

# Use of the Intradermal Route for Rabies Vaccine Post-Exposure Prophylaxis in Ontario

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## Overview

In 2018, the World Health Organization (WHO) Strategic Advisory Group of Experts (SAGE) on Immunization endorsed the use of a shortened intradermal (ID) rabies vaccine schedule as a safe, immunogenic, and dose-sparing alternative to the intramuscular (IM) route of administration for rabies post-exposure prophylaxis (PEP).<sup>1</sup> In contrast, the rabies chapter of the Canadian Immunization Guide, last updated in January 2015, recommends the use of the IM route of administration for rabies vaccine for PEP, and the ID route of administration is acceptable for use only when administered for the purposes of pre-exposure prophylaxis of immunocompetent persons.<sup>2</sup> The National Advisory Committee on Immunization (NACI) began an evidence review of ID and IM dose- and time-sparing vaccine regimens in 2019, but this work was suspended in 2020 due to the COVID-19 pandemic.<sup>3</sup>

At the request of the Ministry of Health, the Ontario Immunization Advisory Committee (OIAC) met on June 1, 2022 to review the topic of the ID route of administration for rabies vaccine for PEP and to provide advice on whether recommendations for its use in Ontario should be made. This document summarizes the information reviewed by the OIAC, including protocols and recommendations in other jurisdictions; evidence and knowledge gaps; and potential benefits and feasibility considerations for the implementation of the ID route of administration for PEP in the Ontario context.

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## Recommendation

Rabies vaccine for post-exposure prophylaxis should continue to be provided using the intramuscular route of administration in Ontario at this time.

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## Background

Rabies post-exposure prophylaxis (PEP) generally consists of thorough washing of the wound with soap and water and, based on a risk assessment of the exposure, a rabies vaccine series, plus rabies immune globulin in persons who are immunologically-naïve (i.e., no past history of completing a schedule of rabies vaccine). While IM administration of rabies vaccine is generally considered the gold standard,<sup>2</sup> in 2010, WHO SAGE recommended the ID use of rabies vaccine (2-site ID regimen, given as 0.1 mL per site [total of 0.2 mL] on days 0, 2, 7, and 28) as an equally safe and immunogenic alternative for PEP for immunologically-naïve persons that can be dose-sparing and cost-saving compared to the IM route (1-site IM regimen of 1.0 mL on days 0, 3, 7, 14, and 28).<sup>4</sup> In 2018, WHO SAGE endorsed the use of shortened

PEP regimens for both ID (2-site regimen on days 0, 3, and 7) and IM (1-site regimen on days 0, 3, 7 and between days 14-28) routes.<sup>1</sup> The updated PEP schedules further enhance savings and programmatic feasibility for underserved populations in rabies-endemic countries while maintaining high individual efficacy, based on the most recent evidence.<sup>5</sup> The shortened ID regimen uses at least 25% fewer vaccine vials than the IM regimen, and up to 85% fewer vaccine vials as the number of patients seen in clinics increases. Modelling estimates suggest that for every 1000 vials of rabies vaccine, almost 500 additional patients could be treated using a shortened ID PEP regimen compared to the standard 4-dose IM PEP regimen.<sup>1,6</sup>

In Canada, there are two inactivated rabies vaccines authorized for use via the IM route of administration: human diploid cell rabies vaccine (IMOVAX Rabies) and purified chick embryo cell rabies vaccine (RABAVERT).<sup>2</sup> The ID route of administration for rabies pre-exposure prophylaxis (PrEP) of immunocompetent persons has been considered an acceptable off-label use by NACI since 2005.<sup>7</sup> NACI recommends that rabies vaccines should only be given for PrEP via the ID route by fully-trained staff when there is a well-established cold chain, and preferably when a large group of individuals are being vaccinated at the same time, to reduce wastage of vaccine when using a 1.0 mL vial of vaccine for a 0.1 mL ID dose. In addition, NACI recommends that antibody titres should be assessed at least 14 days following completion of the vaccine series if using the ID route for PrEP, due to studies showing lower antibody titres with ID administration compared to IM; the potential for improper administration that may cause the vaccine to be injected subcutaneously rather than intradermally; and the possibility for delivery of a suboptimal dose of vaccine if the proper syringe and needle are not used.<sup>2,7</sup>

The rabies chapter of the Canadian Immunization Guide, last updated in January 2015, recommends the use of the IM regimen only for PEP (1-site IM on days 0, 3, 7, and 14 for immunocompetent persons, with an additional dose on day 28 for persons who are immunocompromised or taking chloroquine or other antimalarials).<sup>2</sup> An update to the rabies chapter, including a review of guidance in the context of WHO-recommended PEP schedules, was suspended due to the COVID-19 pandemic, and is included in NACI's work plan for 2022-2024.<sup>3</sup>

In a jurisdictional scan, most Canadian provinces and territories, including Ontario, recommend PEP regimens that align with the NACI recommendations.<sup>8</sup> Alberta and British Columbia (BC) implemented the ID route of administration due to shortages in vaccine and/or rabies immune globulin following a fatal human rabies case occurring in BC in 2019 that received considerable media attention and an increase in consultations and requests for PEP.<sup>9</sup> In Alberta, PEP can be administered over four visits using the ID route (2-site 0.1 mL) or the IM route (1-site 1.0 mL) on days 0, 3, 7, and 14. ID administration is the preferred route for PEP in immunocompetent, immunologically-naïve persons (unless contraindicated) when operationally feasible and client appointments can be scheduled on the same day.<sup>10</sup> In BC, the 4-dose IM route or the shortened ID route as currently recommended by WHO (2-site 0.1 mL on days 0, 3, and 7) are recommended, with the addition of serological testing on day 14 for the latter. Persons found to have an inadequate immune response can receive additional doses (2-site ID 0.1 mL) on day 14.<sup>11</sup>

The Australian Technical Advisory Group on Immunisation, United Kingdom Health Security Agency, and United States Advisory Committee on Immunization Practices (ACIP) recommend only the IM route for PEP.<sup>12-14</sup> The ACIP Rabies Working Group reviewed the 2018 WHO SAGE guidance in 2020, and ACIP reaffirmed the use of the current IM schedule for PEP in 2021, with several considerations including ID use is off-label for vaccines licensed in the US (IMOVAX Rabies and RABAVERT); key studies informing WHO SAGE guidance on PEP were based on vaccines not licensed in the US and in countries where rabies is endemic; and anticipated limited cost- and dose-savings.<sup>15,16</sup>

# Evidence Summary and Considerations

## Immunogenicity and Safety

- Systematic reviews and meta-analyses have shown both ID and IM routes of PEP provide adequate short-term immune response, although some evidence suggests that the IM route induces higher titres than the ID route.<sup>1,17-20</sup>
- There is evidence of a strong anamnestic response to booster at 1 year, and as long as 5 years, in individuals previously vaccinated with any PEP regimen irrespective of the dose and route of administration of the primary series.<sup>17</sup>
- The ID PEP regimen is effective in protecting against death due to rabies. Reported ID PEP failures resulted from high-risk exposures (e.g., bites to face/neck or direct nerve inoculation) and/or protocol deviations.<sup>1,18</sup>
- The safety profile of vaccines administered via the ID route are generally similar to the IM route, although minor local adverse events, such as erythema, pain, swelling, and pruritus, were more common after ID route.<sup>1,18,19</sup>

## Implementation Considerations

- In Ontario, health care providers (HCPs) in a variety of settings (e.g., emergency departments, family doctors' offices, walk-in clinics) administer PEP by the IM route to patients who present with a potential exposure to an animal with rabies. Public health units support the HCP's risk assessment and provide the requested amount of vaccine vials and rabies immune globulin for PEP as needed. Numerous changes would be required to implement the ID route in Ontario. Immunizers would need additional supplies for the ID route (e.g., different needle sizes than provided in the vaccine packages), education/training, and a communications strategy for HCPs and public health units to explain the change and its rationale. Implementation of the ID route of administration in other jurisdictions has been facilitated by more centralized systems of rabies exposure assessment, including public health authorization prior to PEP initiation, and centralized models of vaccine administration and related training.
- If improper technique is used, there is a risk of medical errors with ID injections (e.g., inadvertent subcutaneous injection, suboptimal dose of vaccine administered).<sup>2</sup>
- Additional consideration would need to be given to the optimal vaccine schedule and need for serological testing when using the ID route for PEP.
  - Systematic reviews and meta-analyses of immunogenicity and safety have examined heterogeneous PEP regimens and included vaccines not currently licensed in Canada, and ID regimens, where recommended, differ across jurisdictions.
  - The ID route is dose-sparing and requires less volume of vaccine than the IM route. However, opened vaccine vials must be discarded if the remaining contents are not used within 6–8 hours of opening.<sup>1</sup> If patient appointments cannot be scheduled on the same day and at the same location, then there will be limited savings in the volume of vaccine used due to vaccine wastage.

- If serology is recommended following ID PEP, potential cost savings of the ID route may be limited as four healthcare visits (three for vaccine, one for serology) will still be required, similar to the IM route of administration (four vaccine visits).
- The ID route may be more acceptable to patients if fewer healthcare visits are required. Individuals may be more likely to complete the vaccine series, in particular if time off of work or transportation are challenges to accessing healthcare in a timely way. In contrast, for a person with a fear of needles, more injections on a single visit may be less acceptable.

There is evidence of the effectiveness and safety of the ID route of administration. However, there is insufficient rationale to recommend this off-label use of rabies vaccine for PEP at this time due to the infrequent and sporadic nature of human rabies exposures in Ontario, resulting in limited cost savings and logistical challenges associated with using the ID route in settings where ID injections are not commonly used. OIAC recognizes the potential for the ID route to provide surge capacity if there is a high demand for rabies vaccine and may consider a future recommendation for the use of the ID route if there were a rabies vaccine shortage in Ontario that could be addressed through coordinated vaccine delivery and use of the ID route of PEP.

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## About the Ontario Immunization Advisory Committee

The OIAC is a multidisciplinary scientific advisory body that provides evidence-based advice to Public Health Ontario (PHO) on vaccines and immunization matters including vaccine program implementation in Ontario, priority populations and clinical guidance. The focus of the OIAC's work is on publicly-funded vaccines and immunization programs in Ontario, including COVID-19 and those under consideration for new programming. For more information about the OIAC and its members contact [secretariat@oahpp.ca](mailto:secretariat@oahpp.ca)

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## OIAC Members

Dr. Jessica Hopkins, co-chair  
Chief Health Protection and  
Emergency Preparedness Officer  
Public Health Ontario

Dr. Jeffrey Pernica, co-chair  
Head, Division of Infectious Disease  
Department of Pediatrics  
McMaster University

Dr. Juthaporn Cowan  
Associate Scientist  
The Ottawa Hospital Research Institute

Dr. Vinita Dubey  
Associate Medical Officer of Health  
Toronto Public Health

Dr. Julie Emili  
Associate Medical Officer of Health  
Region of Waterloo

Dr. Mariam Hanna  
Pediatric Allergist and Clinical Immunologist

Susie Jin  
Pharmacist

Dr. Allison McGeer  
Professor, Laboratory Medicine and  
Pathobiology  
University of Toronto  
Dalla Lana School of Public Health

Dr. Justin Pousseau  
Scientist  
The Ottawa Hospital Research Institute

Dr. Maurianne Reade  
Family Physician; Associate Professor  
Northern Ontario School of Medicine

Richard San Cartier  
Clinical Team Lead  
N'Mninoeyaa Aboriginal Health Access  
Centre

Fairleigh Seaton  
Director, Infectious Disease Prevention  
and Environmental Health  
Kingston, Frontenac and Lennox &  
Addington Public Health

Dr. Wendy Whittle  
Maternal Fetal Medicine Specialist  
Mount Sinai Hospital

## OIAC Ex-Officio Members

Tara Harris  
Manager  
Immunization and Emergency Preparedness  
Public Health Ontario

Robert Lerch  
Director (Acting)  
Health Protection and Surveillance Policy  
and Programs Branch  
Ministry of Health

Dr. Daniel Warshafsky  
Associate Chief Medical Officer of  
Health (Acting)  
Office of Chief Medical Officer of Health,  
Public Health  
Ministry of Health

Dr. Sarah Wilson  
Public Health Physician  
Public Health Ontario



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