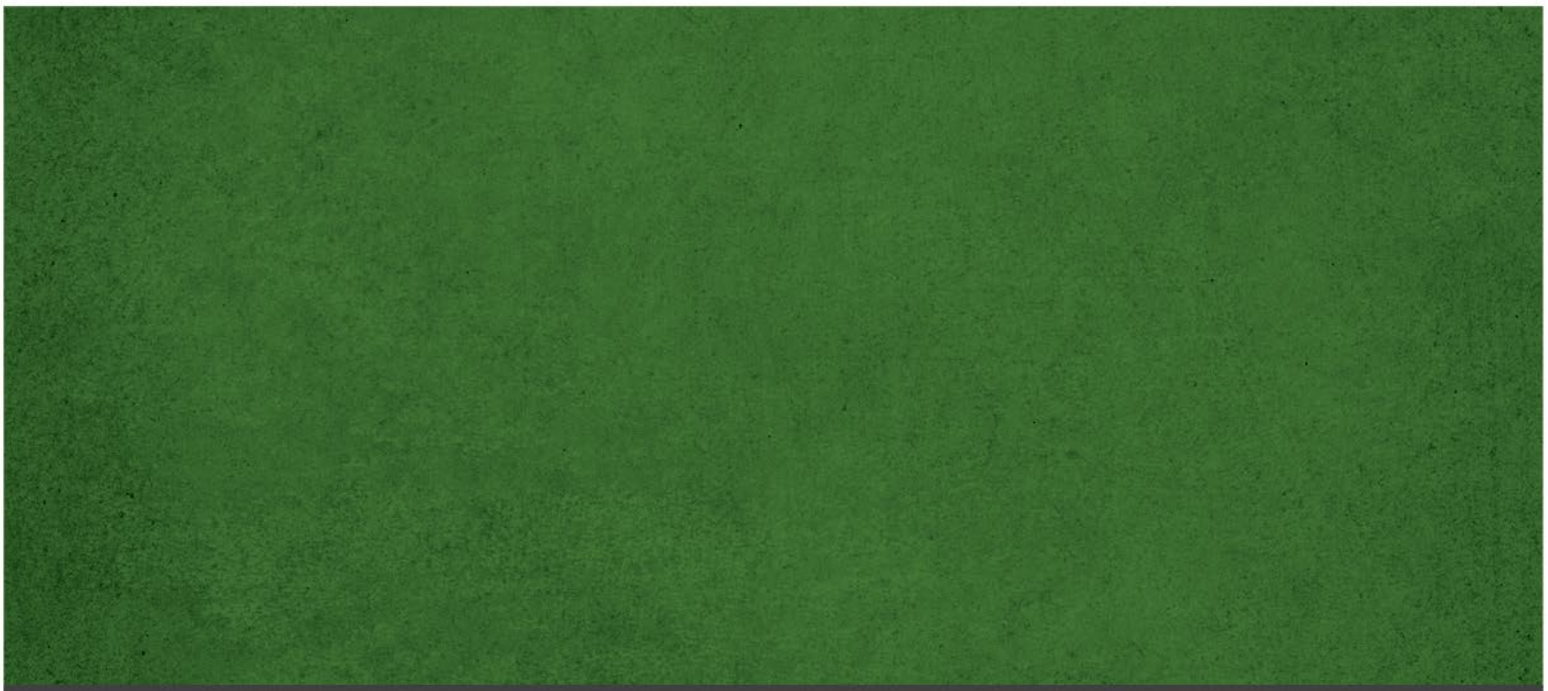
An Advisory Committee Statement (ACS)

National Advisory Committee on Immunization (NACI)

Updated Guidance for Use of Rabies Vaccine for Pre-Exposure Prophylaxis (PrEP)



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— Public Health Agency of Canada

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Preamble

The National Advisory Committee on Immunization (NACI) is an External Advisory Body that provides the Public Health Agency of Canada (PHAC) with independent, ongoing and timely medical, scientific, and public health advice in response to questions from PHAC relating to immunization.

In addition to burden of disease and vaccine characteristics, PHAC has expanded the mandate of NACI to include the systematic consideration of programmatic factors in developing evidence-based recommendations to facilitate timely decision-making for publicly funded vaccine programs at provincial and territorial levels.

The additional factors to be systematically considered by NACI include: economics, ethics, equity, feasibility, and acceptability. Not all NACI statements will require in-depth analyses of all programmatic factors. While systematic consideration of programmatic factors will be conducted using evidence-informed tools to identify distinct issues that could impact decision-making for recommendation development, only distinct issues identified as being specific to the vaccine or vaccine-preventable disease will be included.

This statement contains NACI's independent advice and recommendations, which are based upon the best current available scientific knowledge. This document is being disseminated for information purposes. People administering the vaccine should also be aware of the contents of the relevant product monograph. Recommendations for use and other information set out herein may differ from that set out in the product monographs of the Canadian manufacturers of the vaccines. Manufacturer(s) have sought approval of the vaccines and provided evidence as to its safety and efficacy only when it is used in accordance with the product monographs. NACI members and liaison members conduct themselves within the context of PHAC's Policy on Conflict of Interest, including yearly declaration of potential conflict of interest.

Table of Contents

I. Introduction

Rabies is a rare but almost universally fatal infection. Treatment of rabies is almost always ineffective once symptoms develop, however rabies can be prevented through the use of rabies post-exposure prophylaxis (PEP) after an exposure to a potentially rabid animal or the rabies virus in a laboratory setting.

Rabies pre-exposure prophylaxis (PrEP) is recommended for those whose occupational and/or recreational activities increase their risk of exposure to potentially rabid animals or the rabies virus in a laboratory setting. PrEP simplifies the PEP regimen for those with recognized exposure to potentially rabid animals or the rabies virus in a laboratory setting, and, used with regular serology, offers benefits for those at higher risk who may have exposures that are unrecognized. The purpose of this Advisory Committee Statement is to provide updated recommendations for the use of PrEP for individuals at increased risk for rabies exposures. The statement also provides guidance on PEP schedules for those who have been previously vaccinated.

Background

Since the first edition of the Canadian Immunization Guide (CIG) in 1979[1], in addition to post-exposure guidance, NACI has made recommendations for pre-exposure prophylaxis (PrEP) with available rabies vaccines for select populations at increased risk of exposure to potentially rabid animals or the rabies virus. Human diploid cell vaccine (HDCV) has been available in Canada since 1980 and purified chick embryo cell vaccine (PCECV) became available in 2005. In the Second Edition of the CIG in 1984[2], both the intramuscular (IM) (with IM involving 1.0 mL given at 1 site per dose) or intradermal routes (ID) (with ID involving 0.1 mL given at 1 site per dose) routes could be used to deliver PrEP on days 0, 7 and 21. However by the Third Edition of the CIG in 1989[3] only the IM route was recommended as there was no authorized ID product available in Canada. In the June 1, 2005 Advisory Committee Statement[4], NACI again recommended that 1-site intradermal (ID) administration could be considered for rabies PrEP in most individuals, with assessment of serology 1 month after administration (later changed to 2 weeks) to ensure adequate protection,[4] however IM administration was the gold standard (ID administration was an off-label recommendation as there was no rabies vaccine authorized for ID use). For IM administration, the PrEP schedule was days 0, 7 and 21 and for ID, the schedule was days 0, 7, 21 or 28. In 2014, the PrEP schedule was changed for both IM and ID administration to 0, 7 and between 21 to 28 days[5].

Routine serology for all those who received PrEP was recommended in the First Edition of the CIG in 1979[1] based on use of older, less effective and no longer used hamster kidney tissue culture or duck embryo vaccines, with additional doses for those who failed to develop antibodies. Boosters every 2 years were recommended for those who continued to practice in a high-risk occupation or those whose titres fell below the required threshold. By the Second Edition of the CIG in 1984[2], for those who received HDCV, serology after vaccination was only recommended for those with continuing high risk of exposure including certain veterinarians and laboratory workers every 2 years or 6 months respectively, with a booster for those with inadequate titres; this serology recommendation for HDCV and PCECV has continued up to the publication of this

NACI Advisory Committee Statement. In 2009, NACI made specific recommendations for PrEP in those likely to encounter bats as part of their work[6].

In 2018, the World Health Organization (WHO) updated its recommendation with regard to PrEP and PEP, with recommendations for PrEP consisting of two doses of rabies vaccine on days 0 and 7 using either 2-site intradermal (ID) or 1-site intramuscular routes of administration[7] (see Appendix A, Table A.1 for a comparison of the WHO recommendations and NACI recommendations prior to this Advisory Committee Statement). The updated WHO recommendations prompted a number of countries, including Canada, to re-assess rabies recommendations for their jurisdictions.

The focus of this NACI Advisory Committee Statement is to re-assess Canada's rabies PrEP recommendations given the updated WHO recommendations with the aim of determining whether strategies that use fewer numbers of doses or 2-site intradermal administration (which requires lower vaccine dosages than intramuscular administration) produce a similar immune response and therefore are expected to provide similar benefits compared to current PrEP strategies. Using fewer doses or lower volume of vaccine and reducing the need for serologic testing in some circumstances are potentially cost saving and/or require fewer patient visits, potentially increasing acceptability of PrEP for those for whom it is recommended. Using fewer doses or lower volume of vaccine and also less rabies immunoglobulin (which is not needed for PEP in those who have received PrEP) helps prevent and/or mitigate shortages of these products. The risk groups who are recommended to receive PrEP have also been redefined in this Advisory Committee Statement, and some guidance is also provided on the PEP regimens for those who previously received PrEP. Finally, recommendation related to interchangeability of products and routes of administration have been updated or added.

Policy questions:

The main policy questions addressed by NACI are as follows:

1. Should a 2-dose rabies vaccination schedule be used instead of a 3-dose schedule for rabies PrEP?
2. Should the 2-site ID route of administration of rabies vaccine be considered equivalent to the 1-site IM route of administration for rabies PrEP? The 1-site ID route of administration was not addressed as this option is no longer recommended by the WHO for PrEP.

Related policy questions included:

1. What schedules should apply for those recommended to receive PrEP, in terms of number of doses, route of administration and serology?
2. Should there be any modifications to the recommendations for PrEP for special populations (i.e., people who are immunocompromised, older adults, during pregnancy or for those taking chloroquine or hydroxychloroquine)?
3. Should serology continue to be routinely offered after ID PrEP?
4. What should the post-exposure management be for those who previously only received 1 dose of rabies vaccine and other pre-exposure vaccination that differed from recommended schedules?

Note that this statement provides some guidance with regard to rabies post-exposure prophylaxis (PEP) recommendations for those who previously received pre-exposure prophylaxis. NACI will be undertaking a future review of recommended PEP regimens.

II. Methods

To address the policy questions outlined above, NACI, with the assistance of the NACI Rabies Working Group, prepared this Advisory Committee Statement using the standardized NACI approach[8,9] which includes the following broad steps:

1. Knowledge synthesis: retrieval and summary of individual studies and assessment of the quality of the evidence from individual studies;
2. Synthesis of the body of evidence of benefits and harms, considering the quality of the synthesized evidence and magnitude of effects observed across the studies;
3. Use of a published, peer-reviewed framework and evidence-informed tools to ensure that issues related to ethics, equity, feasibility, and acceptability (EEFA) are systematically assessed and integrated into the guidance[9];
4. Translation of evidence into recommendations.

More specifically, for the development of this NACI Advisory Committee Statement and the recommendations in this statement, the NACI Rabies Working Group and NACI reviewed the burden of human rabies in Canada, and groups at increased risk for rabies. The NACI Secretariat, with the support of the Rabies Working Group, conducted a systematic review of the immunogenicity of 1, 2 and 3 doses of rabies vaccine, and 1-site intramuscular (IM) compared to 2-site intradermal (ID) routes of administration[10]. Information on the safety of ID administration was obtained from review of the relevant articles from the systematic review. As well, a jurisdictional scan was conducted of pre-exposure prophylaxis (PrEP) recommendations from several international jurisdictions. Consultation was sought from the Canadian Immunization Committee (CIC), the Committee to Advise on Tropical Medicine and Travel (CATMAT) and other key stakeholders. To inform the EEFA analysis, consultation was sought from the Public Health Agency of Canada's Public Health Ethics Consultative Group (PHECG).

The key research questions for this statement included:

1. How do the immunological outcomes (geometric mean titres and seroconversion) differ for recipients of 1, 2 or 3 doses of rabies PrEP? and
2. How do the immunological outcomes (geometric mean titres and seroconversion) differ for recipients of rabies PrEP via 1-site IM vs 2-site ID routes of administration?

For the assessment of the boostability (i.e., the ability to demonstrate an increased immune response to an additional or booster dose) of 2 and 3 doses of rabies vaccine and 1-site IM and 2-site ID routes of administration, the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) tool was used. To support recommendations contingent on boostability, two Evidence to Decision (EtD) frameworks were reviewed (one to compare the boostability of 2 and 3 doses, and the other to compare the boostability of 1-site IM and 2-site ID administration). These EtD frameworks were prepared by the NACI Secretariat and presented to the Rabies Working Group and NACI to guide recommendation development.

Preliminary recommendations prepared by the Rabies Working Group were presented to NACI on February 19, 2025, with more in-depth recommendations presented on June 17, 2025 and with follow-up discussions on September 24 and 25, 2025. The recommendations section includes relevant considerations and the rationale for the recommendations. This statement also includes knowledge gaps to guide future surveillance and research initiatives.

A note on language:

NACI recognizes that not all people giving birth or breastfeeding will identify as women or mothers. The writing in this statement uses a gender additive approach where the term “woman” is used alongside gender neutral language. This is intended to demonstrate a commitment to redress the historic exclusion of trans and non-binary people, whilst avoiding the risk of marginalizing or erasing the experience of women within the health care environment. When citing research, NACI refers to the language used in the study. However, in line with best practice, it is recognized that when discussing or caring for individuals in a one-on-one capacity, language and documentation should reflect the gender identity of the individual.
Finally, NACI acknowledges the dynamic nature of language. It is likely that language deemed to be suitable or affirming in one context may not translate across others, and over the coming years will likely change and evolve with respect to appropriate representations.

III. Epidemiology

III.1 Background, risk factors, and clinical presentation

Rabies is an almost universally fatal viral infection caused by ribonucleic acid (RNA) viruses in the *Lyssavirus* genus of the *Rhabdoviridae* family, which have a distinct cylindrical or bullet-shaped appearance[11]. There are 18 different types of lyssaviruses.[12] Rabies virus is the most well-known and is the main cause of rabies in humans, but all lyssaviruses have the potential to cause disease in people. All mammals, including bats, are susceptible to lyssaviruses. Almost all lyssaviruses species have been found in bats, with rabies virus being found in bats in the Americas, European bat Lyssavirus type 1 and 2 found in bats in Europe and Australian bat Lyssavirus found in Australia [13]. Rabies virus also occurs in carnivores in most parts of the world, with dogs being the most common reservoir and vector, particularly in Asia and Africa[14].

There are a number of rabies virus variants that tend to exist within their reservoir hosts (e.g., canine rabies strains in dogs; skunk rabies strains in skunks; arctic fox rabies strain in foxes, and bat rabies strains in bats), however spillover of these variants to other mammals, including humans, can occur[11]. Canine rabies variants, which are prominent in dogs in other parts of the world and responsible for most human rabies cases in the world, have been eliminated from Canada, the United States and Mexico. In Canada, bats, skunks, foxes and raccoons are the main reservoirs of rabies virus[15]. People in Canada can be exposed to rabies from these animals or other animals (e.g., dogs, cats, cattle) that are not themselves reservoir species (including dogs in Canada) but can be infected by reservoir species. Bats anywhere in Canada can be infected with rabies, while rabies epidemiology in non-bat mammals varies by jurisdiction. International travel can also be a source of rabies virus exposure for those living in Canada.

Rabies virus is most often transmitted to humans through saliva from the bite of an infected mammal[11]. Rabies virus is rarely transmitted through direct contact of infectious material (either saliva, nerve tissue, or cerebral spinal fluid) to mucous membranes or breaks in the skin, or from transplantation or respiratory inhalation. Scratches only pose a risk if contaminated with saliva or other infectious material (nerve tissue, or cerebral spinal fluid). Rabies virus is not transmissible through intact skin.[16]

Rabies virus is neurotropic (tends to localize to neural tissues). Once deposited into the muscle or other peripheral tissue, most often through the bite of an infected animal, it proliferates in these tissues for a variable period of time. The virus then gains access to the peripheral nervous system and spreads to the central nervous system in a retrograde fashion (i.e., moving backward along the nerves toward the brain). Once in the brainstem and brain, symptoms can develop and continued replication results in anterograde spread (i.e., moving forward along the nerves away from the brain) to the salivary gland as well as to other parts of the body, following which exposure to saliva or neural tissue or fluids can result in spread to another host.[16]

Rabies antibodies (either from rabies vaccine or rabies immunoglobulin) are thought to act on the virus as it proliferates in the peripheral tissues at the exposure site and to be relatively ineffective once the virus enters the peripheral and central nervous system[17]. Unlike other viruses, the rabies virus itself is not believed to induce a protective immune response and may not induce a memory response in those who have been previously vaccinated[18,19], therefore rabies vaccine and/or rabies immunoglobulin are required after an exposure to produce the antibodies to inactivate the rabies virus in the peripheral tissue.

The incubation period of the rabies virus can vary from days to several years (average 1 to 3 months)[11,20]. Exposures such as bites to highly innervated areas such as the face, neck and hands are potentially higher risk for the development of rabies than exposure in other less innervated areas of the body, although exposure to all areas of the body can result in infection. Exposure to highly innervated areas may also result in shorter incubation periods. In addition, the incubation periods may be shorter in head and neck exposures due shorter distance for the virus to travel to the brain.[21]

Risk in humans largely relates to interaction of potentially rabid animals, with those at increased risk including: veterinarians and veterinary staff, animal control and wildlife workers, persons who are involved in trapping, handling bats or cave exploration (spelunkers), and some travellers. Laboratory workers who handle live rabies virus are also at increased risk of rabies virus exposure.[5] Children are also at higher risk of acquiring rabies potentially due to an increased likelihood of approaching animals, and the higher possibility of being bitten in the face[22,23].

Rabies is almost uniformly fatal. Clinical stages include an incubation period, a prodromal period (fever, nausea, vomiting, malaise) and then acute neurologic disease that presents as either encephalitis (agitation, anxiety, hyperactivity, hydrophobia, hallucinations) or paralysis, both of which ultimately result in coma and death[11,20].

III.2 Disease distribution

III.2.1 Human rabies

Rabies occurs on all continents, with the exception of Antarctica[24]. It is estimated that approximately 59,000 human deaths from rabies virus occur globally each year, with most due to dog exposures in Asia and Africa[25]. Cases of rabies are rare in Canada; since rabies reporting started in Canada in 1924 to October 2025, there have been 28 cases of human rabies (all fatal) in 6 provinces (2 in Alberta, 2 in British Columbia, 1 in Nova Scotia, 9 in Ontario, 12 in Quebec, and 2 in Saskatchewan)[15]. The last case of rabies that was transmitted to a human from a non-bat mammal in Canada was in 1967 in Ontario. Since then, all cases of rabies in Canada have been from either bat exposures in Canada or exposures to rabid animals outside of Canada. The most recent cases of human rabies in Canada were in Ontario in 2024 and British Columbia in 2019, both of which were due to exposure to rabid bats[15]. Updated information on cases of human rabies is available online.

III.2.2 Animal rabies

In Canada, bats, skunks, foxes and raccoons are the main rabies virus reservoirs, but other animals can become infected from these reservoir species, including dogs, cats and cattle. For updated information on animals found to have rabies by Canadian province or territory each year, see Rabies in Canada[26]. A map of the distribution of rabies virus variants in Canada is available online[27]. It should be noted that most testing for animal rabies occurs after animals have been in contact with a human or domestic animal or as part of special studies, so rabies in wildlife is likely to be considerably underreported.

IV. Vaccine

IV.1 Uses of rabies vaccines

Rabies vaccines are used for pre-exposure prophylaxis (PrEP) for those at increased risk for rabies exposures and also used for post-exposure prophylaxis (PEP) after an exposure to a potentially rabid animal, based on recommendation from the clinician and/or public health professionals.

If rabies **post-exposure prophylaxis (PEP)** is indicated after an exposure to a potentially rabid animal, the first step consists of cleaning and flushing the wound for 15 minutes with soap and water. For those who have never been previously appropriately vaccinated against rabies, PEP includes rabies immunoglobulin (20 International units/kilogram (IU/kg), with as much as possible infiltrated at the wound site(s) and the remainder injected at a distant intramuscular (IM) site) and 4 or 5 IM doses of rabies vaccines with doses on days 0, 3, 7 and 14 and an additional dose on day 28 for those who are immunocompromised or taking chloroquine (which would also apply to hydroxychloroquine). The Canadian Immunization Guide has referred to concurrent administration of rabies vaccine with “other antimalarials” as requiring a vaccine dose on day 28, however there is no evidence that other antimalarials are a concern with regard to the response to rabies vaccine, and therefore the reference to “other antimalarials” has been removed in this NACI Advisory

Committee Statement. For those who have been previously appropriately vaccinated against rabies (i.e., as previous PrEP or PEP), PEP only requires 2 IM doses of vaccine on days 0 and 3; rabies immunoglobulin is not indicated.

Pre-exposure prophylaxis (PrEP) is recommended for certain populations who may be at increased risk for rabies exposures (e.g., people with occupational exposure to animals; laboratory workers handling the rabies virus; certain travellers; spelunkers; and trappers [and prior to this NACI Advisory Committee Statement, also hunters]).

Prior to the recommendations in this Statement, PrEP was administered as 3 doses of rabies vaccine on day 0, 7 and 21 to 28. Administration via the IM route (1.0 mL) was the gold standard, although a smaller (0.1 mL) dosage via the 1-site intradermal (ID) route could also be used. Serology has been recommended at least 2 weeks after completing PrEP using the 1-site ID route of administration. This Advisory Committee Statement provides updated recommendations with regard to the PrEP schedules for some risk groups and the use of 2-site ID PrEP (See Recommendation section).

PrEP primes the immune response so that it can be rapidly boosted with rabies vaccine after an exposure. However, although unclear, it is generally not believed that the rabies virus itself can reliably trigger or enhance protective immune responses. Therefore, PEP is recommended after an exposure, including for those who have been previously vaccinated. Vaccine given as PEP results in a rapid anamnestic response in those who have previously received PrEP, with an antibody response noted by 7 days after the first PEP vaccine dose in those who had previously received PrEP[28]. In contrast, in those who have not been previously vaccinated, antibody response may not be present on day 7[29-32] and takes approximately 10 to 14 days to achieve near 100% seroconversion.[31-33] Due to the rapid anamnestic response in those who have been previously vaccinated, rabies immunoglobulin is not recommended as part of the PEP regimen in those who previously received appropriate PrEP.

For those who may have unrecognized exposures to rabies virus (such as those with regular/frequent bat exposures or who work with the rabies virus in a laboratory setting) and therefore may not seek PEP after an exposure, titres are checked regularly and boosted if they fall below 0.5 IU/mL. Although not truly a correlate of protection, rabies antibody titres of equal to or greater than 0.5 IU/mL are used as an indicator of an adequate response to the rabies vaccine. For those who potentially have unrecognized exposures (who will not seek PEP if their exposure is unrecognized), regular serologic testing is intended to determine if a booster dose is needed to maintain circulating titres that can offer rabies protection against the unrecognized exposure.

IV.2 Preparation(s) authorized for use in Canada

Two rabies vaccines are authorized for use in Canada and can be utilized for both pre-exposure prophylaxis (PrEP) and post-exposure prophylaxis (PEP):

- IMOVAX® Rabies (inactivated, human diploid cell rabies vaccine), Sanofi Pasteur Ltd. (HDCV)

- RABAVERT (inactivated, purified chick embryo cell rabies vaccine), Bavarian Nordic A/S (PCECV)

Key characteristics of these rabies vaccines is summarized in Appendix A, Table A.2.

IV.3 Clinical evidence regarding rabies vaccine immunogenicity by dose number or route of administration

As rabies vaccine effectiveness data comparing dose schedules and routes of administration are not available and a commonly used standard for vaccine response based on seroconversion exists, NACI's review focused on immunogenicity data. A brief summary of the methods and key evidence used to inform decision-making are outlined below. More details on the methodology, results of each analysis and characteristics of included studies, as well as risk of bias assessments, can be found in the published review[10].

NACI performed a systematic review and meta-analysis of available evidence comparing the antibody response of 1-, 2- and 3-dose primary schedules of rabies vaccines (human diploid cell vaccines [HDCV], purified chick embryo cell vaccines [PCECV] and purified Vero cell rabies vaccines [PVRV]), as well as evidence comparing 2-site intradermal (ID) and 1-site intramuscular (IM) routes of administration. Only studies that assessed 2-site ID were included in the review, as 2-site ID was the recommendation by the World Health Organization (WHO); studies that assessed 1-site ID administration were excluded a priori from our review as this route was not recommended by the WHO. Meta-analyses of included studies were conducted in three ways: studies that directly compared either two different numbers of doses or two different routes of administration; studies which allowed comparison of schedules within the same participants/groups of participants; and analyses that pooled relevant data from across included study arms.

The primary outcome was seroconversion (the percent of subjects with titres at or above 0.5 IU/mL), and the secondary outcome was geometric mean titres (GMTs). Both outcomes were assessed in the short-term after the primary series, in the long-term without a booster, and after a booster dose. Short- and long-term responses are most important for those who may have unrecognized exposures and therefore may not seek post-exposure prophylaxis (PEP), while the boostability of the response is most important for those with recognized exposures who are expected to seek PEP as recommended.

While all of the available evidence was used to inform NACI's recommendations, only a subset of the data was used to inform the GRADE certainty of evidence assessments. The GRADE certainty of evidence assessments were only used to inform policy decisions regarding those with recognized exposure to potentially rabid animals who were expected to seek post-exposure prophylaxis, and therefore focused on boostability. Seroconversion after the booster dose was considered the critical outcome. Only studies that directly compared 2 and 3 doses or directly compared 2-site ID with 1-site IM for 2 or 3 doses after the booster dose were included in the GRADE assessment.

IV.3.1 Immunogenicity of 2 doses compared to 3 doses

Overall, most participants seroconverted (at or above 0.5 IU/mL) shortly following the primary series, with 2 or 3 doses by either route of administration. However, for those who received their doses via 1-site IM administration, GMTs were lower in the short-term for those who received 2 doses compared to 3. Over time, there was a decline in titres in all groups and a related drop in seroconversion, with maintenance of titres at or above 0.5 IU/mL being significantly lower for those receiving 2 IM doses compared to 3 IM doses. Following the administration of a booster dose, both 2- and 3- dose schedules were boosted to levels higher than the observed response to the primary series, with elevated GMTs that were not significantly different between groups and almost 100% of participants seroconverted (range of 99.7 to 100%, based on analyses that pooled relevant data from across included study arms) in both 2- and 3-dose groups given by either the 1-site IM or 2-site ID routes of administration.

In a GRADE assessment of studies which directly compared 2- to 3-dose primary series schedules for boostability, there was no difference in the percent of participants who seroconverted following a booster dose of rabies vaccine (high certainty of evidence; Appendix A, Table A.3).

IV.3.2 Immunogenicity of a 1 dose compared to 2 doses

Individuals who received a 1-dose primary schedule were significantly less likely to seroconvert following that dose and significantly less likely to remain seroconverted over time, compared to individuals who received a 2-dose primary series (with either a 1-site IM or 2-site ID route of administration). GMTs were also significantly lower immediately following the primary dose/series for those who received a single IM dose compared to a 2-dose IM primary series. While there was a considerable drop in GMTs over time in all groups, in the long-term, GMTs were significantly lower in those who received a single dose primary schedule (for both IM and 2-site ID routes of administration) compared to those who received a 2-dose primary series. Following the administration of a booster dose, both 1- and 2-dose primary dose/series were boosted to GMT levels higher than the response to the primary dose/series and were not significantly different between groups. Almost 100% of participants seroconverted in both 1- (range 97.6 to 100%, based on analyses that pooled relevant data from across included study arms) and 2- (range 99.7 to 100%) dose groups given by either the IM or 2-site ID route of administration.

IV.3.3 Immunogenicity of 2-site intradermal compared to 1-site intramuscular

The immune response comparing 2-site intradermal (ID) to 1-site intramuscular (IM) administration was compared for each of the 1-, 2- and 3-dose primary schedules. Seroconversion and GMTs were generally similar between 2-site ID and 1-site IM routes of administration in the short-term, long-term and after the booster dose. However, there were a few analyses for which GMTs were significantly lower using the 2-site ID route compared to the 1-site IM route, but this effect was not consistently observed across different analyses.

In a GRADE assessment of studies directly comparing seroconversion after the booster dose of 1-site IM to 2-site ID administration, there were no differences in the percent of individuals with

titres greater than or equal to 0.5 IU/mL, for both 2- or 3-dose primary series (high certainty; Appendix A, Table A.4).

IV.3.4 Ability to boost over time since the primary series

The NACI evidence review found that both 2- and 3-dose schedules (both IM and 2-site ID) demonstrate the ability to boost (with 99.7 to 100% achieving titres ≥0.5 IU/mL after the booster dose, based on analyses that pooled relevant data from across included study arms). The evidence review defined a booster dose as a dose at least 180 days after the start of the primary series, with most studies included in the review providing the booster dose at 1 year from the primary series. However, post-exposure prophylaxis can be required many years after a primary series. While 3-dose primary series have been shown to be boostable out to 21[34] and 24[35] years after a primary series, data beyond 2 years are very limited for studies of 2-dose schedules; 1 study showed boostability between the second and third year after the primary series in approximately 13 people (with a 2-site ID primary series)[36] and another showed boostability at 10 to 11 years in 6 recipients with 2-dose primary series schedules (most receiving an IM primary series)[35]. An additional study showed boostability at 24 to 28 months after the primary dose in 44 recipients who received 1-dose via the 2-site ID route[37].

IV.4 Serological testing

Serologic testing is used in some circumstances to ensure an adequate immune response (generally considered greater than or equal to 0.5 IU/mL) is achieved or maintained over time. Serology after rabies pre-exposure prophylaxis is recommended under the following circumstances:

1. At regular intervals if the vaccinated person is in certain risk groups who may have unrecognized exposures in order to determine if a booster dose is needed to maintain rabies antibody titres.

2. If the vaccinated person is immunocompromised.

3. As of this Advisory Committee Statement, if the person is taking chloroquine or hydroxychloroquine.

4. If products other than purified chick embryo cell vaccine (PCECV) or human diploid cell vaccine (HDCV) were use. As of this Advisory Committee statement, use of purified Vero cell rabies vaccine (PVRV) is also no longer an indication for serology.

5. If 1-site (0.1 mL) intradermal (ID) administration is used.

   As of this Advisory Committee Statement, NACI is recommending ID administration be given at 2-sites as per the WHO recommendation for PrEP and is no longer recommending 1-site ID administration. Using 2-site ID administration provides double the dose per visit (0.2 mL) compared to 1-site administration (0.1 mL), and provides the ability to elicit an immune response in 2 different lymphatic drainage sites. NACI's systematic review showed that 2-site ID and 1-site intramuscular (IM) administration provided generally similar seroconversion, however in a few analyses geometric mean titres (GMTs) were

lower for 2-site ID administration compared to 1-site IM administration. NACI has updated its recommendations to indicate that serology is not indicated based solely on use of ID administration of rabies vaccine if given at 2 sites.

See Recommendation section for updates on the use of serology.

IV.5. Vaccine safety

Rabies vaccines have had a favourable safety profile for decades. Given the safety of 3 doses of rabies vaccine used for PrEP, 2 doses are expected to be as safe or safer. Local reactions (erythema/hyperpigmentation, localized swelling, induration, pain, pruritus) are more commonly reported with ID than IM vaccination, however for both ID and IM administration, local reactions are mild and transient with spontaneous resolution within a few days[38,39]. Systemic reactions do not appear to be more common with ID compared with IM administration routes[38-40].

Further details on local reactions, systemic adverse events, serious adverse events, precautions and contraindications are available in the Rabies Vaccine Chapter of the Canadian Immunization Guide.

IV.6 Interchangeability of products and routes of administration

Prior to this Advisory Committee Statement, NACI recommended that wherever possible, a primary immunization series should be completed with the same product. However, if it was not feasible to do so, purified chick embryo cell vaccine (PCECV) and human diploid cell vaccine (HDCV) were considered interchangeable. People who required a booster dose of rabies vaccine could be given PCECV or HDCV, regardless of the vaccine used for the primary series. NACI has previously recommended serology if a vaccine other than PCECV and HDCV was used, which would include purified Vero cell rabies vaccines (PVRV). However, PVRV are widely used in many countries; these vaccines were used in 54 of 106 of study arms (51%) in the NACI systematic review and are among the prequalified rabies vaccines listed by the World Health Organization (WHO)[41]. In NACI's systematic review of 2- and 3-dose schedules stratified by route of administration, the immune responses generated by PCECV, HDCV and PVRV were similar.

Prior to this Advisory Committee Statement, NACI had no recommendations regarding using the IM and ID routes of administration for different doses in the same primary series. NACI's systematic review found that the IM and 2-site ID route had generally similar seroconversion rates, and for geometric mean titres, the 1-site IM route induced a higher immune response than the 2-site ID route in a few analyses but not in the others.[10]

An observational study in India by Ravish et al. assessed the impact of changes in the route of administration (IM and 2-site ID) during post-exposure prophylaxis (N=47) or changes in the administered product (type or brand of PCECV and PVRV) during post-exposure prophylaxis (N=43). By day 14 after doses on day 0, 3 and 7 all subjects had seroconverted with GMTs of 14.8 IU/mL (range 7.5 to 22.5) in the group with the change in route of administration and 11.8 IU/mL (range 7.5 to 15.5) in the group with the change in product type/brand. All subjects also received equine rabies immunoglobulin into and around the wound site, however the use of rabies immunoglobulin should not substantially contribute to the measured titres.[42]

Recommendation 4 provides updated NACI guidance regarding interchangeability incorporating PVRV and also on using the IM and 2-site ID routes of administration in the same primary series. Refer to Principles of Vaccine Interchangeability in Part 1 of the Canadian Immunization Guide for additional general information.

V. Vaccination of specific populations

V.1 Immunization of people who are immunocompromised

Based on limited studies and consistent with other vaccines, the immune response to rabies vaccine is less robust in people who are immunocompromised. A few studies have demonstrated less than optimal seroconversion in people who are immunocompromised for both pre-exposure prophylaxis (PrEP)[32,43] and post-exposure prophylaxis (PEP)[44,45]. A study by Garcia Garrido et al. demonstrated only 90% seroconversion (47/52 individuals) 7 days after two-dose simulated PEP given at 1 year after the primary series in those with chronic autoimmune disease on immunosuppressive monotherapy (TNF-alpha inhibitors or conventional immunomodulators) who received a 3-dose primary series of intramuscular (IM) PrEP on days 0, 7 and 21 to 28[43].

The World Health Organization (WHO) PrEP recommendations for those who are immunocompromised are for: a 3-visit schedule either via the intradermal (ID) (2-site) or IM routes of administration on days 0 and 7 and 21 to 28; or a 2-visit schedule, either ID (2-site) or IM on days 0 and 7 with serology at 2 to 4 weeks after the first dose to assess whether additional doses are needed[46].

NACI recommends that PrEP be given at the optimal time to maximize the immune response (i.e., after the immunocompromised state resolves or at least 14 days before a planned immunocompromised state) (see the Immunization of Immunocompromised Persons chapter of the Canadian Immunization Guide). Prior to this Advisory Committee Statement, NACI recommended that if the rabies vaccine must be given while a person is immunocompromised, it should be given by the IM route only (with 3 doses on days 0, 7 and 21 to 28) and followed by serology 7 to 14 days post-vaccination. See Recommendation 2 for updated recommendations where 2-site ID administration is now considered an acceptable choice for those who are immunocompromised, with serology recommended following both 2-site ID and intramuscular (IM) administration.

V.2 Immunization of older adults

Studies have shown that the immune response to rabies vaccine is somewhat reduced in older adults (over 50 or 60 years of age) compared to younger adults for both PrEP[47-49] and PEP[33,50]. One study found a faster rate of decline of titres after the primary series in older adults compared to younger adults[51] and another found a longer time to reach the maximum geometric mean titre in older adults compared to younger participants[33].

Older adults receiving rabies PrEP for travel or for most occupational purposes are expected to seek PEP after an exposure, therefore the boostability of the vaccine is most important. Overduin

et al. assessed boostability of a primary dose/series given as 1-dose IM, 1-dose 2-site ID and 2 doses IM. All older adults (>50 years of age) seroconverted with 2-dose IM simulated PEP (on days 0 and 3) given 6 months from the primary dose/series, as did almost all younger adults (18 to <50 years of age)[47].

The WHO[7] has no specific recommendations for older adults. NACI also has no specific recommendation for older adults except in Table 1 with regard to the frequency of serology for those in the "high risk" group.

V.3 Immunization during pregnancy and breastfeeding

NACI indicates that pregnancy is not a contraindication for post-exposure prophylaxis with rabies vaccine and rabies immunoglobulin, but it would be prudent to delay pre-exposure immunization during pregnancy, unless there is a substantial risk of exposure[5]. Rabies vaccine should be given as indicated during breastfeeding[52].

Several studies where rabies vaccine has been given as PEP did not find any safety concerns during pregnancy[53-55].

NACI has not changed its advice (as noted above) regarding rabies vaccine in pregnancy or breastfeeding.

V.4 Immunization while taking chloroquine or hydroxychloroquine

Administration of chloroquine (and potentially also hydroxychloroquine) with rabies vaccine can result in lower rabies geometric mean titres (GMTs) for both ID[56,57] and IM[58] administration.

Prior to this Advisory Committee Statement, NACI indicated that the ID route should not be used for those taking chloroquine. NACI indicated that if a decision is made to give PrEP by the ID route to a person requiring chloroquine, chloroquine use must be delayed for at least 1 month after vaccination or given only if the person has been found to have an adequate titre post-vaccination. This recommendation is no longer applicable. See footnote c of Table 1 for Recommendation 1 for updated recommendations regarding rabies vaccine and chloroquine/hydroxychloroquine that indicates that 2-site ID or IM administration can be used and both routes of administration should be followed by serology in those taking chloroquine/hydroxychloroquine.

VI. Economics

Although the standard NACI guidance development process includes consideration of economic evidence, such evidence was not deemed necessary for this statement. Rabies PrEP is typically administered to protect individuals based on specific occupational or personal risk factors.

VII. Ethics, equity, feasibility and acceptability considerations

VII.1 Ethics considerations

NACI engaged the Public Health Agency of Canada's Public Health Ethics Consultative Group (PHECG) regarding the ethical considerations of changing the number of doses (from 3 to 2) and use of intradermal (ID) administration. The PHECG consultation report describes both proposed guidance changes to be ethically justifiable based on evidence from NACI's systematic review suggesting approximate equivalence. PHECG noted that alignment with the updated World Health Organization (WHO) recommendations would both promote coherence and demonstrate responsiveness to new evidence. It should be noted that subsequent to the PHECG consultation, the Rabies Working Group and NACI also assessed the ability of the primary series to boost over time, which resulted in NACI recommendations that deviate somewhat from those of the WHO (see Recommendation 2).

As rabies is a fatal disease, PHECG recommended clear communication regarding the changes to the pre-exposure prophylaxis (PrEP) schedule as well as the importance of seeking post-exposure prophylaxis (PEP).

VII.2 Equity considerations

NACI considered that equity may be increased as costs would be reduced if the number of PrEP doses was reduced from 3 to 2 and/or if the ID route of administration was used with the vial being used to vaccinate several recipients (noting that rabies vaccine vials must be used within 6 hours of reconstitution).

VII.3 Feasibility considerations

Intradermal (ID) administration of vaccines is less frequently used than intramuscular (IM) administration, and therefore there is less provider familiarity with ID administration in Canada. Studies with ID administration were often carried out in centres already familiar with its use, and feasibility was not identified as a consideration in the 2018 WHO rabies guidance[7]. NACI consulted with the Canadian Immunization Committee (CIC) and the Committee to Advise on Tropical Medicine and Travel (CATMAT) regarding feasibility of implementing ID vaccine administration. In general, CIC and CATMAT expressed that ID vaccine administration, where implemented, has been feasible. Possible concerns regarding ID administration include training for proper ID administration, risk of improper administration, and acceptability by vaccine providers. See Appendix B for information on "How to administer rabies vaccines via the 2-site intradermal (ID) route".

VII.4 Acceptability considerations

Reduction in the number of doses could be more acceptable for patients and providers due to reduced costs and time required for the decreased number of vaccine visits, but less acceptable for patients if there is uncertainty regarding effectiveness.

Use of ID administration could be more acceptable for patients due to reduced costs (if the vial is used to vaccinate several recipients). However, it could also be less acceptable for patients as 2

injections are required at each visit, there is possibly more local reactogenicity and ID administration could raise concerns if there is any uncertainty about its effectiveness. Use of ID administration could also be less acceptable for vaccine providers as 2 injections are required per visit and some vaccine providers may not be as familiar with ID administration.

There are a few studies regarding acceptability of rabies vaccination which have found that time and financial burden of treatment are contributing factors to not completing rabies vaccine schedules, although none are specific to Canada[59,60]. Ensuring easy, affordable access for those who are recommended to receive rabies pre-exposure prophylaxis will support acceptability of the vaccine.

VIII. Recommendations

These recommendations are intended to support individuals, organizations, provinces and territories making immunization decisions.

Following the thorough review of available evidence summarized above, NACI makes the following recommendations.

See Table 3 for explanation of strength of NACI recommendations.

NACI will continue to carefully monitor the scientific developments related to rabies pre-exposure prophylaxis and will update recommendations as evidence evolves.

Recommendation 1 - Who should receive pre-exposure prophylaxis

Recommendation 1a: NACI recommends rabies pre-exposure prophylaxis for the following individuals:

- **people who work with the rabies virus in a research or vaccine production laboratory;**
- **people with regular/frequent bat exposures (e.g., contact with bats, enters high-density bat environments, people who perform necropsies on bats);**
- **people who routinely perform necropsies on mammals due to suspected rabies;**
- **rabies diagnostic laboratory workers**;
- **veterinarians;**
- **veterinary staff;**
- **veterinary students;**
- **animal control workers;**
- **animal shelter workers;**
- **wildlife workers.**

(Strong NACI recommendation)

Recommendation 1b: NACI recommends rabies pre-exposure prophylaxis may be offered for:

- **recreational trappers;**
- **recreational spelunkers; and**
- **travellers to areas where rabies vaccine is recommended.**

(*Discretionary NACI recommendation).*

- For international travel, comprehensive recommendations for this population can be found through the Committee to Advise on Tropical and Travel Medicine (CATMAT)[61]. Consult the Government of Canada's Travel Advice and Advisories pages[62] to determine whether the rabies vaccine may be recommended for a specific international travel destination. After selecting the destination country, the rabies information can be found in the 'Health' section, under 'Pre-travel vaccines and medications'.
- Note that those in Recommendation 1b who also have occupational risks (as per Recommendation1a) are strongly recommended to receive pre-exposure prophylaxis.

Considerations and rationale:

Compared to previous NACI guidance, three distinct risk groups (i.e., "very high risk", "high risk" and "moderate risk") have been named and examples of types of people in each risk group identified, which may differ from how some of these types of people were previously grouped. For example, all types of people with possible exposure to live potentially rabid non-bat mammals have been placed in the "moderate risk" group and there is no longer a distinction based on the epidemiology in the area. This change was made due to more emphasis on the fact that these workers are expected to generally have recognized exposures and therefore to seek post-exposure prophylaxis after an exposure, so previous serology recommendations are generally no longer needed for this group, irrespective of the epidemiology of rabies in the area.

Hunters are no longer considered a group at increased risk for rabies exposure as the risk is generally presumed to be low.

NACI previously did not have "strength of recommendations" assigned to groups recommended to receive PrEP, which have now been included in this NACI Advisory Committee Statement. The discretionary recommendation for recreational trappers, recreational spelunkers and travellers (unless these people also have an occupational risk listed in Recommendation 1a) is because the risk in these groups is expected to be somewhat lower than those with occupational exposure risks. The recommendation for travellers is also consistent with 2026 guidance entitled *Statement on pre-exposure vaccination against rabies and animal bite prevention in the traveller* from CATMAT[61].

Recommendation 2 – Schedules and serology by risk groups (also see Table 1 and accompanying footnotes for additional details)

NACI recommends the following rabies vaccine schedules and serology for those receiving rabies pre-exposure prophylaxis *(Strong NACI recommendation):*

For those who are not immunocompromised:

1) ***For the "very high risk" and "high risk" groups*** (***see Table 1***)***:***
   - **Three- (3) dose primary series of rabies vaccine on days 0, 7 and 21 to 28.**

   For "moderate risk" group (see Table 1):
   - **Two- (2) dose primary series of rabies vaccine on days 0 and 7 to 28.**
   - **For those whose risk is expected to extend beyond 3 or more years, a booster dose is also recommended, ideally at 12 to 24 months after the second dose. If there is uncertainty about how long the rabies exposure risk is expected to last, the booster is recommended.**
   - **For those who are only expected to be at risk for less than 3 years, the booster is not needed.**

2) **One-site intramuscular (IM) (1.0 mL) or 2-site intradermal (ID) (0.1 mL at each site) routes of administration can be used for rabies pre-exposure prophylaxis. Serology is no longer indicated based solely on use of ID administration of rabies vaccine if given at 2 sites.**

3) **For those in the "very high risk" or "high risk" groups (i.e., with ongoing risk of exposure to the rabies virus in a laboratory or at ongoing risk of exposure to potentially rabid animals that may go unrecognized), periodic serology is recommended as per Table 1.**

For those who are immunocompromised:

1) **Three- (3) dose primary series of rabies vaccine on days 0, 7 and 21 to 28 (including for those in the "moderate risk" group) (see Table 1).**

2) **One-site intramuscular (IM) (1.0 mL) or 2-site intradermal (ID) (0.1 mL at each site) routes of administration can be used.**

3) **Serology is recommended regardless of route of administration, with testing performed between 2 to 4 weeks (or at least 1 week if results are needed sooner) after completion of the 3-dose primary series and any subsequent booster doses (if subsequent booster doses are needed).**

   - **If the titre is below 0.5 IU/mL, an additional dose of rabies vaccine should be administered followed by another serologic test (at 2 to 4 weeks or at least 1 week from the additional dose). The additional dose and serology should be**

repeated again if the titre is less than 0.5 IU/mL after the first additional dose. If the titre remains below 0.5 IU/mL after the second additional dose, consultation with a specialist or public health official is recommended.

- **In addition to serology after the primary series or any booster doses, if a person who is immunocompromised is in the "very high risk" or "high risk" groups (i.e., risk groups with potentially unrecognized exposures), they should also follow the recommendations for regular periodic serology as outlined in Table 1.**

4) **If possible, administer rabies pre-exposure prophylaxis at a time to maximize the immune response (e.g., begin the primary series after the immunocompromised state has resolved or complete the primary series at least 2 weeks before a planned immunocompromised state).**

See Immunization of Immunocompromised Persons chapter of the Canadian Immunization Guide) for additional information on immunocompromising conditions.

Table 1. Rabies pre-exposure prophylaxis vaccination schedule and serology recommendations by risk group for individuals who are immunocompetent and for those who are considered immunocompromised

Note: All rabies PrEP schedules can be administered using the 1-site IM or 2-site ID[a] routes, including any subsequent booster doses if these are needed

Risk groups	**Examples**	**Schedule** Using 1-site intramuscular (IM) (1.0 mL) or 2-site intradermal (ID)[a] (0.1 mL at each site) routes of administration	**Serology[b] [c]**
IMMUNOCOMPETENT			
Very high risk Potentially unrecognized exposures[d]	People who work with the rabies virus in a research or vaccine production laboratory	3-dose primary series on days 0, 7 and 21 to 28 [e, f]	Every 6 months[g]
High risk Potentially unrecognized exposures[d]	People with regular/frequent bat exposures (e.g., contact with bats, enters high-density bat environments, people who perform necropsies on bats); People who routinely perform	3-dose primary series on days 0, 7 and 21 to 28[e, f]	Every 2 years[g] For those who are immunocompromised or 65 years of age and older, routine serologic testing can be performed more frequently (i.e., between every 6

	necropsies on mammals due to suspected rabies; Rabies diagnostic laboratory workers		months to 2 years) as per clinical discretion. Also see Immunocompromised section in Table 1 below for serology recommendations after the primary series or booster doses for those who are immunocompromised
Moderate risk Mainly recognized exposures	Veterinarians; Veterinary staff; Veterinary students; Animal control workers; Animal shelter workers; Wildlife workers; Spelunkers; Travellers to areas where rabies vaccine is recommended[h]; Trappers	**Risk expected to extend 3 or more years or duration of risk is uncertain** 2-dose primary series on days 0 and 7 to 28[e, i]; A booster dose is also recommended, ideally 12 to 24 months after the second dose[f]	Generally not recommended[j]
		Risk expected to be less than 3 years 2-dose primary series on days 0 and 7 to 28[e, i];	
IMMUNOCOMPROMISED [k]			
Individuals who are considered immunocompromised[k]	All risk groups identified above	3-dose primary series on days 0, 7 and 21 to 28[e, f]	Serology at between 2 and 4 weeks after the primary series, and after any subsequent/booster doses. If results are needed sooner, testing can be performed at 1 week following the completion of the primary series or booster dose.[l] If an immunocompromised person is in the “very high risk” or “high risk” groups (i.e., groups with potentially unrecognized exposures), they should also follow the recommendations for regular periodic serology as outlined above in this table

Considerations for Recommendation 2 and footnotes for Table 1

a. **Intradermal administration**:

- Intradermal (ID) administration is off-label and this off-label use should be discussed with the person receiving the vaccine.
- Two-site (2-site) ID administration requires 0.1 mL ID at each of 2 distinct body locations (e.g., left and right side) on the same visit. The safest practice is to use a separate needle and syringe for each site of the 2-site ID dose[63]. Based on recommendations by the World Health Organization (WHO), the body sites for ID injections are the deltoid region, or the anterolateral thigh or suprascapular regions[7].
- Based on recommendations from the WHO, the rabies vaccine should be used within 6 hours of reconstitution[46]. Using the ID route of administration, more than 1 person can receive vaccine from the same reconstituted vial of rabies vaccine if given within a 6-hour period, which can be cost saving. Strict infection prevention and control precautions are required when using the same vial on multiple individuals (see the Infection Prevention and Control section of the Vaccine Administrations Practices Chapter of the Canadian Immunization Guide).
- See Appendix B for information on "How to administer rabies vaccines via the 2-site intradermal (ID) route".

b. Rabies titres below 0.5 IU/mL:

If rabies antibody titres fall below 0.5 IU/mL, a booster dose given as 1-site IM or 2-site ID should be administered. Serologic testing is not needed after the booster, with the exception of individuals considered immunocompromised (see last row in Table 1) or taking chloroquine/hydroxychloroquine. Ongoing serologic testing should continue at recommended frequencies following the booster dose.

c. **Chloroquine and hydroxychloroquine**:

If possible, complete the PrEP primary series at least 2 weeks before beginning chloroquine or hydroxychloroquine. If this is not possible,1-site intramuscular (IM) or 2-site intradermal (ID) administration can be used and serology should be performed between 2 and 4 weeks after completing the primary series or booster dose, regardless of the route of administration; if results are needed sooner, testing can be performed at 1 week following the completion of the primary series or booster dose. See footnote l of Table 1 for guidance regarding titres less than 0.5 IU/mL.

d. **Potentially unrecognized exposures:**

The "very high risk" and "high risk" groups are at risk due to regular activities that may result in exposures they may not recognize and therefore they may not seek post-exposure prophylaxis (PEP) as recommended (such due an unrecognized breach in personal protective equipment in a laboratory worker or person performing a necropsy, or when working with bats). These groups are recommended to have periodic serology and boosting if titres fall below 0.5

IU/mL to maintain a sustained titre equal to or greater than 0.5 IU/mL in case of an unrecognized exposure where PEP is not sought.

e. **Second dose timing:**

The minimum interval between the first and second dose is 7 days.

If a day 0, 3 and 7 schedule was used (such as in an incomplete post-exposure prophylaxis schedule), the second dose (day 3) should be ignored for future pre-exposure prophylaxis (PrEP) considerations (i.e., a day 0, 3, and 7 schedule should be considered as 2 doses with respect to future PrEP). Complete post-exposure prophylaxis schedules (at least 4 doses on day 0, 3, 7 and 14) are considered valid as any future PrEP.

f. **Third/booster dose timing:**

The minimum interval between the second and third/booster dose is 14 days. Although delayed third/booster doses (beyond 3 or more years from the second dose) are not optimal due to limited evidence regarding boostability, a delayed third/booster dose schedule is still considered acceptable as a 3-dose schedule.

g. **Laboratory workers**:

Some laboratories that work with the rabies virus may require serology after a primary series before beginning work with live rabies virus. Follow laboratory-specific recommendations.

h. **Travellers:**

- For international travel, comprehensive recommendations for this population can be found through the Committee to Advise on Tropical and Travel Medicine from CATMAT[61]. Consult the Government of Canada's Travel Advice and Advisories pages[62] to determine whether the rabies vaccine may be recommended for a specific international travel destination. After selecting the destination country, the rabies information can be found in the 'Health' section, under 'Pre-travel vaccines and medications'.
- Travellers for whom rabies vaccine is recommended who are departing in less than 7 days from initiating the primary series should still receive 1 dose before departure if rabies vaccination is being considered and should be counselled that they have not received a full pre-exposure prophylaxis (PrEP) vaccination series. They should be counselled that they require full post-exposure prophylaxis (PEP) (including rabies immunoglobulin) on an urgent basis after an exposure. Additional dose(s) in the PrEP schedule can be received at the travel destination based on a risk-benefit assessment (including consideration of duration of travel, activities during travel and availability of rabies immunoglobulin for PEP should it be needed) or on returning from travel if future travel or other exposures to potentially rabid animals are anticipated.

i. **Schedules for the "moderate risk" group:**

- Pre-exposure prophylaxis schedules that deviate from days 0, 7 and 21 to 18 are off-label and off-label use should be discussed with the person receiving the vaccine.
- If the second dose is given 7 days or more after the first dose, it is considered valid and sufficient for risk that is expected to last less than 3 years. If the second dose is given 3 or more years from the first dose and ongoing protection is needed, a third dose at least 2 weeks after the second dose is recommended.

j. **Serology for the "moderate risk" group:**

For those who are immunocompetent in the "moderate risk" group, regular serologic testing is generally not recommended as this group is likely to have only recognized exposures. However, those in the "moderate risk" group who may have unrecognized exposures can obtain periodic serology in consultation with their health care provider, and receive a booster dose if their rabies antibody titre falls below 0.5 IU/mL. Note that those who are immunocompromised are recommended to receive serology after the primary series and any booster doses.

k. **People who are immunocompromised:**

For vaccination of people who are immunocompromised, if possible, administer pre-exposure prophylaxis at a time to maximize the immune response (e.g., begin after the immunocompromised state has resolved, or complete the primary series at least 2 weeks before a planned immunocompromised state) (see Immunization of Immunocompromised Persons chapter of the Canadian Immunization Guide).

l. Serology less than 0.5 IU/mL in people who are immunocompromised, or taking chloroquine or hydroxychloroquine, or have used products or routes of administration that are not recommended:

If the rabies antibody titre is less than 0.5 IU/mL in a person who: is immunocompromised; taking chloroquine or hydroxychloroquine; or had used products or routes of administration that are not recommended, then an additional dose of rabies vaccine should be administered followed by another serologic test (at 2 to 4 weeks or at least 1 week from the additional dose). The additional dose and serology should be repeated again if the titre is less than 0.5 IU/mL after the first additional dose. If the titre remains below 0.5 IU/mL after the second additional dose, consultation with a specialist or public health official is recommended.

Summary of evidence and rationale:

- NACI's systematic review and associated literature reviews found that, although seroconversion (defined as antibody titres of equal to or greater than 0.5 IU/mL) is equivalent in the short-term for 2- and 3-dose schedules for both IM and 2-site ID administration, the percentage of people with titres equal to or greater than 0.5 IU/mL falls

over time and are less well maintained in the long term for 2-dose compared to 3-dose IM schedules[10]. In Overduin et al. 32% of participants aged 18 to less than 50 years who received 2-dose IM schedules on days 0 and 7 had titres below 0.5 IU/mL by 6 months after the primary series[47]. Therefore for those with the potential for unrecognized exposures, the authorized on-label, 3-dose rabies PrEP schedule (days 0, 7 and 21 to 28)[64,65] is recommended.

- Vaccine principles would suggest that if a primary series induces a primary immune response, it should also induce a durable memory response[66]. Data supports the ability of a 3-dose schedules to boost over extended time periods[34,35,67]. However, there is very limited data regarding the boostability of 2-dose schedules beyond the start of the third year after the primary series[35]. Therefore, for those with ongoing or recurrent risk of exposure to potentially rabid animals expected to extend beyond 3 or more years from the primary series, 3 doses or 2 doses plus a booster dose schedules are recommended. If there is uncertainty about how long the rabies exposure risk is expected to last, the booster is recommended. As based on vaccine principles, the immune response is generally better with longer intervals between doses[66], the third/booster dose for those in the "moderate risk" group is ideally recommended at 12 to 24 months after completing the 2-dose primary series, but can be given as early as 14 days after the second dose. If the second dose is given 3 or more years from the first dose and ongoing protection is needed, a third dose at least 2 weeks after the second dose is recommended given that there is good data on the long term boostability of 3 dose schedules.
- In NACI's systematic review, 2-site ID administration was generally similar to 1-site IM administration with regard to seroconversion for 1, 2 and 3 doses of rabies vaccine. Some limited differences in geometric mean titres (GMTs) were observed, with titres higher for IM than 2-site ID in some analyses but not in other analyses[10].
- In NACI's systematic review, geometric mean titres (GMTs) for all schedules decreased over time[10]. Those who have ongoing risk of exposure to rabies virus in a laboratory or at ongoing risk of exposure to potentially rabid animals that may not be recognized (and therefore they may not seek post-exposure prophylaxis) should have periodic serology, with a booster dose if titres fall below 0.5 IU/mL.
- Although studies are limited, evidence suggests the immune response for immunocompromised individuals is less robust, with one study of individuals receiving immunosuppressive therapy reporting only 90% seroconversion following simulated PEP booster doses[43]. By contrast, in NACI's systematic review, seroconversion after the booster dose for people who were mostly not immunocompromised ranged from 99.7 to 100% (based on analyses that pooled relevant data from across included study arms) when the primary series was 2 or 3 doses[10]. See Section 5.1"Immunization of people who are immunocompromised" for more details. A 3-dose schedule on days 0, 7 and 21 to 28 (using either 1-site IM or 2-site ID routes of administration) is therefore recommended for people who are immunocompromised, with serologic testing between 2 to 4 weeks (and at least 1 week) after completing the primary series and any subsequent booster doses that may be required.

Recommendation 3 – Post-exposure prophylaxis for those who received pre-exposure prophylaxis

NACI recommends that all recipients of pre-exposure prophylaxis (PrEP) should be counselled about the importance of seeking post-exposure prophylaxis (PEP) after an exposure to a potentially rabid animal or the rabies virus in a laboratory setting. ***(Strong NACI recommendation)***

Table 2 outlines PEP guidance for those who previously received PrEP or at least 1 dose of rabies vaccine. Clinical discretion is required in managing specific circumstances, including in managing people who are immunocompromised considering that the degree of immunocompromise is variable depending on the underlying condition and immunocompromising medication(s).

Note that NACI will be undertaking a future review of recommended post-exposure prophylaxis (PEP) regimens. See the Rabies Chapter of the Canadian Immunization Guide for additional details on PEP administration.

Table 2. Post-exposure prophylaxis (PEP) guidance for those who previously received pre-exposure prophylaxis (PrEP) or at least 1 dose of rabies vaccine

Note that clinical discretion is required in managing specific circumstances.

Pre-exposure prophylaxis (PrEP) or rabies vaccination previously received	**Post-exposure prophylaxis (PEP) guidance**[a] • Note that day 0 refers to the first day of starting PEP and not the day of exposure • See Footnote "a" regarding route of administration • See the Rabies Chapter of the Canadian Immunization Guide for additional details on PEP administration
IMMUNOCOMPETENT	
At least 3 doses (including 2 doses plus a booster)[b]	2 doses of rabies vaccine on days 0 and 3 No rabies immunoglobulin
2 doses with the second dose administered less than 3 years in the past[b]	2 doses of rabies vaccine on days 0 and 3 No rabies immunoglobulin
2 doses with the second dose administered 3 or more years in the past[b]	Rabies immunoglobulin and 4 doses of rabies vaccine on days 0, 3, 7 and 14[c].
1 dose of rabies vaccine[d]	Rabies immunoglobulin and 4 doses of rabies vaccine on days 0, 3, 7 and 14[c].

IMMUNOCOMPROMISED[e]	
At least 3 doses and demonstration of adequate serology after completion of the primary series (equal to or greater than 0.5 IU/mL)[b]	**Those who are moderately to severely immunocompromised at the time of the exposure:** • Rabies immunoglobulin and 5 doses of rabies vaccine on days 0, 3, 7, 14 and 28 • Determine serology 7 to 14 days after the last dose [f] **Those who are mildly immunocompromised or no longer immunocompromised at the time of the exposure:** • 2 doses of rabies vaccine on days 0 and 3 • No rabies immunoglobulin • Determine serology 7 to 14 days after the last dose [g]
At least 3 doses without demonstration of adequate serology after completion of the primary series (no serology test or result less than 0.5 IU/mL)	• Rabies immunoglobulin and 5 doses of rabies vaccine on days 0, 3, 7, 14 and 28 • Determine serology 7 to 14 days after the last dose [f]
2 or fewer doses (with or without serology)	• Rabies immunoglobulin and 5 doses of rabies vaccine on days 0, 3, 7, 14 and 28 • Determine serology 7 to 14 days after the last dose [f]

a. As of the publication of this statement, NACI only recommends the intramuscular (IM) route for rabies post-exposure prophylaxis (PEP) [5], however provincial/territorial guidance may differ. Please check provincial/territorial guidance regarding PEP regimens. NACI will be reviewing its recommendations regarding PEP guidance.
b. For information on recommended schedules see Table 1, with footnote e providing minimum intervals for the second dose and footnote f providing minimum intervals for the third dose.
c. An additional dose on day 28 is indicated for those who are taking chloroquine or hydroxychloroquine followed by serology 7 to 14 days after the last dose.
d. For those who are not immunocompromised and not taking chloroquine/hydroxychloroquine, if the 1 dose of rabies vaccine was administered more than 1 week and less than 1 month prior to the onset of post-exposure prophylaxis (PEP), rabies immunoglobulin is not needed and only 3 additional doses of rabies vaccine are needed on days 0, 4 and 11, with day 0 being the start of vaccination for PEP and the

schedule respecting the intervals between doses for the second and third dose (4 days) and third and fourth dose (7 days) in a routine PEP schedule for those not previously vaccinated.

e. Refers to the person who was immunocompromised either when the pre-exposure prophylaxis was administered and/or when the post-exposure prophylaxis is needed. Refer to the Immunization of immunocompromised persons chapter of the Canadian Immunization Guide for additional information.
f. As of the writing of this NACI Advisory Committee statement, guidance in the Rabies chapter of the Canadian Immunization Guide indicates that if the antibody response is not acceptable (i.e., less than 0.5 IU/mL), the patient should be managed in consultation with their physician and appropriate public health officials to receive a second rabies vaccine series. RabIg should not be repeated at the initiation of this second course. Serology should be repeated 7 to 14 days following this second PEP series. If the titre remains below 0.5 IU/mL, consultation with a specialist or public health official is recommended.
g. If the antibody response is less than 0.5 IU/mL, the patient should receive two additional doses given 3 days apart. Serology should be repeated 7 to 14 days following the second of these two repeat doses. If the titre remains below 0.5 IU/mL, consultation with a specialist or public health official is recommended.

Summary of evidence and rationale:

- Studies have demonstrated that 3-dose rabies pre-exposure prophylaxis (PrEP) schedules remain boostable over time, with studies demonstrating boostability beyond 20 years from the primary series[34,35]. The authorized schedule for available rabies vaccines are 3 doses on days 0, 7 and 21 (or 21 or 28 for RABAVERT), and the authorized schedule for post-exposure prophylaxis (PEP) in those previously vaccinated is 2 doses of rabies vaccine on days 0 and 3[64,65]. Similarly, the 2-dose vaccine PEP schedule on days 0 and 3 would also be appropriate when PrEP was given as 2 doses plus a booster dose.
- The need for full rabies PEP (including rabies immunoglobulin) if the second dose in a 2-dose primary series was 3 or more years in the past is due to limited data regarding boostability in the third year or later with a 2-dose primary schedules:
    - Only one study showed boostability 3 or more years after a 2-dose primary series (all 6 participants had a boostable response 10 to 11 years after a 2-dose primary series)[35].
    - It is possible that recommendations may change in the future as data accumulates on the boostability of 2-dose schedules over time.
- The World Health Organization (WHO) currently recommends that those who have only received 1 dose of rabies vaccine should receive full PEP, including rabies immunoglobulin[7]. NACI's systematic review demonstrated good boostability of 1-dose schedules[10], and there is some limited data on boostability between the second and third year after the primary single dose[37].
    - It is possible that as data increases on the bootability of 1-dose schedules over time from the primary series, recommendations may change regarding those who have received only 1 dose of rabies PrEP.

- Although having previously received only 1 dose of PrEP would generally require a full PEP regimen including rabies immunoglobulin, NACI is making an exception in footnote d of Table 2 by recommending only vaccination for rabies PEP if the previous 1 dose of rabies vaccine was given more than 1 week but less than 1 month before starting rabies PEP, provided the individual is not considered immunocompromised and not taking chloroquine/hydroxychloroquine. This exception is consistent with WHO and NACI recommendations that if rabies PEP begins with rabies vaccination only, rabies immunoglobulin should not be administered if more than 7 days has passed since the start of PEP vaccination[5,7] because circulating antibodies will begin to appear after day 7 from the first dose[7]. An outer limit of 1 month for this exception was chosen to be precautionary.

- The immune response to rabies vaccine as pre-exposure prophylaxis in those who are immunocompromised is less robust than in those who are not immunocompromised (see Section 5.1, Immunization of people who are immunocompromised), therefore guidance on use of PEP in those who are immunocompromised and previously received PrEP is more conservative. Full PEP, including rabies immunoglobulin and 5 doses of rabies vaccine followed by serology 7 to 14 days after the last dose, is recommended for those who are moderately to severely immunocompromised at the time of exposure, even if they have previously received PrEP as recommended. Those who are immunocompromised and received less than recommended PrEP (i.e., less than 3 doses of vaccine or had no evidence of titre equal to or greater than 0.5 IU/mL after 3 doses of rabies vaccine) are also recommended to receive full PEP including rabies immunoglobulin and 5 doses of rabies vaccine followed by serology 7 to 14 days after the last dose.
    - The recommendation for full PEP in those who are moderately to severely immunocompromised is generally consistent with World Health Organization (WHO) recommendations that state that immunocompromised individuals (such as HIV-infected persons who are not receiving antiretroviral therapy (ART) or who are receiving ART but do not meet minimum CD4 cell count criteria) should receive full PEP including rabies immunoglobulin, even if previously vaccinated[7].
    - See footnote f and footnote g of Table 2 for information on responding to serology results that are less than 0.5 IU/mL.

Recommendation 4 – Interchangeability of products and routes of administration

NACI recommends a rabies vaccine primary series should be completed with the same product whenever possible. However, if it is not feasible to do so, purified chick embryo cell vaccine (PCECV), human diploid cell vaccine (HDCV) and purified Vero cell rabies vaccine (PVRV) are considered interchangeable within the primary series.

NACI recommends that the same route of administration be used for all doses in the rabies vaccine primary series whenever possible. However, if this is not feasible, a change in the route of administration (1-site IM to 2-site ID or vice versa) during a rabies vaccine primary series is acceptable.

(Strong NACI recommendation)

Additional Considerations:

- If the product (using PCECV, HDCV, or PVRV) or route of administration (using 1-site IM or 2-site ID) is changed during the rabies vaccine primary series, the series should not be restarted and vaccination should continue according to the schedule; interchanging these products or routes of administration does not require serologic testing after primary series completion, unless serology is needed for other reasons as per Table 1.
- Booster doses do not need to be given using the same product or route of administration as the rabies vaccine primary series.
- If vaccines other than PCECV, HDCV or PVRV are included in a PrEP primary series or used as a booster, serology should be assessed with testing optimally done between 2 to 4 weeks (and at least 1 week) after completing the primary series or booster, but if necessary, testing can be done at a later time. See footnote l of Table 1 for management of titres less than 0.5 IU/mL.
- If 1-site intradermal (ID) administration (which is no longer recommended) was included in a PrEP primary series or used as a booster, serology should be assessed with testing optimally done between 2 to 4 weeks (and at least 1 week) after completing the primary series or booster, but if necessary, testing can be done at a later time. See footnote l of Table 1 for management of titres less than 0.5 IU/mL.

Summary of evidence and rationale:

- NACI's systematic review of 2- and 3-dose schedules stratified by route of administration found that the immune responses generated by PCECV, HDCV and PVRV were similar.
- NACI's systematic review found that 1-site IM and 2-site ID routes of administration of rabies vaccine had generally similar seroconversion rates, and for geometric mean titres, the 1-site IM route induced a higher immune response than the 2-site ID route in a few analyses but a similar response in other analyses[10].
- An observational study demonstrated robust immune responses to the first 3 doses of rabies post-exposure prophylaxis (given on days 0, 3, and 7) with changes in route of administration or product type/brand during the administration of the 3 doses[42].

Table 3. NACI recommendations: Strength of recommendation

Strength of recommendation	**Strong**	**Discretionary**
Wording	"should/should not be offered"	"may/may not be offered"
Rationale	Known/anticipated advantages outweigh known/anticipated disadvantages ("should"), **or** Known/Anticipated disadvantages outweigh known/anticipated advantages ("should not")	Known/anticipated advantages are closely balanced with known/anticipated disadvantages, **or** uncertainty in the evidence of advantages and disadvantages exists
Implication	A strong recommendation applies to most populations/individuals and should be followed unless a clear and compelling rationale for an alternative approach is present.	A discretionary recommendation may be considered for some populations/individuals in some circumstances. Alternative approaches may be reasonable.

IX. Research and surveillance priorities

After review of the existing evidence, NACI has identified the need for further research to address current knowledge gaps where data are absent or limited. NACI recognizes that there may be studies already in progress that may address some of these gaps, but the findings of these studies were not available at the time of review. Knowledge gaps and priority areas for research are listed below.

Virology-related priorities:

- The ability of rabies viral exposure to induce an anamnestic response in those who are previously vaccinated
- The ability of rabies vaccination to affect rabies virus once the virus is in the peripheral nervous system
- The role of cellular immunity in the response to rabies vaccine

Vaccine-related priorities:

- Boostability of primary series over time for 1- and 2-dose primary schedules
- Surveillance of titres in those who receive routine serology to inform frequency of serology required based on schedule and route of administration of pre-exposure prophylaxis (PrEP)
- Vaccine effectiveness of schedules with a reduced number of doses and schedules using 2-site intradermal administration
- Additional studies of immunogenicity in individuals who are immunocompromised and in older adults
- Ongoing monitoring of safety in pregnant women and pregnant individuals

Acceptability and feasibility priorities:

- Adherence with PrEP schedules
- Adherence with seeking PEP after an exposure to a potentially rabid animal, including in those who received PrEP
- Acceptance and feasibility of 2-site intradermal administration by providers and patients

Abbreviations

ACS	Advisory Committee Statement
ART	Antiretroviral therapy
CATMAT	Committee to Advise on Tropical Medicine and Travel
CI	Confidence interval
CIC	Canadian Immunization Committee
EEFA	Ethics, equity, feasibility, acceptability
EtD	Evidence to Decision framework
GMTs	Geometric mean titres
GRADE	Grading of recommendations, assessment, development, and evaluation
HDCV	Human diploid cell vaccine
HIV	Human immunodeficiency virus
HSCT	Hematopoietic stem cell transplantation
ID	Intradermal
IM	Intramuscular
IU	International units
IU/kg	International units/kilogram
IU/mL	International units/millilitre
NACI	National Advisory Committee on Immunization
PCECV	Purified chick embryo cell vaccine
PEP	Post-exposure prophylaxis
PHAC	Public Health Agency of Canada
PHECG	Public Health Agency of Canada's Health Ethics Consultative Group
PrEP	Pre-exposure prophylaxis
PVRV	Purified Vero cell rabies vaccine
RCT	Randomized controlled trial
RR	Relative risk
RNA	Ribonucleic acid
WHO	Word Health Organization

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Appendix A

Table A.1. Comparison between the National Advisory Committee on Immunization (NACI) rabies recommendations prior to this Advisory Committee Statement and World Health Organization (WHO) April 2018 rabies recommendations

	NACI prior to December 2025	**WHO from 2018[7]**
Rabies PrEP	• 3 doses of rabies vaccine on days 0, 7 and between days 21 to 28 • 1-site IM gold standard but could use 1-site ID • Serology recommended after ID administration and after vaccination of people who are immunocompromised. Serology also recommended for some occupational groups	• 2 doses of rabies vaccine on day 0 and 7 • 2-site ID preferred but could use 1-site IM • No serology recommended after ID administration, or for people who are immunocompromised, unless people who are immunocompromised received only 2 doses. Serology also recommended for some occupational groups
Rabies PEP (for NOT previously vaccinated)	• 4 doses of rabies vaccine on days 0, 3, 7 and 14 • Immunocompromised or taking chloroquine or other antimalarial extra dose on day 28, followed by serology for immunocompromised • 1-site IM, ID not recommended **AND** • 20 IU/kg of rabies immunoglobulin on day 0, with as much of the dose as possible given at the wound/exposure site; give remainder at a distant site IM	Rabies vaccine as: • 2-site ID on days 0, 3 and 7; **OR** • 1-site IM on days 0, 3, 7 and between day 14 to 28; **OR** • 2- site IM on day 0 and 1-site IM days 7 and 21 **AND after category III exposures only** • 20 IU/kg of rabies immunoglobulin with as much of the dose as possible given at the wound/exposure site; **do not** give remainder at a distant site
Rabies PEP (for previously vaccinated)	• Rabies vaccine 1-site IM on days 0 and 3 • ID not recommended	Rabies vaccine: • 1-site ID on days 0 and 3; **OR** • 4-site ID on day 0; **OR** • 1-site IM on days 0 and 3

Table A.2. Key characteristics of rabies vaccines authorized for use in Canada[a]

	IMOVAX® Rabies[65]	RABAVERT[64]
Manufacturer	Sanofi Pasteur Limited	Bavarian Nordic A/S
Date of initial authorization in Canada	April 1, 1980	April 29, 2005
Type of vaccine	Inactivated, human diploid cell rabies vaccine (HDCV)	Inactivated, purified chick embryo cell vaccine (PCECV)
Composition	• Rabies virus (WISTAR Rabies PM/WI 38 1503-3M strain) • Human albumin • Neomycin • Phenol red • Water for injection	• Flury LEP strain of rabies virus • Amphotericin B • Chlortetracycline • Disodium edetate • Human serum albumin • Hydrogen chloride • Neomycin • Ovalbumin • Polygeline • Potassium-L-glutamate • Sodium chloride • Sucrose • Trometamol • Water for injection
Indications	For the active immunization of individuals of all age groups to prevent disease caused by the rabies virus For both pre-exposure prophylaxis and post-exposure prophylaxis	For pre-exposure vaccination, in both primary series and booster doses against rabies in all age groups Post-exposure prophylaxis against rabies in all age groups
Storage requirements	Store at 2° to 8°C. Do not freeze. Product which has been exposed to freezing should not be used.	Store protected from light at 2° to 8°C.
Reconstitution	Reconstitute the freeze-dried vaccine in its vial by introducing the diluent into the vial of powder. Gently swirl the contents until completely dissolved. The suspension should be clear or slightly opalescent red to purplish red and free from particles.[b]	Slowly inject the entire contents of the diluent (1 mL) into the vaccine vial. Mix gently to avoid foaming. The white, lyophilized powder dissolves to give a clear to slightly opalescent, colourless to slightly pink solution.[b]

a. See Recommendations section in this Advisory Committee Statement for NACI recommendations regarding schedules, routes and dosage.

b. The product monographs indicate to use the vaccine immediately after reconstitution[64,65], however the World Health Organization indicates that the vaccine can be used up to 6 hours after reconstitution[46].

For complete prescribing information for IMOVAX® Rabies and RABAVERT, consult the product leaflet or information contained within Health Canada's authorized product monographs available through the Drug Product Database[64,65].

Table A.3. Summary of findings for 2- compared to 3-dose schedules of rabies vaccine.

No. of studies	Study design	Route of administration[a]	No. of events/ No. of participants		Effect		Certainty	Importance	Comments
			2 doses	3 doses	Relative effect (95% CI)	Absolute effect (95% CI)			
Seroconversion (follow-up: ≥7 days post-booster; assessed with titre level above 0.5 IU/mL)									
4[67-70]	RCTs	1-site IM	474/474 (100.0%)	243/243 (100.0%)	**RR 1.00** (0.99 to 1.01)	**0 fewer per 1,000** (from 10 fewer to 10 more)	HIGH [b]	Critical	A 2-dose primary series schedule does not reduce seroconversion rates post-booster when compared to a 3-dose primary series.

[a] No studies which directly compared 2 doses of 2-site ID to 3 doses of 2-site ID doses were identified.
[b] Although there are a limited number of RCTs which directly compared 2 to 3 doses and were primarily conducted in healthy adult populations, due to substantial observational and non-randomized data not included in the GRADE analysis but considered in the evidence synthesis[10] which include larger numbers of people who are representative of most populations eligible to receive PrEP, there were no concerns related to indirectness of the data.

Table A.4. Summary of findings for 2-site ID compared to IM administration of rabies vaccine.

No. of studies	Study design	Schedule	No. of events/ No. of participants		Effect		Certainty	Importance	Comments
			2 doses	3 doses	Relative effect (95% CI)	Absolute effect (95% CI)			
Seroconversion (follow-up: ≥7 days post-booster; assessed with titre level above 0.5 IU/mL)									
1[70]	RCTs	2 doses	139/139 (100.0%)	268/268 (100.0%)	**RR 1.00** (0.98 to 1.02)	**0 fewer per 1,000** (from 20 fewer to 20 more)	HIGH [a]	Critical	2-site ID administration of 2 dose schedules of rabies vaccines does not reduce seroconversion post-booster when compared to IM administration.
2[71,72]	RCTs	3 doses	41/41 (100.0%)	38/38 (100.0%)	**RR 1.00** (0.93 to 1.07)	**0 fewer per 1,000** (from 70 fewer to 70 more)	HIGH [a]	Critical	2-site ID administration of 3 dose schedules of rabies vaccines does not reduce seroconversion post-booster when compared to IM administration.

[a] Although there are a limited number of RCTs which directly compared 2 to 3 doses and were primarily conducted in healthy adult populations, due to substantial observational and non-randomized data not included in the GRADE analysis but considered in the evidence synthesis[10] which include larger numbers of people who are representative of most populations eligible to receive PrEP, there were no concerns related to indirectness of the data

Appendix B

How to administer rabies vaccines via the 2-site intradermal (ID) route

Introduction:

Rabies vaccine for pre-exposure prophylaxis (PrEP) can be administered by either the intramuscular (IM) or intradermal (ID) routes. Administration using the ID route for IMOVAX® Rabies and RABAVERT vaccines is considered off-label, as at this time ID administration of these products is not authorized by Health Canada. The off-label use should be discussed with the person receiving the vaccine.

If the ID route is used for rabies PrEP, the recommendation is that a 2-site approach be used which is 2 injections of 0.1 mL each, given at the same visit, each at a different injection site/limb, for a total dose of 0.2 mL (e.g., 0.1 mL at the left injection site/limb and 0.1 mL at the right injection site/limb at each visit). The safest practice is to use a separate needle and syringe for each injection site[63]. It should be noted that WHO guidance indicates that 0.2 mL can be withdrawn from the vial into an insulin syringe and the same needle and syringe used to inject 0.1 mL into each site[73].

Preparing the vaccine:

Rabies vaccines should be reconstituted with the provided diluent, as per the product monographs:

- IMOVAX® Rabies Product Monograph[65]
- RABAVERT Product Monograph[64]

If the vial will be used for vaccinating more than 1 person (which is possible when the vaccine is given intradermally), it should be used within 6 hours of reconstitution and should be stored at 2 to 8°C and protected from light[46]. The date and time the product should be discarded (i.e., 6 hours after reconstitution) should be written on the vial, for example: “Discard by (time) on (date)”.

Intradermal (ID) injections require a 26 to 27 gauge needle that is 1.0 cm in length[74].

Proper infection prevention and control is very important in preparing the vaccine, including wiping the stopper with a suitable disinfectant (e.g., isopropyl alcohol) and allowing it to dry before each puncture of the vial[74]. Given that the same vial could be used on multiple individuals if the vaccine is given intradermally, strict care should be taken to ensure that a needle that has been used for injection never re-enters the vial. Steps to ensure that the vial is not inadvertently re-punctured with a used needle include: returning any unused vaccine to the refrigerator after drawing up and before beginning to administer the vaccine; and promptly activating the safety mechanism and discarding the used needle and syringe in the sharps container after vaccine administration (never place a used needle and syringe down on the work station). See the Infection Prevention and Control section of the Vaccine Administrations Practices Chapter of the Canadian Immunization Guide.

The Vaccine administration practices chapter of the Canadian Immunization Guide indicates that the syringes be loaded with vaccine immediately before administration. Pre-loading of syringes is strongly discouraged but may be considered in specific circumstances; specific principles for preloading are outlined in the Canadian Immunization Guide.

Intradermal injection sites:

As per the World Health Organization, for all age groups, the recommended injection sites for intradermal rabies vaccine injections are the deltoid region, or the anterolateral thigh or suprascapular regions[46]. For 2-site administration, the left and right sides should be used if possible (e.g., 0.1 mL in the area over the right deltoid and 0.1 mL in the area over the left deltoid).

Intradermal injection technique:

For intradermal injections, the needle is inserted just below the skin with the bevel up at a 5 to 15 degree angle to the skin. The injection should produce a noticeable pale elevation of the skin known as a wheal. A wheal is an area of the skin that is raised like a blister or bubble. The presence of a wheal 6 mm to 10 mm in diameter indicates that the vaccine has been correctly administered into the dermis. Do not rub the injection site. If a 6 mm to 10 mm wheal does not form, remove and discard the used needle and syringe and repeat the procedure with a new needle and syringe at a separate anatomic injection site (e.g., different limb or suprascapular region) or in the same anatomic injection site but separated by at least 2.5 cm (1 inch)[74].

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