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TECHNICAL BRIEF

Management of Rabies Post-exposure Prophylaxis and Assessment of Vaccine Series Initiated Outside of Canada

Published: April 2024

Introduction

This document is intended for use by clinicians and public health professionals who are involved in the assessment and administration of rabies post-exposure prophylaxis (rPEP). It addresses management of individuals who initiated an rPEP series outside of Canada, as well as considerations regarding the management of common rPEP errors and schedule deviations.

Topics of discussion include:

Background

Rabies is a viral zoonotic central nervous system infection that is transmissible to humans through the saliva of an infected mammal.[1] Once symptoms develop, rabies infection in humans is almost always fatal.[1] Transmission to humans most commonly occurs through a bite from an infected animal, and less commonly, through introduction of infectious saliva via a scratch, mucous membrane or unbroken skin.[1] The risk of exposure to the virus varies by country and animal species.[1,2] In Canada, bats, raccoons, foxes and skunks are the primary reservoir for rabies, although domestic dogs, cats and livestock may also be infected and become a source of human exposure.[1] If indicated, post-exposure prophylaxis (rabies immunoglobulin (RIG) and rabies vaccine; rPEP) to neutralize the rabies virus at the site of exposure, and before it can enter the central nervous system, should be initiated as soon as possible.[1]

Assessment of the need for rPEP following a potential exposure incident that occurred locally within Ontario or elsewhere in Canada is conducted as per current national and provincial guidance.[1,3] On occasion, individuals may require assessment following a bite or scratch incident involving a mammal outside of Canada. If rPEP is initiated outside of Canada and the individual returns to Ontario before the

vaccine series is completed, questions may arise regarding vaccine effectiveness and how to manage continuation of a series initiated elsewhere, particularly if a vaccine not approved for use in Canada is used, or a regimen other than that outlined in the Canadian Immunization Guide (CIG) has been started. Similarly, if rPEP is started in Ontario and rabies vaccine and/or RIG are not administered as per current Ontario or Canadian guidance, questions may arise regarding rPEP effectiveness and how to adjust the administration schedule for remaining doses of vaccine (if applicable).

This *At a Glance* document provides an overview of factors to consider when assessing rPEP regimens initiated outside of Canada, and considerations for the management of individuals when rPEP is not administered according to the recommended Canadian schedule.

Completion of an rPEP series initiated outside of Canada

Individuals who have initiated rPEP outside of Canada should provide their healthcare provider with all relevant information, including the following:

- Details regarding the exposure incident (animal species, geographic location, whether the bite/scratch was provoked etc.)
- Written or electronic/photographic documentation of the type of rabies immunoglobulin and/or rabies vaccine received
- Vaccine schedule, dates and routes of administration; and
- Any other relevant information provided by the attending overseas healthcare provider.

Assessment of vaccine

Most countries, including Canada, use concentrated and purified cell-culture and embryonated egg-based rabies vaccines (CCVs), which are considered to be both safe and effective in preventing rabies.[1,4] A few countries however, including several in Asia and Latin America as well as Ethiopia, rely on vaccines derived from animal nerve tissue.[4,5] Per the United States Centers for Disease Control and Prevention (CDC), nerve tissue vaccines are generally recognizable by their large volume (5mL) and frequent dosing schedule.[6] Such vaccines are not recommended by the World Health Organization (WHO), and are considered incompatible with CCVs registered for use in Australia and the United Kingdom, as they are less effective in inducing an immune response than CCVs and are associated with more severe adverse reactions in some individuals.[4,5,7,8] Consequently, individuals who have previously received nerve tissue vaccine should be considered immunologically naïve, unless there is a history of documented immunity.[9]

The WHO maintains an online database of rabies vaccines that have been evaluated by the WHO and found to meet WHO standards for quality, safety and efficacy.[10] Rabies vaccines administered outside of Canada can be assessed against this list to see if they have previously been evaluated by the WHO, however, as the submission and assessment process is voluntary, if a client received a vaccine that does not appear on the WHO prequalified list, this should not be inferred to mean that the vaccine was not effective.[10] Per the Australian Immunisation Handbook and the United Kingdom (UK) Health Security Agency (UKHSA), CCVs, including those available in other countries, are considered to be interchangeable with vaccines registered for use in Australia or the UK, which include purified chick embryo cell vaccines (PCECV) and human diploid cell vaccines (HDCV) that are the same type of vaccines available in Canada.[1,5,7,8]

Wherever possible, it is recommended that an immunization series should be completed with the same product, however, if it is not feasible to do so, the PCECV and HDCV vaccines authorized for use in Canada are considered interchangeable.[1] If an individual begins an rPEP series outside of Canada using a CCV, and returns to Canada prior to series completion, then it may be possible to complete the series with a rabies vaccine authorized for use in Canada, following a WHO-approved dosing regimen (Table 1).[1,11] However,

for various reasons rPEP initiated overseas may be inadequate and consideration should be given to restarting a rPEP series if there are any concerns with the quality or administration of the vaccine and/or RIG. See the section on Considerations for restarting the rPEP vaccine series for more details.

Assessment of route and schedule of administration

The CIG recommends that rabies vaccine administered for the purposes of rPEP should be administered via the intramuscular (IM) route, into the deltoid muscle (adults and children aged ≥2 years) or, for children aged <2 years, into the vastus lateralis muscle (anterolateral thigh).[1,12] Vaccine should never be administered in the gluteal region as this may result in a decreased immune response.[1]

Although the WHO provides both a recommended schedule and alternative immunogenic schedules for intradermal (ID) post-exposure prophylaxis (Table 1), only the IM route of administration is currently recommended for rPEP in the CIG and in Ontario.[1,3,13] However, some Canadian provinces (e.g., Alberta and British Columbia), allow for the off-label use of rabies vaccine for rPEP via the ID route of administration.[11,14] If an individual partially completes an rPEP series outside of Ontario following a WHO approved ID administration schedule, then upon return to Ontario if the series is continued it should be completed via the IM route of administration.

Table 1: Canadian and WHO-recommended and alternative rPEP regimens[1,15]

Duration of course	Number of injection sites per clinic visit (days 0,3,7,14,21-28)
Canadian Immunization Guide-recommended IM schedule[1]	
2 weeks*	1-1-1-1-0
WHO-recommended IM schedules[15]	
2 weeks	1-1-1-1-0
3 weeks	2-0-1-0-1
WHO-recommended ID schedule[15]	
1 week (2 sites)	2-2-2-0-0
WHO alternative immunogenic ID schedules[15]	
4 weeks (2 sites)	2-2-2-0-2
4 weeks (4 sites)	4-0-2-0-1
1 week (4 sites)	4-4-4-0-0

*Immunocompromised individuals are recommended to receive a fifth dose of rabies vaccine on day 28[1]

Assessment of Rabies Immunoglobulin (RIG)

RIG provides individuals with immediate passive protection against the rabies virus, and should be administered at the same time as the first dose of rabies vaccine (day 0), using a separate needle, syringe and injection site.[1] Per the CIG, RIG can be administered up to and including the seventh day after a previously-unimmunized individual starts an rPEP vaccine series.[1,15] The Australian Government recommends that if a client is within seven days of receiving their first dose of rabies vaccine for rPEP and there is uncertainty whether RIG was administered, then it should be provided if indicated.[16,17] If an exposure risk assessment indicates that exposure to rabies is highly likely, Ontario guidance advises that rPEP including RIG should be offered to potentially exposed individuals, regardless of the interval following exposure.[3] Similarly, guidance from the BCCDC notes that RIG should be considered on a case-

by-case basis, if the validity of an rPEP series initiated outside of Canada is in question and a decision is made to restart the rPEP series.[11]

RIG can be derived from human blood (hRIG) or purified equine blood (eRIG).[12] While the RIG products approved for use in Canada are both hRIG formulations,[1] some developing countries may administer eRIG, and per the WHO, both types of RIG are considered to have similar clinical effectiveness.[12] If eRIG is administered as part of rPEP in another country, the UKHSA does not require hRIG to be administered.[17] In some countries where hRIG and eRIG are not available, unpurified anti-rabies serum of equine origin may still be in use, and is associated with an increased risk of serious adverse reactions, including anaphylaxis.[18]

RIG dosage is calculated using patient body weight (20 IU/kg) for all age groups, and the resulting volume of RIG should ideally be infiltrated into the wound(s) and surrounding area, using a separate needle for each wound.[1] The maximum volume that is anatomically feasible should be administered, avoiding injection of large volumes of RIG into small body areas with limited tissue as this may result in compartment syndrome.[12] If additional volume of RIG is required to support infiltration of RIG into multiple wounds, RIG may be diluted, using a diluent recommended by the specific product manufacturer and product monograph.[1] The CIG advises that any remaining volume of RIG should be injected intramuscularly, using a separate needle and at a site distant from the site of vaccine administration.[1] The recommended dosage of RIG should not be exceeded as this may inhibit the immune response to rabies vaccine.[8] See Table 2 for a summary of recommendations regarding the management of common rabies vaccine and RIG errors and deviations.

Following administration of hRIG, to ensure an optimal immune response to vaccination, the CIG advises that measles-mumps-rubella (MMR), measles-mumps-rubella-varicella (MMRV) or monovalent varicella vaccines should ideally not be received within 4 months of receiving hRIG.[19] Ideally, these vaccines should be administered at least 14 days prior to administration of hRIG, or at least 4 months afterwards, however RIG should be administered without delay if indicated.[19]

Considerations for restarting the rPEP vaccine series

Consideration should be given to restarting a rabies vaccine series that was initiated outside of Canada (i.e., beginning the rPEP series at day 0) if there are concerns regarding maintenance of cold-chain, use of counterfeit or expired vaccine or RIG, or if a non WHO-approved dosing schedule was used.[11] The Australian Government recommends that if documentation regarding rabies vaccine administered overseas is absent or poor, or if a nerve tissue-derived vaccine was used, then the rPEP series should be restarted.[16]

Recommendations for post-vaccination serology

Post-vaccination serology is not routinely recommended due to the excellent immune response to the rabies vaccine in healthy people immunized with an appropriate regimen. However, in the following situations, the CIG recommends that serology is completed 7-14 days after the vaccine series has been completed, to ensure that the individual has achieved an adequate antibody titre (≥0.5 IU/ml):[1,8,20]

- If a vaccine series was started internationally and completed in Canada (i.e., if a vaccine formulation other than those approved for use in Canada was used), or
- If there has been a substantial deviation from the recommended dosing schedule (see rPEP common errors and deviations), or
- If the ID route of administration was used.

If an rPEP series has been completed in another country and the validity of the series is in question, consider drawing serum for rabies antibody titres, starting a new series of rPEP, and discontinuing the series if the titre returns an antibody level of >0.5 IU/mL.[11]

rPEP Common Errors and Deviations

While there are no established criteria or published literature regarding what constitutes a substantial deviation from the recommended dosing schedule, the CIG recommends that if a dose of rabies vaccine is delayed, it should be given as soon as possible, and the schedule resumed, respecting appropriate intervals between doses.[1] As doses given earlier than the recommended interval may result in a suboptimal immune response, the CIG recommends that if a dose of rPEP is given earlier than recommended, then that dose should be ignored and the dose given at the appropriate interval from the previous dose.[1] The United States Advisory Committee on Immunization Practices states that delays of a few days for individual doses of rabies vaccine for pre- or post-exposure prophylaxis are likely clinically inconsequential once vaccination is initiated, but the effect of longer lapses of weeks or more is unknown.[21,22] Serology should be considered if there is a substantial delay (e.g., of more than a few days) between any doses of the rPEP series.[21,23]

In the event that an error or deviation is recognized in the administration of rPEP, clinicians are advised to report any medication errors and follow-up advice to the client (e.g., monitoring for local or systemic adverse events in the event of a dose exceedance, impact on vaccine/RIG effectiveness, implications for future doses) and as per health care organization reporting practices.[24] Identified errors or deviations should be documented, the cause of the error determined, and solutions to prevent future errors from occurring should be implemented, as applicable.[24]

See Table 2 for a summary of recommendations regarding the management of common rabies vaccine and RIG deviations.

Table 2: Summary of recommendations for the management of common rabies vaccine and RIG errors and deviations

Error	Concern	Resolution
Vaccine given earlier than recommended	Effectiveness may be reduced.	If vaccine is given at less than the recommended interval, the CIG states that dose should be ignored, and the dose administered at the appropriate interval from the previous dose (or as soon as possible if the appropriate interval has passed).[1] Serology should be completed 7-14 days after completion of the vaccine series if there have been substantial deviations from the recommended dosing schedule.[1]
Vaccine given later than recommended	Effectiveness may be reduced, or time to reach a protective titre may be delayed.	The rPEP schedule should be resumed as soon as possible (i.e., the next dose considered as the missed dose), respecting the appropriate intervals from the latest dose.[1,8,12] Serology should be completed 7-14 days after completion of the vaccine series if there have been substantial deviations from the recommended dosing schedule.[1]
Incorrect volume of RIG	Administration of an excess volume of RIG may interfere with immune response and suppress active antibody production[1,8,25] Maximum dose: 20 IU/kg body weight (hRIG)[1,12,26]	In the event of a dose exceedance, monitor for signs and symptoms and seek medical attention if these develop. Serology could be completed 7-14 days after RIG administration to ensure a successful immune response.
RIG not administered at time of rPEP vaccine series initiation	No passive protection. Passive immunisation via administration of RIG is essential for optimal protection of previously-unimmunized individuals who sustain a high risk exposure.[1,12]	RIG may be administered up to and including day 7 after initiation of a rPEP vaccine series.[1] If exposure to rabies is deemed highly likely then offer RIG, regardless of the interval following exposure.[3]

Conclusion

Although human cases of rabies occur rarely in Canada, the invariably fatal nature of the disease emphasizes the need for timely provision of rPEP to individuals who sustain a potential exposure to the rabies virus. Travellers to areas that are endemic for rabies may be at increased risk of exposure and infection. A risk assessment is necessary to assess the need for rPEP, and to determine whether any additional follow-up or corrective measures are needed upon the individual's return to Canada to ensure optimal protection from the rabies virus.

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Citation

Ontario Agency for Health Protection and Promotion (Public Health Ontario). Management of rabies post-exposure prophylaxis and vaccine series initiated outside of Canada. Toronto, ON: King's Printer for Ontario; 2024.

ISBN: 978-1-4868-7813-0

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