

An Advisory Committee Statement (ACS) National Advisory Committee on Immunization (NACI)

NACI Rapid Response - Interim guidance on the use of Imvamune[®] in the context of monkeypox outbreaks in Canada

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contexte des écloisions de variole simienne au 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.

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BACKGROUND

Monkeypox virus is a member of the *Orthopoxvirus* genus, which also includes variola virus (smallpox virus), vaccinia virus, cowpox, and other poxviruses. Monkeypox viruses are zoonotic, therefore infection may occur in contexts where there is contact with wild species that are susceptible to monkeypox viruses. Human-to-human transmission of monkeypox virus also occurs amongst close contacts of people infected with monkeypox. Monkeypox is endemic in Central and West Africa, but there have been cases and outbreaks in non-endemic countries due to international travel or the importation of infected animals from affected areas. There are two distinct clades of monkeypox virus: the Congo Basin (Central African) clade and the West African clade. The Congo Basin clade has caused more severe illness.

Based on historical data, monkeypox has a typical incubation period of 6-13 days from exposure but can range from 5-21 days ⁽¹⁾. The disease is usually self-limiting and resolves within 14 to 28 days. Symptoms include fever, headache, back pain, myalgia, asthenia, lymphadenopathy and skin lesions/rash which typically tend to be more concentrated on the face, extremities, and oral mucous membranes, but can also appear in the genital area. Rash lesions begin as macules and further develop to papules, vesicles, pustules, and then form crusts. The duration of communicability for monkeypox virus may be up to 2-4 weeks, based on limited evidence of PCR detection of monkeypox in the upper respiratory tract ⁽²⁾. Potential complications of monkeypox include secondary bacterial infections, pneumonia, sepsis, encephalitis, and vision loss from corneal inflammation. Monkeypox virus may cause severe disease in young children, individuals who are immunocompromised ⁽³⁾, and those who are pregnant. Information about monkeypox in people who are pregnant is sparse but cases of first trimester miscarriage and stillbirths have been reported ⁽⁴⁾.

In the current 2022 multi-country outbreak, monkeypox cases may have an atypical presentation including oral, genital, and/or anal lesions with or without fever, or systemic symptoms. Person-to-person transmission can occur through direct contact with a person who is infected, including intimate sexual activity, or through shared contaminated objects. The potential for respiratory transmission is unknown at this time but may also be possible.

The 2022 multi-country monkeypox outbreak represents the first incidence of broader community transmission in a number of countries outside of certain regions of Africa. Initial detection in early May 2022 was a family cluster of three cases in the United Kingdom, with one case having recent travel history to an endemic region. On May 15, the World Health Organization (WHO) was notified of four additional confirmed cases, unlinked to travel, and this suggested more extensive community transmission of the virus. Since then, additional cases have been reported in the United Kingdom and internationally, including Canada. By June 7, at least 1,060 confirmed cases from 30 non-endemic countries and territories have been reported in official and media sources according to monitoring by the Global Public Health Intelligence Network (GPHIN). Ten countries have reported at least 10 confirmed cases (the United Kingdom [302], Spain [210], Portugal [166], Canada [81], Germany [80], France [51], the Netherlands [40], the United States [31], Italy [20], and Belgium [17]).

As of June 7, 81 cases of monkeypox had been confirmed in Canada (71 in Quebec, 8 in Ontario, 1 in Alberta, and 1 in British Columbia). According to open-source information, the Quebec cases are mainly men between 30-55 years of age, and they presented to Sexually Transmitted and Blood-Borne Infection clinics in the Montreal area. The infections were suspected to have been acquired in Montreal. Some of the individuals with infection reported links to travel in Belgium and Mexico.

Smallpox vaccines used during the global smallpox eradication programs may provide some protection against monkeypox⁽¹⁾. However, global smallpox vaccination programs ended in 1980 when smallpox was declared eradicated. Discontinuation of smallpox vaccination for travel was recommended by the WHO in 1980 and was no longer required by any country by 1982. Canadians born in 1972 or later have not been routinely immunized against smallpox (unless immunized for other purposes such as travel or work-related risks). For those who have been previously vaccinated for smallpox (i.e., eligible for vaccine in 1980 or earlier), the degree of protection conferred from the smallpox vaccine against monkeypox infection may be up to 85%⁽⁵⁾, however the durability of protection and the degree of protection against the current strain of monkeypox remains unknown.

OBJECTIVE

In the context of the rapidly evolving multi-country monkeypox outbreak, this rapid response was undertaken to provide guidance on the use of an *orthopoxvirus* (Imvamune[®]) vaccine with potential efficacy against monkeypox. Imvamune[®] is stockpiled within Canada's National Emergency Strategic Stockpile for the purposes of national security due to its potential efficacy against variola, the virus that causes smallpox. Due to the unique epidemiology and supply considerations, the planned task for this rapid response was to **consider the use of Imvamune[®] for post-exposure prophylaxis and to summarize the available evidence in support of Imvamune[®] use in this specific current context.**

Unrelated to the current monkeypox outbreak, NACI was also asked to consider **use of Imvamune[®] in laboratory research settings where replicating *orthopoxviruses* are studied.**

NACI and PHAC continue to monitor the evolving scientific data recognizing that the trajectory of the current monkeypox outbreak remains unclear, the situation is rapidly evolving and there may be additional considerations in the coming weeks.

METHODS

On May 26 and May 27, 2022, monkeypox data were discussed and reviewed by the NACI High Consequence Infectious Disease working group (HCID WG), along with input from the Public Health Ethics Consultative Group (PHECG), Canadian Immunization Committee (CIC) NACI's Vaccine Safety Working Group (VSWG) and two LGBTQ2S+ groups from Ontario and BC. The HCID WG reviewed data on the current status of the monkeypox outbreak, along with additional evidence included in published scientific literature and from the manufacturer, regarding the safety, immunogenicity and protection offered by Imvamune[®]. NACI approved these HCID WG recommendations on June 8, 2022.

VACCINE

Imvamune® (also called Modified Vaccinia Ankara-Bavarian Nordic (MVA-BN), Jynneos®, Imvanex®) is a non-replicating, third-generation smallpox vaccine manufactured by Bavarian Nordic. Imvamune® was initially authorized for use in Canada on November 21, 2013, as an Extraordinary Use New Drug Submission (EUNDS) for use by the Canadian Government in an emergency situation for active immunization against smallpox infection and disease in persons 18 years of age and older who have a contraindication to the first or second generation smallpox vaccines. It was subsequently approved under a supplement to the EUNDS on November 5, 2020 for active immunization against smallpox, monkeypox and related *Orthopoxvirus* infections and disease in adults 18 years of age and older determined to be at high risk for exposure ⁽⁶⁾.

Imvamune® contains trace amounts of host cell DNA and protein, benzonase, ciprofloxacin and gentamicin. No preservative or adjuvant is added to the formulation. The MVA virus is also being developed as a vector vaccine platform against other viruses, including tuberculosis, respiratory syncytial virus, Ebola virus and others.

Imvamune differs from previous generations of smallpox vaccines as it is a non-replicating vaccine virus in humans, meaning based on preclinical studies, it is not able to produce more copies of itself ⁽⁷⁾. While Imvamune is capable of replicating to high titers in avian cell lines such as chicken embryo fibroblasts, it is attenuated and has limited replication capability in human cells ⁽⁸⁾.

Preclinical data from previous generation smallpox vaccines showed decreased immune responses when tecovirimat (TPOXX, an antiviral drug from SIGA technologies) was administered concurrently with earlier generation smallpox vaccines ⁽⁹⁾. Due to the differences between previous generation smallpox vaccines and Imvamune®, it is unclear if antivirals could impact protection offered by Imvamune®.

Table 1. Use and overview of key features of IMVAMUNE® vaccine according to product monograph

Product brand name and formulation	IMVAMUNE® Smallpox and Monkeypox Vaccine
Type of vaccine	Modified Vaccinia Ankara-Bavarian Nordic® (live-attenuated, non-replicating)
Date of authorization in Canada	Date of Initial Approval: November 21, 2013 Date of authorization for Monkeypox as expanded indication: November 5, 2020 Date of latest Revision: November 26, 2021
Authorized ages for use	Adults 18 years of age and older
Authorized dose and schedule	Primary Series: Two doses of 0.5 mL (0.5 x 10 ⁸ Infectious Units), 28 days apart Booster dose (2 years after primary series): One dose of 0.5 mL (0.5 x 10 ⁸ Inf.U)

Product brand name and formulation	IMVAMUNE® Smallpox and Monkeypox Vaccine
Potential allergens	Traces of residual host (egg) cell DNA and protein ^a tromethamine ^b (trometamol, tris) benzonase ^c gentamicin and ciprofloxacin ^d
Adjuvant / Preservatives	The vaccine contains no adjuvant or preservatives
Contraindications	<ul style="list-style-type: none"> • Patients who are hypersensitive to this vaccine or to any ingredient in the formulation or component of the container. • Individuals who show hypersensitivity reactions after receiving the first dose of the vaccine should not be given the second dose. • As with other vaccines, vaccination with IMVAMUNE® must be postponed in persons with acute febrile conditions if used for non-emergency (pre-event) prophylaxis.
Storage	<ul style="list-style-type: none"> • Store frozen at -20°C ± 5°C or -50°C ± 10°C or -80°C ± 10°C. • After thawing, the vaccine should be used immediately or can be stored at 2°C – 8°C for up to 2 weeks prior to use. • Do not refreeze a vial once it has been thawed. • Protect from light.
Handling	<ul style="list-style-type: none"> • Thaw at room temperature. The drug product should appear as a pale milky colored homogeneous suspension. • The single-dose vial should be swirled gently (not shaken) for at least 30 seconds to ensure homogeneity upon thawing. • The vaccine must not be used if any foreign particulate matter are visible.
Reconstitution	No
Route of administration	0.5 mL subcutaneous injection, at any site
Syringe and needle selection	<ul style="list-style-type: none"> • Withdraw with a syringe and needle long enough to reach the bottom of the vial. • For injection, needle should be changed to a subcutaneous injection needle

^a In Canada, there are several vaccines manufactured by processes involving hens' eggs or their derivatives, such as chicken cell cultures

^b Tromethamine (trometamol, Tris) may very rarely cause allergic reactions and is found in some medications injected to do tests (contrast media) as well as other medications taken by mouth or injection, and some creams and lotions. Note that this is not a complete list.

^c Benzonase is used for purification of viral vaccines, viral vectors for vaccine, cell and gene therapy, and oncolytic viruses, removing DNA/RNA from proteins and other biologicals; reduction of viscosity caused by nucleic acids; sample preparation in electrophoresis and chromatography and prevention of cell clumping.

^d Gentamicin and ciprofloxacin are used as antibiotics in the treatment of some bacterial infections.

RECOMMENDATIONS

Please see [Table 2](#) for an explanation of strong versus discretionary NACI recommendations. Please see [Appendix A](#) which summarizes the clinical and preclinical data for Imvamune®.

For those without a contraindication to the vaccine:

1. NACI recommendation for the use of Imvamune® as Post-Exposure Prophylaxis (PEP) in adults:

NACI recommends that PEP using a single dose of the Imvamune® vaccine may be offered to individuals with high risk exposures* to a probable or confirmed case of monkeypox, or within a setting where transmission is happening. PEP should be offered as soon as possible and within 4 days of last exposure and can be considered up to 14 days since last exposure. PEP should not be offered to individuals who are symptomatic and who meet the definition of suspect, probable or confirmed case.

After 28 days, if an individual is assessed as having a predictable ongoing risk of exposure, a second dose may be offered. A second dose should not be offered to individuals who are symptomatic and therefore after medical evaluation meet suspect, probable or confirmed monkeypox case definitions.

For individuals who had received a live replicating 1st or 2nd generation smallpox vaccine in the past and who sustain a high risk exposure to a probable or confirmed case of monkeypox, a single dose of Imvamune® PEP may be offered (i.e., as a booster dose).

The benefit of protection against infection should be discussed with a healthcare provider and weighed against the potential risk of recurrent myocarditis for individuals with a history of myocarditis/pericarditis linked to a previous dose of live replicating 1st and 2nd generation smallpox vaccine and/or Imvamune®; a precautionary approach is warranted at this time until more information is available.

(Discretionary NACI Recommendation)

*High risk exposures: to be defined by the Public Health Agency of Canada.

Individuals with high-risk exposures to people infected with monkeypox may derive maximum benefit from PEP if offered very soon after such exposure. However some high-risk exposures may extend beyond 28 days. In situations where confirmed high risk exposures are multiple (i.e., beyond a single case) and expected to be ongoing over a period of weeks, PEP recipients may be offered a second dose 28 days after the first dose.

2. NACI recommendation for Pre-Exposure Prophylaxis (PrEP) for adults at high risk of occupational exposure in a laboratory research setting:

NACI recommends that Imvamune® PrEP may be offered to personnel working with replicating *orthopoxviruses* that pose a risk to human health (vaccinia or monkeypox) in laboratory settings and who are at high risk of occupational exposure. If Imvamune is used, two doses should be given at least 28 days apart. A booster dose may be offered after 2 years if the risk of exposure extends beyond that time. This recommendation does not

apply to clinical diagnostic laboratory settings at this time, due to very low risk of transmission.

For immunocompetent individuals who have received a live replicating 1st or 2nd generation smallpox vaccine in the past and who are at high risk for occupational exposure, a single dose of Imvamune® may be offered (i.e., as a booster dose), rather than the two dose primary vaccine series). This single Imvamune® dose should be given at least two years after the latest live replicating smallpox vaccine dose.

In consultation with a physician, the benefit of protection against infection should be weighed against the risk of recurrent myocarditis for individuals with a history of myocarditis/pericarditis linked to a previous dose of live replicating 1st and 2nd generation smallpox vaccine and/or Imvamune®; a precautionary approach is warranted at this time until more information is available.

(Discretionary NACI Recommendation)

Laboratory workers may be at heightened risk for of occupational exposure to replicating *orthopoxviruses* when working in a research laboratory context. *Orthopoxviruses* that pose a risk to human health include vaccinia and monkeypox. Variola virus (the causative agent of smallpox) was declared eradicated in 1980. Laboratory workers handling *orthopoxviruses* that do not put human health at risk, including those that cause disease only in animals or *orthopoxviruses* that are unable to replicate (including Modified Vaccinia Ankara) should not be offered PrEP. In addition, laboratory workers who work outside of a research laboratory setting, including diagnostic laboratory or specimen transport workers, and people working in clinical health care settings should not be offered PrEP.

3. NACI recommendation for Special Populations:

NACI recommends that Imvamune® vaccine may be offered to the following populations, if recommended to receive vaccine based on exposure risk:

- Individuals who are immunocompromised due to disease or treatment
- Individuals who are pregnant
- Individuals who are lactating
- Children and youth <18 years of age
- Individuals with atopic dermatitis

(Discretionary NACI Recommendation)

Immunocompromised populations (including people living with HIV) may particularly benefit from vaccination as these populations may be at risk for more severe outcomes if infected depending on the nature and degree of the immunosuppression. Although data on the use of Imvamune® in immunocompromised populations are limited, Imvamune® has been tested clinically in people living with HIV (CD4 ≥100 cells/μL) and hematopoietic stem transplant patients (studied two years post-HSCT) and safety was comparable to healthy controls in these populations. There are limited data overall on VE/immunogenicity or safety in immunocompromised populations, but immunosuppression increases risk of negative outcomes due to infection. Live vaccines are usually contraindicated for immunocompromised populations; however, Imvamune® may be safely used in this group as it is considered a non-replicating vaccine ⁽⁸⁾. When using

Imvamune® as PrEP in immunocompromised individuals, 2 doses are recommended regardless of previous smallpox vaccine history.

If at risk for infection, pregnant populations may particularly benefit from vaccination as these populations may be at risk for severe outcomes from disease. Imvamune® has never been tested in persons who are pregnant. Though limited, safety and toxicity studies have identified no concerning safety signals. There is a lack of evidence of safety and efficacy of Imvamune® PEP or PrEP in this group, though at this time there is no reason to believe that vaccination would have any adverse impact on the person who is pregnant or the fetus. Live vaccines are usually contraindicated for pregnant populations; however, Imvamune® may be used in this group as it is considered a non-replicating vaccine. The risks due to monkeypox infection should be weighed against the lack of evidence of vaccine safety.

Lactating populations are not at higher risk for negative outcomes due to monkeypox infection. There are no Imvamune® studies in this population. There is a lack of evidence of safety and efficacy of Imvamune® PEP or PrEP in this group, though at this time there is no reason to believe that vaccination would have any adverse impact on the person who is lactating or the child. There is no information on excretion of vaccine components or antigens into breastmilk; however, this is unlikely as Imvamune® is a non-replicating vaccine.

Although Imvamune® is not authorized for children, this population may be at higher risk of severe outcomes from monkeypox infection and may benefit from vaccination. Indirect evidence of clinical testing of the MVA vector as a viral vector vaccine platform for other vaccines in development, including for RSV, TB and Ebola, indicates that out of almost 2000 vaccine recipients, Imvamune® components are well tolerated in recipients under 18 years of age. There is a lack of evidence of safety and efficacy of Imvamune® PEP or PrEP in this group.

People with atopic dermatitis were a risk group with severe adverse outcomes for earlier generations of smallpox vaccines. From limited clinical testing of Imvamune®, solicited AEs were more frequent in this group including transient worsening of atopic dermatitis symptoms. Historically, previous generations of *orthopoxvirus* vaccines carried a risk of diffuse vaccinia virus infection for individuals with atopic dermatitis. The Imvamune® vaccine was developed to overcome those adverse effects through the use of a non-replicating virus.

4. NACI recommendation for concurrent administration:

Imvamune® given as PEP or PrEP should not be delayed due to recent receipt of an mRNA COVID-19 vaccine. If vaccine timing can be planned (i.e., prior to employment within a research laboratory), NACI recommends that Imvamune® be given at least 4 weeks after or before an mRNA vaccine for COVID-19 .

First generation *orthopoxvirus* vaccines and mRNA COVID-19 vaccines both have a potential risk of cardiac adverse events (myocarditis). Risk for myo- or pericarditis with the newer generation non-replicating attenuated virus vaccine Imvamune® is still unknown. . It would be prudent to wait for a period of at least 4 weeks **before** or **after** the administration of mRNA COVID-19 vaccine in order to prevent erroneous attribution of an AEFI to one particular vaccine or the other. This suggested minimum waiting period between vaccines is **precautionary** at this time. Protection from monkeypox exposure should be prioritized and recent mRNA vaccine receipt should not delay Imvamune® PEP or PrEP if protection is urgent.

Summary of Evidence and Considerations for the Vaccine:

- There continue to be many unknowns about the outbreak of monkeypox virus, including symptoms, modes of transmission and groups at high risk for severe outcomes.
- There is very limited evidence available upon which to base guidance for Imvamune® use for pre- or post-exposure recommendations in any population.
- Data on the pre-exposure use of vaccine are limited to clinical trial settings where data for safety, immunogenicity and efficacy against vaccinia are available.
 - Safety data from clinical testing do not identify any safety signals of concern; however, these data are limited and not predictive of very rare events occurring at a rate below 1/ 10 000.
 - Data for cardiac adverse events of special interest are available from limited clinical testing.
 - Limited immunological data are available to inform the durability of immune responses and the ability for Imvamune® to boost previous anti-*orthopoxvirus* immune responses.
- Data to inform post-exposure use of vaccine are limited to indirect evidence either from preclinical studies in animal models or from smallpox vaccination in the pre-eradication era.
- Data for populations either at risk for more severe outcomes due to monkeypox infection, or who may be at higher risk for adverse events due to vaccination, are even more limited.
 - Small clinical trials of Imvamune® in people living with HIV and in people with atopic dermatitis offer limited safety and immunogenicity data.
 - Imvamune® has never been tested in children (<18y), people who are pregnant or people who are lactating. Limited indirect data for these groups have been used to make recommendations.
- Informed consent when administering Imvamune® PEP or PrEP should include a discussion of the limited data available on monkeypox infection and disease as well as limited data available for the safety and efficacy of Imvamune®.
- NACI continues to monitor and assess the evidence as it emerges and will update its recommendations as needed.

ADDITIONAL INFORMATION

NACI continues to endeavour to make ethical, equitable and evidence-informed recommendations. Given the paucity of data on benefits and risks of Imvamune® in the context of a monkeypox outbreak setting, the use of Imvamune® must balance the benefits and risks of what is known and unknown about the vaccine and the disease.

It is important to obtain informed consent when offering the vaccine, and to clearly explain to potential recipients what is unknown (in addition to what is known) about the vaccine, when discussing potential risks and benefits. This is particularly important for individuals identified by NACI as special populations and for any off-label use in individuals <18 years of age.

Additionally, there is an ethical obligation to conduct close monitoring and surveillance of the use of the vaccine, in order to collect information to inform the response going forward. Both informed consent and post-market safety surveillance will be vital for the ethical implementation of an Imvamune® vaccination program, especially in pediatric populations <18 years of age when the vaccine is being used off-label.

It will be important to closely monitor who is at risk of monkeypox and provide rationale for when vaccination is needed. Additionally, to prevent stigmatization of specific populations and potentially increase vaccine acceptability, the primary focus should be identifying risk factors for transmission of monkeypox (e.g., proximity of contact, sexual activities, specific behaviours) whenever possible, rather than identifying populations perceived to be at a higher risk.

Given the limited clinical evidence on the use of Imvamune® for monkeypox PEP or PrEP, understanding of the need for, and benefit of Imvamune® in the context of a monkeypox outbreak setting is evolving.

Certain behaviours place individuals at increased risk of exposure to the monkeypox virus (e.g., proximity of contact, sexual activities, household member or behaviours that cause exposure to body fluids or fomites). Some populations are at increased risk of severe monkeypox disease due to various biological factors (e.g. individuals who are immunocompromised, pregnant, and/or, young children) and social factors that may intersect. Risk factors of severe disease and risk of exposure may overlap, further increasing risk. Any combination of these factors, as well as varying access to health care services, has the potential for disproportionate consequences for specific populations characterized by increased rates of infection, disease, and severe illness. Program planning should ensure equitable access to vaccination information and services and minimize differences in vaccine acceptance and uptake based on socioeconomic status and other socioeconomic determinants of health that may intersect.

RESEARCH PRIORITIES

1. Further study of the protection offered by Imvamune[®] vaccine against monkeypox infection and disease (in PrEP and PEP scenarios), including:
 - a. Understanding which immune responses are protective against infection and disease and defining protective thresholds
 - b. Understanding how the impact of previous orthopox infection or vaccination impacts the protection offered by Imvamune[®]
 - c. Real-world evidence on the vaccine effectiveness of Imvamune against monkeypox and for the use of single dose PrEP and PEP.
2. Further studies to further inform on the safety of Imvamune[®] vaccine including both clinical trials and post-market safety surveillance.
3. Safety in special populations, including people who are pregnant or breastfeeding, children <18 years of age, and people who are immunocompromised should also be assessed by targeted clinical trials.
4. Further study into the epidemiology of the disease to better understand the modes of transmission, the disease presentation, and to identify the populations at highest risk for severe disease in order to inform and optimize disease prevention strategies.

Table 2. Strength of NACI Recommendations

Strength of NACI Recommendation <i>based on factors not isolated to strength of evidence (e.g., public health need)</i>	STRONG	DISCRETIONARY
Wording	<i>“should/should not be offered”</i>	<i>“may/may not be offered”</i>
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.

ABBREVIATIONS

AD	Atopic dermatitis
AEs	Adverse events
AEFI	Adverse events following immunization
AIDS	Acquired immunodeficiency syndrome
BC	British Columbia
CIC	Canadian Immunization Committee
DART	Developmental and Reproductive Toxicology
EUNDS	Extraordinary Use New Drug Submission
EV	Eczema vaccinatum
HCID WG	High Consequence Infectious Disease working group
HIV	Human immunodeficiency virus
HSCT	Haematopoietic stem cell transplantation
GPHIN	Global Public Health Intelligence
LGBTQ2S+	Lesbian, Gay, Bisexual, Transgender, Queer or Questioning, and Two-Spirit
MVA-BN	Modified Vaccinia Ankara-Bavarian Nordic
NACI	National Advisory Committee on Immunization
PHAC	Public Health Agency of Canada
PCR	Polymerase chain reaction
PEP	Post-Exposure Prophylaxis
PHECG	Public Health Ethics Consultative Groups
PrEP	Pre-Exposure Prophylaxis
RSV	Respiratory Syncytial Virus
TB	Tuberculosis
US	United States
UK	United Kingdom
VE	Vaccine effectiveness
VSWG	Vaccine Safety Working Group
WHO	World Health Organization

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APPENDIX A: CLINICAL AND PRECLINICAL DATA ON IMVAMUNE®

Data for Pre-Exposure Prophylaxis (PrEP)

Safety Data for Imvamune®

The safety of Imvamune was assessed in the limited context of clinical trials and Imvamune® has not been administered at the scale needed to predict low frequency adverse effects. In the limited safety assessments that have been done, no signals of concern for Imvamune® have been identified.

- Imvamune®'s safety has been assessed in 20 completed clinical trials where approximately 13,700 vaccine doses were given to 7,414 subjects⁽¹⁰⁾. The most common local adverse events following immunization (AEFI) were pain, erythema, induration and swelling. The most common systemic AEFI were fatigue, headache, myalgia, and nausea. Most of the reported AEFIs were of mild to moderate intensity and resolved within the first seven days following vaccination.
- Cardiac adverse events of special interest were reported to occur in 1.4% (91/6,640) of Imvamune® recipients, 0.2% (3/1,206) of placebo recipients who were smallpox vaccine-naïve and 2.1% (16/762) of Imvamune® recipients who were smallpox vaccine-experienced. Age was likely not adjusted for between vaccinated groups. Among the cardiac AEFIs reported, 28 were asymptomatic post-vaccination elevation of troponin-I, 6 cases were considered to be causally related to Imvamune® vaccination and included tachycardia, electrocardiogram T wave inversion, abnormal electrocardiogram, electrocardiogram ST segment elevation, abnormal electrocardiogram T wave, and palpitations. **None of the 6 events considered vaccine-related were considered serious.** Despite close cardiac monitoring, no confirmed case of myocarditis, pericarditis, endocarditis or any other type of cardiac inflammatory disease (or related syndromes) was recorded.

Clinical Immunogenicity and Indirect Evidence of Protection by Imvamune®

There are no data indicating the efficacy or effectiveness of Imvamune® vaccination against monkeypox infection or disease in the context of PrEP or PEP. Clinical data for Imvamune® PrEP are limited to clinical immunogenicity or indirect protection from vaccinia (the virus used for 1st or 2nd generation smallpox vaccines). There is no established threshold above which immune responses to any *orthopoxviruses* are considered protective therefore the interpretation of the decline or boosting of immune responses remains unclear. Clinical protection from symptoms of vaccinia infection may not be indicative of protection against monkeypox.

- In a Phase 3⁽¹¹⁾ randomized, open-label active-controlled non-inferiority trial, 440 smallpox vaccine naïve adults were randomly assigned to receive 2 doses of Imvamune® 4 weeks apart followed by one dose of the second generation replicating smallpox vaccine (to

observe for effect of Imvamune® on vaccinia vaccine cutaneous reaction) or one dose of the second generation replicating smallpox vaccine alone.

- Imvamune® immune responses (binding and neutralization) were detectable by week 2. At week 6 after dose 2, immune responses peaked at or beyond responses to 1-dose of previous generation, replicating vaccine.
- At the time of peak titres, all participants in the Imvamune® group had seroconverted and 97.3% of participants in the previous generation group had seroconverted. At time points when previous generation has historically been considered to be protective (weeks 2 and 4), seroconversion rates were similar between both groups.
- Previous vaccination with Imvamune® prevented the formation of a full major cutaneous reaction in the majority of participants (77.0%) after vaccinia vaccination/infection at week 8 in the MVA group, as compared with a rate of full major cutaneous reaction of 92.5% in the vaccinia-only group. The maximum lesion area of the major cutaneous reaction was significantly reduced (by 97.9%) when vaccinia vaccination was preceded by Imvamune® vaccination.
- In Phase 2 clinical testing ^(12, 13), immune responses after one or two doses of Imvamune® declined after 2 years. One or two doses of Imvamune® were able to boost previously generated immune responses within 7 days to the level of those achieved after the 2 dose primary series.
- Small studies have demonstrated that Imvamune® is able to boost pre-existing immunological memory from previous *orthopoxvirus* vaccines.
 - A small study of 18 participants who received previous generation, replicating smallpox vaccines showed that at baseline, 22% of previous vaccinees had detectable immune responses to orthopox antigens and by day 28 after Imvamune® vaccination, 100% of previous vaccinees had seroconverted ⁽¹⁴⁾.
 - Another study included 200 vaccinia-experienced subjects. By day 14 following a single dose of Imvamune® 95.5% seroconverted ⁽¹⁵⁾.
 - In additional study vaccinia-experienced subjects received either 1 (n=58) or 2 doses (n=62) of Imvamune®. Seroconversion rates in neutralizing antibody titers two weeks following the final dose were 77.6% and 90.0%, respectively ⁽¹⁶⁾.

Preclinical Immunogenicity and Efficacy Data for Imvamune®

Given the limited clinical data available to demonstrate Imvamune® efficacy and effectiveness against monkeypox infection and disease, insight may be gained from preclinical data for MVA-BN (the non-replicating virus in Imvamune® vaccines). Immune responses and protection from disease outcomes have been demonstrated across different animal models however it remains unclear the degree to which preclinical results will predict outcomes in humans.

- In murine models, a single pre-exposure dose of MVA-BN induced a comparable immune response (antibody levels and T cell response) and survival to a lethal challenge with vaccinia and mousepox as vaccination with previous generation replicating smallpox vaccines. This was observed both with immunocompetent as well as immunosuppressed animals ⁽¹⁷⁻²⁰⁾.
- In non-human primate models, the efficacy of MVA-BN was tested in comparison against lethal monkeypox challenge. Across all studies, 80-100% of MVA-BN-vaccinated animals survived compared to 0-40% of control animals ⁽²¹⁻²³⁾.

- Animal testing was also conducted on black-tailed prairie dogs. Vaccination with Imvamune® protected the animals from death and modified the severity of rash illness ⁽²³⁾.

Data for Post-Exposure Prophylaxis (PEP)

Safety Data for Imvamune®

There are no safety data available to demonstrate the safety of Imvamune® in the context of PEP. However, the safety of Imvamune® in a PEP context can be inferred from studies in a PrEP context. It is unclear how previous *orthopoxvirus* exposure could affect Imvamune® safety.

Clinical Immunogenicity and Indirect Evidence of Protection by Imvamune®

There are no data indicating the efficacy or effectiveness of Imvamune® vaccination against monkeypox infection or disease in the context of PrEP or PEP. Clinical data for Imvamune® PEP can be inferred from clinical pre-exposure testing where immunological responses were detected within 2 weeks of vaccination ⁽²⁴⁾. Timing of PEP could be inferred from studies of early generation smallpox vaccines; however, it is unknown how these smallpox studies directly relate to protection from monkeypox by Imvamune®.

- From historical study of previous generation smallpox vaccines, the median effectiveness in preventing smallpox disease with vaccination at 0–6 h, 6–24 h, and 1–3 days after exposure was estimated as 93%, 90%, and 80%, respectively, and effectiveness in modifying disease among those who develop illness was estimated as 80%, 80%, and 75%, respectively ⁽²⁵⁾.

Preclinical Immunogenicity and Efficacy Data for Imvamune®

Given the limited clinical data available to demonstrate Imvamune® efficacy and effectiveness against monkeypox infection and disease, insight may be gained from preclinical data for MVA-BN (the non-replicating virus in Imvamune® vaccines). Immune responses and protection from disease outcomes have been demonstrated across different animal models however it remains unclear the degree to which preclinical results will predict outcomes in humans.

- In murine models, a single post-exposure dose of MVA-BN induced a comparable immune response (antibody levels and T cell response) and survival to a lethal challenge with vaccinia and mousepox as vaccination with replicating smallpox vaccines. This was observed both with immunocompetent as well as immunosuppressed animals ^(26, 27).
- After a lethal dose of monkeypox in prairie dogs, vaccination with MVA-BN one day after exposure conferred a survival rate of 80% compared to 25% for unvaccinated animals ⁽²⁸⁾. Vaccination three days after exposure conferred a survival rate of 38% with MVA-BN.

Imvamune in Special Populations

Data are even more limited for populations either at risk for more severe outcomes due to monkeypox infection, or who may be at higher risk for adverse events due to vaccination. Small clinical trials of Imvamune® in people infected with HIV and in people with atopic dermatitis offer limited safety and immunogenicity data. Imvamune® has never been tested in children (<18y), people who are pregnant or people who are lactating, though limited data may be available from testing the MVA vaccine platform for other viruses. Limited indirect data for these groups have been used to make recommendations.

Immunocompromised individuals:

- Immunocompromised individuals, including those receiving immunosuppressive therapy, are a very heterogeneous population some of whom may respond differently to vaccines and thus require unique considerations regarding immunization
- The use of Imvamune® in immunocompromised patients is supported by clinical trials which include more than 690 individuals living with human immunodeficiency virus (HIV) (CD4 ≥ 100 cells/μL).
 - Phase 2 non-randomized trial POX-MVA-011 included 482 individuals living with HIV (CD4+ count 200–750 cells/μL) in the US ⁽²⁹⁾.
 - Phase 1/2 non-randomized trial POX-MVA-010 included 91 individuals living with HIV (CD4+ count ≥350 cells/mm³) in the US ⁽³⁰⁾.
- Compared to people without HIV, individuals with HIV may have lower immune responses to one dose of Imvamune® and may have decreased durability of immune responses ⁽³⁸⁾.
 - However, one paper explored a 3-dose schedules and double standard dose in a small number of subjects. Phase 2 randomized trial POX-MVA-037 included 87 individuals with a history of AIDS (had a documented CD4 cell nadir of <200 cells/μL any time prior to screening) in the US ⁽³¹⁾.
- Imvamune® was well tolerated in 20 individuals who received hematopoietic stem cell transplant at least two years prior to study enrollment and were not exposed to immunosuppressive medication for at least 30 days prior to enrollment, with no serious adverse events. Self-limited local discomfort was the most frequent reactogenicity ⁽³²⁾.
- The safety profile of Imvamune® in individuals who are immunocompromised has been shown to be comparable to that recorded for healthy individuals. There were no instances of progressive vaccinia ⁽³⁰⁾.

Pregnant and lactating people:

- The safety and efficacy of Imvamune® has not been formally evaluated in pregnancy, and there are limited data on the use of Imvamune® in pregnancy. During the clinical trial program, 29 pregnancies were reported and no safety signals were identified. No congenital abnormalities were observed and complication rates were in line with expected background rates ⁽⁸⁾.
- Developmental and Reproductive Toxicology (DART) studies in rats and rabbits indicated no evidence of vaccine-related fetal malformations or variations, and no adverse effects on female fertility or pre-weaning development ^(6, 33, 34).
- Data on Imvamune® in people who are pregnant or lactating is very limited, however, at least one other vaccine using MVA as a vector is being tested in people who are pregnant:
 - A Phase 3 Ebola vaccine trial of 2853 in pregnant women to assess the safety, reactogenicity and immunogenicity of a 2-dose regimen: an adenovirus-based viral

vector vaccine followed by MVA-Filo vaccine. No data are yet available for this study⁽³⁵⁾.

Children (< 18 years old):

- Although Imvamune® is not licensed in, and has not been studied in children, several paediatric studies of other vaccines using MVA as a vector (often at a considerably higher dose than used in Imvamune®) have been undertaken with a reassuring side effect profile.
 - A Phase 3 Ebola vaccine trial of an MVA-based vaccine containing antigens from the Ebola virus (MVA-BN-Filo) included children (age 1-17 years) from Sierra Leone. In total, 432 children received the active product MVA-BN-Filo 1x10⁸ InfU. This is double the MVA dose compared to the Imvamune® product monograph.
 - The most frequent solicited local AE was injection site pain in all age groups. The percentage of participants with at least one solicited systemic event was 4.9-15.4% after MVA-BN-Filo, 4.2-10.4% after MenACWY and 0-10.4% after placebo.
 - The most frequent solicited systemic AEs in children 4-17 years were headache, fatigue and chills, while in children 1-3 years of age, they were decreased appetite, decreased activity and pyrexia.
 - The percentage of participants with at least one solicited systemic event was 16.1-18.9% after MVA-BN-Filo, 25-31% after MenACWY comparator and 13-29% after placebo⁽³⁶⁾.
 - A Phase 2 measles vaccine (MVA-mBN85B) partially randomized, controlled trial included 90 healthy children aged 6 months to 6 years in South Africa. The three treatment arms were: half-dose compared to Imvamune®, double dose compared to Imvamune® versus Rouvax control^(37, 38).
 - There were no serious adverse events. The incidence was low for Grade 3 solicited local AEs (after 1st vaccination: 13.3% and 46.7%, for Low dose and Normal dose, respectively; after 2nd vaccination: 11.1% and 21.4%, respectively) and general AEs (after 1st vaccination: 13.3% and 10%, respectively; after 2nd vaccination: 7.4% and 3.6%, respectively).
 - Local reactogenicity with the Normal dose was higher than with the Lower dose, suggesting dose-effect.

Individuals with atopic dermatitis:

- Evidence on the safety and immunogenicity of Imvamune® in individuals with atopic dermatitis (AD) or eczema is available from Phase 1⁽³⁹⁾ and Phase 2⁽⁴⁰⁾ clinical trials. Overall, Imvamune® is well tolerated in individuals with AD, though individuals with AD may experience a higher frequency of local and systemic reactogenicity compared to those without AD.
 - In a Phase 2 study in adults receiving 2 doses of Imvamune® 4 weeks apart, solicited AEs (erythema, swelling, and systemic AEs) were more frequent in participants with AD compared to those without AD (61.2% vs 49.3%, 52.2% vs 40.8%, and 70.1% vs 56.4%, respectively), with the difference mostly due to events of mild to moderate severity.
 - In a Phase 1 study in adults receiving 2 doses of Imvamune® 4 weeks apart, 7% of participants with active AD or a history of AD experienced a transient worsening of AD symptoms, but there was no indication or trend that could be detected that indicated that vaccination worsened the intensity of AD.
 - No deaths, cases of eczema vaccinatum (EV) or myopericarditis were observed.

- Immune responses (binding antibodies, neutralizing antibodies, seroconversion rates and CD8 T cell responses) were comparable between individuals with and without AD.

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