Table 1 at the end of this document. Note that not all schedules are approved for all vaccine products and/or vaccine recipient ages. Discussion of excursions from the schedules follows.

1. Minimum Interval[2-4]

Schedules provide recommended intervals, for example, 0, 1, and 6 months. Wait the recommended interval when possible though some circumstances may necessitate providing a vaccine dose earlier than the recommended interval. Minimum intervals have been determined for some schedules and are just that – the minimum duration between vaccine doses that ensures adequate immune response. Sometimes the recommended interval and minimum interval are the same.

The minimum intervals must be met and, if not, the dose needs to be repeated. Minimum intervals are provided in Table 1. Minimum intervals are intended to determine validity of past vaccine doses and/or for catching up on an interrupted series. When scheduling future doses in individuals who have received doses on time or are starting a series, use the recommended interval. The Saskatchewan Immunization Manual (SIM) accepts a 4 day grace period in which, if a dose has been administered up to four days before the minimum interval, it can be considered valid.[3] *The 4 day grace period does not*

apply to accelerated vaccine schedules. Below are some example scenarios. See Table 1 for minimum intervals.

- The schedule for **HAV** is 0 and 6 months; the minimum interval is 24 weeks
  - Example: the individual received the 2nd dose at 3 months
    - This dose cannot be considered valid because it does not meet the minimum interval. The dose will need to be repeated at least 24 weeks from the invalid dose (at least 24 weeks after the dose received at 3 months).
- One of the schedules for **HBV** is 0, 1, and 6 months
  - Example: the individual received the 2nd dose at 25 days
    - The minimum interval between the 1st and 2nd doses is 4 weeks. While the second dose was received before the minimum interval, it was within the grace period (not more than 4 days before the minimum interval) and is considered valid.
  - Example: the individual received the 2nd dose at 1 month and the 3rd dose at 18 weeks (4½ months)
    - The 2nd dose is appropriate.
    - While the 3rd dose was received less than 5 months after the second dose, it does meet the minimum intervals between both the 2nd dose (8 weeks) and 1st dose (4 months) and is valid.
- One of the schedules for **HBV** is 0, 7 days, 21 days, and 12 months
  - Example: individual received the 2nd dose at 7 days and the 3rd dose at 20 days
    - The 2nd dose is appropriate.
    - The 3rd dose was received less than 14 days after the 2nd dose and, while it was only one day early, the 4-day grace period does not apply to accelerated schedules; the 3rd dose is invalid and needs to be repeated at least 14 days after the invalid dose (at least 14 days after the dose received at day 20).

2. Extending an Interval (Delayed Dose) [4,5]

Extending an interval does not negatively impact the immunogenicity of the HA and HB vaccines; if the interval has been extended, provide the dose as soon as possible and continue with the schedule, meeting at least minimum intervals if more than one dose is required to complete the series. **There is no need to repeat doses or restart the series**.

- One of the schedules for **HAHB combination vaccine** is 0, 1, and 6 months.
  - Example: the individual presents for the 2nd dose 6 months after the first dose
    - Provide the 2nd dose now and provide the final dose at least 5 months after the 2nd dose (= minimum interval, found in Table 1).
  - Example: the individual received the 1st dose in January 2014 and 2nd dose in February 2014 but has not received the 3rd dose.
    - Provide the 3rd dose now and consider the series complete.
- EXCEPTION: HBV or HAHB combination vaccine alternate (2-dose) schedule not completed before the age of 16 years. HBV schedule is an adult dose at 0 and 6 months in those 11 to 15 years of age. HAHB vaccine schedule is an adult dose at 0 and 6 months in those 6 months* to 15 years of age.
  - Example: the individual received 1st HBV dose of the alternate schedule at the age of 12 years and presents at age 17 years.

- This 2-dose schedule has only been validated for those 11 to 15 years of age. Essentially, this individual has received one adult dose but needs to now complete a 3-dose series. Because the individual is younger than 20 years, the pediatric 3-dose series is appropriate.
    - Provide 2nd dose (pediatric HBV) now as the recommended interval of 1 month has been met.
    - Provide 3rd dose (pediatric HBV) 5 months after the 2nd dose (no earlier than 8 weeks).

*The HAHB vaccine is authorized for ages 1 year and older; however, CIG indicates HAHB vaccine can be used in infants as young as 6 months if both HAV and HBV are indicated.[6]

3. Completion of Series Using Different Products[1,6,7]

When possible, complete a series using the same product for all doses.

- In cases in which the original product is not available, **using another brand is acceptable**; use the appropriate dose of the brand on hand.
- Note: the concentrations and units vary between products. CIG considers, when necessary, all available HAV products interchangeable[7] and all available HBV products interchangeable[6]. Always use the volume indicated for the appropriate dose (adult or pediatric) of the product being used.
    - Example: the adult dose of Havrix® is 1 mL (1440 ELISA units).[8] The adult dose of Avaxim® is 0.5 mL (160 ELISA units).[9] If 1 mL Havrix® were used for the first dose and now Avaxim® is all that is available, administer 0.5 mL Avaxim® to complete the series for an adult.
- When necessary, **monovalent series can be completed using HAHB combination vaccine and HAHB combination vaccine series can be completed with monovalent vaccine**.
    - This situation should be avoided, if possible.
    - This may result in extra doses of one or both of the HAV/HBV components; there is no danger in receiving extra doses.[5]
    - Keep in mind, extending intervals is not detrimental to immunogenicity, though full immunogenicity does not occur until completion of the series. Consider waiting for availability of original monovalent or HAHB combination vaccine product.
        - Consider upcoming risk of exposure, if any expected. (E.g. Twinrix unavailable and individual with no expected upcoming exposure to HA or HB viruses presents for the final dose at 6 months; it is reasonable to wait until Twinrix becomes available to provide final dose instead of finishing series with monovalent products so long as risk of exposure does not change.)
    - HA component
        - Each dose of the HAHB combination vaccine (Twinrix) contains half the HA antigen of the monovalent product making completion of series in these situations tricky. (Twinrix adult dose contains 720 ELISA units HA antigen per 1 mL[10]; Havrix® adult dose contains 1440 ELISA units HA antigen per 1 mL.[8])
            - See CIG Hepatitis A Vaccine for completion of HA series with HAHB combination vaccine when started with monovalent and vice versa.
    - HB component

        - The amount of HB antigen is the same in each dose of monovalent vaccine as HAHB combination vaccine making completion of series easier when interchanging monovalent with HAHB combination vaccines and vice versa.
- **Pediatric products can be used for adult doses** and vice versa when the appropriate product is not available.
    - If two injections are required to achieve an adult dose, administer at separate sites at least 2.5 cm apart.[3]
        - E.g. Achieve an adult dose of Engerix-B by using 2x pediatric prefilled syringes.
    - When preparing a pediatric dose using an adult formulation in a vial, withdraw the correct volume and discard the remaining contents of the vial if not used within 1 hour of opening[12] as all products are single-use vials.
    - When preparing a pediatric dose using an adult formulation in a pre-filled syringe, discard excess volume before administering. **This practice is only condonable for products with gradations on the syringe.** Check the specific product; many syringes do not have gradations.

Booster Doses

- **Unlike some vaccines such as tetanus, routine booster doses of HAV and HBV following successful completion of a series are not recommended for most individuals**.[1,6,7]
    - Note that monographs state long-term protection is thought to be at least 20 years for HA[9] and 15 years for HB,[12] which may leave the impression that booster doses should be received 20 and 15 years following HA and HB immunization, respectively. Again, there are no current recommendations to provide routine booster doses.
    - **Exceptions**: immunocompromised individuals and those with chronic renal disease who have successfully responded to **HBV** series may require intermittent doses based on anti-HBs titres. See SIM Chapter 7, Appendix 7.4: High Dose Hepatitis B Immunization Algorithm and CIG for details.
- If anti-HBs titres have been drawn and found to be undetectable in an *immunocompetent* individual who has received a proper HBV series, is a booster dose required?
    - Immunocompetent individuals who develop an anti-HBs titre of at least 10 IU/L (adequate anti-HBs titre) following the completion of a recommended schedule are considered **protected for life**.[6]
    - In immunocompetent individuals, it is possible for titres to fall below 10 IU/L and even become undetectable over time; however, immune memory persists.[6]
    - For some types of workers, immunization against HBV is important and if post-vaccination anti-HBs testing documentation is not available, titres may be drawn to assess immune status.[6] Based on titre results, one or more doses of Hepatitis B may be recommended. See SIM Chapter 10 Hepatitis B Re-Vaccination Assessment Algorithm.

Repeat Doses

- Individuals at high risk of HB infection or complications (see CIG and SIM Chapter 7, Appendix 7.4 High Dose Hepatitis B Immunization Algorithm for details) who do not develop anti-HBs titres of at least 10 IU/L after the initial HBV series should receive a second HBV series.[6,12]

- Additional vaccine doses received in a second immunization series will produce a protective antibody response in 50% to 70% of healthy adults and children who did not initially respond to the vaccine.[6]
- Individuals who fail to respond to 3 additional doses of vaccine are unlikely to benefit from further immunization and should be counselled on alternative risk reduction measures.

Last Minute Travel

- A common scenario is individuals presenting for HAV, HBV, or HAHB combination vaccine for upcoming travel without enough time to complete the series.
- Confirm the vaccination needs based on individual's immune status (including vaccination history), individual risk factors, and HA and HB risk at destination.
- See Tables 2 & 3 for dose recommendations according to immune status and time of presentation.

Table 1 – Recommended and Minimum Intervals (MI) of Common Schedules for Vaccination of Hepatitis A and Hepatitis B Viruses

Schedule	1st dose	2nd dose	3rd dose	4th dose
Hepatitis A Monovalent Vaccine[7]				
Standard	0	6 months§ MI: 24 weeks[2]		
Hepatitis B Monovalent Vaccine[6]				
Standard (Preferred)	0	1 month MI: 4 weeks[2,6]	6 months MI from 2nd dose: 8 weeks[2] MI from 1st dose: 4 months[6]	
Accelerated (Engerix-B^)	0	1 month†	2 months†	12 months‡
Rapid (Engerix-B^) (≥ 20 years)	0	7 days†	21 days†	12 months‡
Alternate (11-15 years)	0	4-6 months* MI: 16 weeks[2]		
Hepatitis A/ Hepatitis B Combination Vaccine[6]				
Standard	0	1 month MI: 4 weeks[13]	6 months MI from 2nd dose: 5 months[13] MI from 1st dose: not established	
Alternate (6 months¥-15 years)	0	6-12 months‡		
Rapid (≥ 19 years)	0	7 days†	21 days†	12 months‡

MI= minimum interval

§ The recommended interval varies among products between 6-12 months and 6-36 months.[14,15]
^ This regimen is only officially approved for Engerix-B and not Recombivax HB®; however, there is no reason Recombivax HB® could not be used for this regimen if Engerix-B is not available.
† No minimum interval has been established but because these are accelerated regimens, observe recommended intervals.
‡ Minimum interval not established.
* Depending on product.
¥ The HAHB vaccine is authorized for ages 1 year and older; however, CIG indicates HAHB vaccine can be used in infants as young as 6 months if both HAV and HBV are indicated.[6]

Table 2 –Recommended Hepatitis A and Hepatitis B Monovalent Vaccine Schedules for Travellers According to Time before Departure

Age	Presents fewer than 21 days before departure	Presents at least 21 days but fewer than 28 days before departure *Also consider in those requiring HBV and staying in country > 6 months and/or needing to mount quick response*	Presents at least 28 days before departure
Vaccine Required: Hepatitis A Only‡			
Adult & Peds¥	Standard 0, 6§ months	Standard 0, 6§ months	Standard 0, 6§ months
Vaccine Required: Hepatitis B Only			
Adult	Standard Provide dose now; resume schedule at appropriate intervals upon return.† OR Rapid Provide dose now & at 7 days; resume schedule at appropriate intervals upon return.†^	Rapid Provide dose now, at 7, & 21 days; 4th dose at 12 months.^	Standard 0, 1, 6 months
Peds¥	Standard Pediatric Provide dose now; resume schedule at appropriate intervals upon return.† OR Alternate (11-15 years) **Use adult dose** 0, 4-6 months†	Standard Pediatric Provide dose now; resume schedule at appropriate intervals upon return.† OR Alternate (11-15 years) **Use adult dose** 0, 4-6 months†	Standard Pediatric 0, 1, 6 months

HBV = hepatitis B vaccine; Peds = pediatric

‡ Protective antibody concentrations against hepatitis A develop in ≥95% of vaccinees within one month of the first dose.[16] This response, along with the long incubation period of hepatitis A (15 to 50 days, average 28 days[7]), means most individuals who receive one dose the day before departure are protected.

¥ Check product monographs for approved ages of pediatric doses/products.

§ The recommended interval among products varies between 6-12 months and 6-36 months.[13,16]

† Provides some, but not full, protection against hepatitis B prior to departure.

^ This regimen is only officially approved for Engerix-B and not Recombivax HB®; however, there is no reason Recombivax HB® could not be used for this regimen if Engerix-B is not available

Table 3 –Recommended Hepatitis A and B Combination Vaccine Schedules for Travellers According to Time before Departure

Age	Presents fewer than 21 days before departure	Presents at least 21 days but fewer than 28 days before departure *Also consider in those requiring HBV and staying in country > 6 months and/or needing to mount quick response*	Presents at least 28 days before departure
Adult (≥ 19 years)	Separate standard schedules of monovalent products for 1st dose[17]: Provide 1 dose now of HAV‡ and 1 dose of HBV† Resume schedule with HAHB combination vaccine at 1 & 6 months	Rapid Provide dose now, at 7, & 21 days; 4th dose at 12 months	Standard 0, 1, 6 months
Peds	Alternate (6 months¥ - 15 years) **Use adult dose†** 0, 6-12 months	Alternate (6 months¥ - 15 years) **Use adult dose†** 0, 6-12 months	Standard Pediatric (6 months¥ - 18 years) (0, 1, 6 months) OR Alternate (6 months¥ - 15 years) **Use adult dose** 0, 6-12 months

HAHB = hepatitis A and hepatitis B; HAV = hepatitis A vaccine; HBV = hepatitis B vaccine; Peds = pediatric

‡ Protective antibody concentrations against hepatitis A develop in ≥ 95% of vaccinees within one month of the first dose.[16] This response, along with the long incubation period of hepatitis A (15 to 50 days, average 28 days[7]), means most individuals who receive one dose the day before departure are protected.

† Provides some, but not full, protection against hepatitis B.

¥ The HAHB vaccine is authorized for ages 1 year and older; however, CIG indicates HAHB vaccine can be used in infants as young as 6 months if both HAV and HBV are indicated.[6]

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