An Advisory Committee Statement (ACS)

National Advisory Committee on Immunization (NACI)

NACI Rapid Response: Updated interim guidance on Imvamune® in the context of ongoing monkeypox outbreaks

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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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I. BACKGROUND

On June 10, 2022, in the context of the rapidly evolving monkeypox outbreak, NACI provided options for the use of the Imvamune® vaccine (Modified vaccinia Ankara-Bavarian Nordic [MVA-BN]) for post-exposure vaccination against monkeypox [(1)]. NACI recommended that a single dose of the Imvamune® vaccine may be offered to people with high-risk exposures to a probable or confirmed case of monkeypox, or within a setting where transmission is happening. A second dose may be offered after 28 days if an assessment indicates an ongoing risk of exposure. Since NACI issued guidance in early June, the monkeypox pandemic has remained ongoing across numerous Canadian jurisdictions [(2)].

As of September 16, 2022, nine Canadian provinces and territories have publicly reported 1,363 cases of monkeypox [(3)]. Over 95% of confirmed cases with available information self-identified as gay, bisexual, and other men who have sex with men (gbMSM), and 52% as living with human immunodeficiency virus (HIV). In response to the outbreak, PHAC has distributed over 110,000 doses of Imvamune® vaccine to provinces and territories, and over 70,000 people have been vaccinated with at least one dose as of August 28th [(3)].

Canadian jurisdictions experiencing ongoing monkeypox outbreaks have built on the foundation of NACI guidance on the use of Imvamune®. Specifically, jurisdictions with active monkeypox outbreaks have expanded eligibility for Imvamune® vaccine administration beyond post-exposure use based on the limited feasibility of case and contact identification. All jurisdictions have shown flexibility in the approach, responding to the reality of the outbreak in their jurisdiction, and leveraging strong partnerships with gbMSM communities to implement their vaccine programs.

In consideration of ongoing community transmission and restricted vaccine supply, Canadian provinces and territories and a number of vaccine stakeholders have indicated the need for national guidance on pre-exposure vaccination, including identification of priority populations for pre-exposure vaccination programs and guidance on the potential use of dose-sparing strategies (i.e., extended dosing intervals and/or fractional intradermal dosing). This follows recent implementation of intradermal (ID) dose-fractioning schedules for Imvamune® (Jynneos®) in the US [(4)] (and Europe [(5)]).

While individuals self-identifying as gbMSM who engage in activities associated with higher risk (e.g., multiple and/or anonymous sexual contacts) remain at the highest risk of exposure to monkeypox, there is theoretical concern that other groups may also be at increased risk of disease exposure (such as sex workers independent of biological sex and gender, and people exposed to infectious material such as staff or volunteers in settings where monkeypox may be circulating). In addition to those at increased risk of exposure, other population groups may be at increased risk of disease severity following

infection and could theoretically benefit from changes to currently-recommended vaccine guidance.

OBJECTIVE

In the context of the evolving multi-country monkeypox outbreak, this rapid response was undertaken to provide additional guidance on the use of the Imvamune® vaccine as pre-exposure vaccination, including the definition of priority populations for pre-exposure vaccination programs, and the relevance of dose-sparing strategies (i.e., extended dosing intervals and fractional dosing).

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 months.

DEFINITIONS

MSM: Man or Two-Spirit identifying individual who has sex with another person who identifies as a man, including but not limited to individuals who self-identify as trans-gender, cis-gender, Two-Spirit, gender-queer, intersex, and non-binary and who also identify as gay, bisexual, or pansexual.

Pre-exposure vaccination: Vaccine dose(s) administered prior to any potential exposure to monkeypox; also sometimes referred to as pre-exposure immunization or prophylaxis.

Post-exposure vaccination: Vaccine dose(s) administered shortly following a known exposure to monkeypox, or a setting where transmission is happening; also sometimes referred to as post-exposure prophylaxis.

II. METHODS

On August 22, 2022 the NACI High Consequence Infectious Disease working group (HCID WG) convened to discuss and review data on the evolving monkeypox outbreak. Input was provided by the Public Health Ethics Consultative Group, Canadian Immunization Committee (CIC), NACI's Vaccine Safety Working Group, and the National Emergency Strategic Stockpile (NESS). That same date, Montreal Public Health and Ontario Ministry of Health presented emerging evidence on the ongoing monkeypox outbreaks, including epidemiological trends and Imvamune® vaccine programs to the HCID WG. The communities and groups considered at higher risk of monkeypox exposure were identified after considering current and projected epidemiology. Three groups representing 2SLGBTQI+ communities and one group representing sex workers were consulted to provide stakeholder input on the acceptability of vaccine strategies. The HCID WG reviewed data on the current status of the monkeypox outbreak in Canada and globally, along with additional evidence included in published scientific literature and from the manufacturer, regarding the safety, immunogenicity and

protection offered by Imvamune®. Modelling information on the impact of dose sparing strategies when vaccine supply is limited was also reviewed. NACI approved these HCID WG recommendations on September 16, 2022.

III. EVIDENCE SUMMARY

IV.1 Burden of disease

Since the beginning of 2022 and as of September 5, 59,996 confirmed cases of monkeypox and 18 deaths from monkeypox infection have been reported to the World Health Organization (WHO) from 102 Member States across all 6 WHO regions [6]. Since May 2022, a high proportion of cases have been reported from countries without previously documented monkeypox transmission, including Canada. Due to an unexpectedly large number of cases and continuing transmission, as well as the potential impact of disease spread in affected countries and internationally, the WHO declared the ongoing monkeypox outbreak a Public Health Emergency of International Concern on July 23, 2022 [7].

The current international outbreak continues to primarily affect men who identify as gbMSM and who have reported recent sex with one or multiple partners [8]. The majority of the individuals self-identifying as gbMSM who are diagnosed with monkeypox have reported no contact with a person known to have a confirmed monkeypox infection [9-11]. The severity of disease of the current outbreak has generally been low, with fewer reported hospitalizations, intensive care unit (ICU) admissions, and deaths (case fatality rate of <0.1%) compared to historical outbreaks [11-14]. The majority of hospital admissions have been for pain management or management of disease complications [9, 11, 14, 15]. However, monkeypox infection has additional impacts including risk of functional impairment due to severe pain related to lesions (e.g., difficulties swallowing, urinating and defecating) or scarring, as well as socio-economic impacts (e.g., loss of income/social interaction when isolating).

As of September 14, 2022, 91 cases of monkeypox have been reported among healthcare workers globally in non-endemic countries in 2022, where only three of these cases were reported to have had occupational exposure [16]. In the cases with occupational exposure, the individuals were deemed to have been exposed while collecting diagnostic samples. While actively monitored, no cases among healthcare workers in Canada due to occupational exposure have been reported.

The clinical presentation in the current outbreak differs from the historical symptoms described for monkeypox, with fewer cases experiencing prodromal systemic symptoms and more experiencing genital rashes without spread to other parts of the body [12, 13, 17]. Systemic symptoms, previously described as prodromal, have also occurred concurrently or after the initial appearance of rash. The most frequently reported symptoms include rash (75%), fever (61%), and lymphadenopathy (18%) [8]. Other less

commonly reported atypical clinical presentations include penile edema, secondary bacterial infection, rectal perforation, solitary lesion, and polymorphic lesions [9]. Asymptomatic infections have been described [18, 19], but there is currently no clear evidence of asymptomatic transmission. At least 25% of cases have been reported to have a concomitant sexually transmitted infection [9, 13, 20-22].

As of September 16, 2022, nine Canadian provinces and territories have publicly reported 1,363 cases of monkeypox [3], with outbreak characteristics that have been similar to those observed internationally. Over 95% of confirmed cases have been in men 18-44 years of age who self-identify as gbMSM and as having multiple and/or new sex partners. Among those with known HIV status, 52% reported living with HIV. As of September 7, 2022, there have been 35 monkeypox associated hospitalizations, including three ICU admissions, with no reported deaths in Canada [23].

The monkeypox viruses circulating in Europe, US and Canada are predominantly subvariants of the B.1 strain of Clade II (former West African Clade) [24, 25]. A recent case series from India reported two cases of the A.2 strain of Clade II among travellers from the United Arab Emirates [25]. The A.2 strain is similar to the strain associated with monkeypox cases detected in the United States in 2021 [25], however this strain has not been linked to major clusters [26]. There is currently no evidence to suggest whether either strain is more infectious or virulent.

IV.2 Emerging evidence on safety and effectiveness of Imvamune® in the context of ongoing monkeypox outbreaks

Post-market surveillance data on Imvamune®

Available post-marketing data on Imvamune® safety is limited, but suggests that the vaccine is well tolerated. An observational study from France (preprint article) reported that the first dose of Imvamune® administered as post-exposure vaccination (n=276; median age 19 years [interquartile range, 14-25]) was well tolerated with no severe adverse events reported [27]. Approximately half reported local pain and 15% reported fatigue (median duration of 4 days); no fever or other systemic symptoms were described. In the United Kingdom, following the identification of a Monkeypox imported case in 2019, 17 contacts received Imvamune® as post-exposure vaccination, which included infants and young children, with no known adverse events [28]. In Canada, the majority of adverse events following immunization reported to the passive surveillance system were non-serious and primarily include injection site reactions and fatigue [29].

Efficacy and Effectiveness of Imvamune® in the context of a monkeypox outbreak

There is currently no evidence on the efficacy of a two-dose primary series of Imvamune® (given as either pre- or post-exposure vaccination) against monkeypox

infection, transmission or severe disease. However, emerging evidence suggests individuals vaccinated with 1 dose of Imvamune® and who remain at high risk of exposure following vaccination may be at risk of infection post-vaccination [27, 30].

Please see the Appendix A for a summary of evidence on the safety, immunogenicity and effectiveness of MVA-BN when administered off-label using fractional doses or delayed second doses.

For additional information on the safety, immunogenicity, and efficacy of Imvamune® and related MVA vaccines, please see the June 10, 2022 NACI Rapid Response: Interim guidance on the use of Imvamune® in the context of monkeypox outbreaks in Canada.

IV. RECOMMENDATIONS

Following the review of available evidence summarized above, NACI makes the following recommendations for public health level and individual level decision-making.

Please see Table 1 for a more detailed explanation of the strength of NACI recommendations and grade of the body of evidence.

NACI is carefully monitoring the evolving epidemiology, including potential identification of additional risk factors for monkeypox, as well as the scientific developments related to the safety, effectiveness, and duration of protection of Imvamune®. As the current outbreak evolves and new risk factors or groups at higher risk are identified, the criteria for those who should be vaccinated may change.

Recommendations

Pre-exposure vaccination

1.1. In the context of an active monkeypox outbreak, NACI recommends that immunization using the Imvamune® vaccine should be offered to individuals with highest risk of monkeypox. After considering current and projected outbreak epidemiology, NACI recommends the following individuals/groups be considered for vaccination with Imvamune®:

- **Men who have sex with men (MSM), and individuals who have sex with MSM, and who meet at least one of the following criteria:**
  - **Having two or more sexual partners or being in a relationship where at least one of the partners has other sexual partners**
  - **Having had a confirmed sexually transmitted infection acquired in the last year**
  - **Engage in sexual contact in sex-on-premises venues**

  OR:

- **Individuals who self-identify as sex workers regardless of self- identified sex/gender**

  OR:

- **Staff or volunteers in sex-on-premises venues where workers may have contact with fomites potentially contaminated with monkeypox, without the use of personal protective equipment**

1.2. Those with a prior documented history of monkeypox infection need not be vaccinated.

(*Strong NACI recommendation*)

Summary of evidence, rationale, and additional considerations:

- Imvamune® vaccine has no known safety signals and is generally well tolerated.
- Although the available evidence is limited, Imvamune® is likely to provide protection against symptomatic monkeypox infection when provided pre-exposure.
- Evidence is limited in pediatric populations <18 years, and use in pediatric populations would be considered off-label.
- Consistent with international epidemiology, individuals who self-identify as gbMSM are primarily affected by the monkeypox outbreak in Canada, with over 95% of cases to date reported in men self-identifying as gbMSM with multiple and/or new sex partners.
- International reports of the ongoing outbreak since May 2022 suggest the majority of the individuals self-identifying as gbMSM who are diagnosed with monkeypox have reported no contact with a person known to have a confirmed monkeypox infection. Therefore, contact tracing and limiting vaccine use to post-exposure vaccination in areas with active community spread, has proven challenging.
- Sex workers may also be at high risk of exposure in regions with active monkeypox spread due to multiple/anonymous sex partners, although data are limited.
- Communities/groups listed as being at highest risk for monkeypox were identified considering the current epidemiological activity of monkeypox in Canada and abroad. However, it remains unknown what future course monkeypox epidemiology will take. As the current outbreak evolves and new risk factors or groups at higher risk are identified, then the criteria for those who should be vaccinated may change.
- Following stakeholder engagement with groups representing the gbMSM community as well as a group representing sex workers, NACI acknowledges the concern some stakeholders have regarding risk of monkeypox both in terms of health and potential socioeconomic consequences of monkeypox infections. Relatively high acceptability regarding Imvamune® amongst those recommended for vaccination in this guidance is expected.
- Very few monkeypox infections related to occupational exposure among healthcare workers have been reported globally in non-endemic countries since January 2022. Healthcare workers and clinical diagnostic laboratory workers who are in contact with patients or their clinical diagnostic specimens but who work in environments with training and control measures in place to mitigate risk of unprotected exposures or infections in healthcare settings are not recommended for pre-exposure vaccination at this time.

- NACI continues to recommend pre-exposure vaccination with Imvamune® vaccine for those working in research laboratory settings with replicating orthopoxviruses as outlined in the June 10, 2022 NACI Rapid Response on the Interim Use of Imvamune® in the Context of a Monkeypox Outbreak. Although there are limited data in priority populations, NACI continues to recommend that Imvamune® vaccine may be offered to individuals who are immunocompromised due to disease or treatment, individuals who are pregnant; individuals who are breastfeeding, children and youth <18 years of age where infection could have significant negative outcomes.

2. In the context of the ongoing monkeypox outbreak and limited vaccine supply, dose sparing strategies should be considered in order to expand vaccination coverage to a broader population currently considered for pre-exposure vaccination[1]:
(*Strong NACI recommendation*)

2.1. Among immunocompetent adults currently considered for pre-exposure vaccination[1], the first dose of Imvamune® can be prioritised in order to extend the potential protective impact broadly across populations most at risk of exposure.

- **Second doses should be offered as soon as demand for first doses among eligible individuals has been met. Individuals should receive their second dose at least 28 days after the first dose, provided they are at ongoing risk of exposure. This may result in an extended interval strategy, where the second dose is offered beyond the minimum authorised interval (28 days).**

- **Individuals considered moderately to severely immunocompromised and currently eligible for pre-exposure vaccination[1] should be prioritized to receive two doses of the Imvamune® vaccine administered at the authorized interval (28 days between doses).**

[1] Based on current epidemiology, NACI recommends the following individuals/groups be considered for pre-exposure vaccination with Imvamune®: Men who have sex with men (MSM), and individuals who have sex with MSM, AND who meet at least one of the following criteria: 1) Having two or more sexual partners or being in a relationship where at least one of the partners has other sexual partners; 2) Having had a confirmed sexually transmitted infection acquired in the last year, or 3) Engage in sexual contact in sex-on-premises venues. Additionally, regardless of sex or gender, individuals who self-identify as sex workers regardless of self- identified sex/gender and staff or volunteers in sex-on-premises venues where workers may have contact with fomites potentially contaminated with monkeypox without the use of personal protective equipment. Those with a prior documented history of monkeypox infection need not be vaccinated.

2.2. NACI recommends that, in the context of limited Imvamune® vaccine supply, off-label intradermal administration (0.1 mL per dose) can be used among immunocompetent adults when given as a second dose following a first dose given subcutaneously, provided dose sparing and safe administration practices are feasible.

- **Individuals who are <18 years of age, at risk of keloid scars, or moderately to severely immunocompromised should be offered Imvamune® vaccine using the subcutaneous route of administration only.**

- **Personnel involved in preparing and administering the vaccine should be provided adequate training before implementing intradermal administration. Jurisdictions should have protocols to minimize the risk of dose wastage and to reduce the potential of contamination of the vials if single-dose vials are to be used for multiple doses. If a vial is used for multiple doses, it should be discarded after 6 hours following first puncture. For more information, please refer to the Quick reference guide on use of Imvamune® for health care professionals in the context of monkeypox outbreaks in Canada.**

3. NACI recommends that, when supply is not constrained, Imvamune® pre-exposure vaccination should be offered as a two-dose primary series, with at least 28 days between first and second sub-cutaneous doses, for individuals currently eligible for pre-exposure vaccination[1].

(*Strong NACI recommendation*)

Summary of evidence, rationale and additional considerations for Recommendations 2 and 3:

- At this time, Imvamune® is the only vaccine authorized for use in Canada under an Extraordinary Use New Drug Submission (EUNDS) for the indication of active immunization against smallpox, monkeypox and related Orthopoxvirus infections, and is currently only available to provinces and territories through PHAC. Domestic supply in response to the ongoing monkeypox outbreaks must consider current/future emergency preparedness (e.g., smallpox preparedness).
- Considering current and forecasted limitations to both Canadian and global Imvamune® supply, and the unknown epidemiological trajectory of monkeypox in Canada, NACI explored dose-sparing strategies to maximize vaccine coverage for those at high risk of monkeypox exposure.
- Although the available evidence is limited, in the short-term, one dose of Imvamune® vaccine is likely to provide some protection against symptomatic infection when provided as vaccination prior to any exposure.
- In the current outbreak context, dose-sparing strategies via intradermal administration may be most optimal when used as a second dose. This is in light

of feasibility limitations for broad and rapid intradermal vaccine deployment and the greater body of evidence regarding a complete dose.
- Internal PHAC modelling reviewed by NACI based on Canadian supply projections suggested that expanding vaccine coverage by extending dose intervals of the Imvamune® vaccine and using 1-full (SC) and 1-fractional (ID) dose could have short-term public health benefits in preventing infections while vaccine supply is constrained as long as three or more fractional doses could be extracted from each vial.
- There is limited clinical evidence on Imvamune® when provided as a fractional ID dose, and relative vaccine effectiveness compared to two doses administered via SC injection is unknown. A National Institutes of Health-led Phase 2 clinical trial compared different routes of administration of Imvamune® among healthy participants. Based on neutralizing antibody levels following vaccination, Imvamune® given by a fractional ID dose was considered immunologically non-inferior to a full dose administered via SC injection. Severe (>3cm) and long-lasting (>30 days) local reactions were more frequently reported with ID injection compared to subcutaneous injection however the frequency of systematic reactogenicity did not differ among the two groups. Refer to the Appendix A for additional detail.
- Improperly administered ID doses should be discussed with an expert in vaccines or local public health authority for guidance on accepting the dose and considering it valid, or repeating the dose.
- Informed consent should transparently include the known and unknown benefits and risks and acknowledgement of the off-label nature of Imvamune® administered via intradermal route.
- As Imvamune® is formulated as a single dose vial and does not contain preservatives, when used for multiple doses, the vial must be discarded after 6 hours from first puncture in order to reduce the risk of contamination of the vial or infection.
- In situations where individuals received a first dose of Imvamune using an ID route, then the dose should be considered valid.
- Individuals with history of a documented infection with monkeypox following the receipt of the initial vaccine dose need not be vaccinated.
- NACI will continue to review emerging evidence on Imvamune® vaccine effectiveness, the duration of protection, immunogenicity, and safety, including real-world evidence from jurisdictions that have recommended ID administration as a dose sparing strategy (e.g., US, Europe).

Post-exposure vaccination

4. NACI continues to recommend the use of Imvamune® as a post-exposure vaccination (also known and referred to as post-exposure prophylaxis) to individuals who have had high risk exposure(s) to a probable or confirmed case of monkeypox, or within a setting where transmission is happening. A

post-exposure vaccine dose should be offered as soon as possible, preferably within 4 days of last exposure but can be considered up to 14 days of last exposure. It should not be offered to individuals who are symptomatic and who meet the definition of suspect, probable or confirmed case.

(***Strong NACI Recommendation***)

- The strength of this recommendation has been updated since initial NACI guidance was published on June 10, 2022, based on accumulating evidence on the safety of Imvamune®. The recommendation strength is now aligned with the strength of evidence pertaining to pre-exposure vaccination with Imvamune®.

For additional information, please refer to the NACI rapid response: Interim guidance on the use of Imvamune® in the context of monkeypox outbreaks in Canada, issued June 10, 2022.

Table 1. Strength of NACI recommendations

Strength of NACI Recommendation based on factors not isolated to strength of evidence (e.g., public health need)	**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.

V. SUMMARY TABLE (IMMUNIZATION SCHEDULE)

Table 2: Immunization schedule for Imvamune® in the context of the 2022 monkeypox outbreak

Dose Number	Pre-Exposure Vaccination[a,b]		Post-Exposure Vaccination[a,b]	
	Immunocompetent adults	**Moderately to Severely Immunocompromised and/or <18 years of age and/or increased risk of keloid scars**	**Immunocompetent adults**	**Moderately to Severely Immunocompromised and/or <18 years of age and/or increased risk of keloid scars**
Dose 1	0.5mL, SC	0.5 mL, SC	0.5 mL, SC, within 4 days since exposure, can be considered up to 14 days	0.5 mL, SC within 4 days since exposure, can be considered up to 14 days
Dose 2	0.5mL, SC, 28 days after dose1 (supply not constrained) OR 0.5mL SC administered ≥ 28 days after dose 1 (constrained supply) OR 0.1 mL, ID (constrained supply only)	0.5mL, SC 28 days after dose 1	0.5mL, SC, (if at ongoing risk of exposure)	0.5mL, SC (if at ongoing risk of exposure)

[a]Immunocompetent individuals recommended for Imvamune® pre-exposure or post-exposure vaccination should receive a single dose if they have previously been vaccinated with a live replicating 1st or 2nd generation smallpox vaccine (i.e., as a booster dose). However, individuals considered moderately to severely immunocompromised should receive two doses, regardless of previous smallpox vaccination.

[b]Pre-exposure or post-exposure vaccination is not indicated for individuals who meet the definition of suspect, probable or confirmed monkeypox case or with prior history of infection with monkeypox.

In the context of constrained supply, for immunocompetent individuals, the first dose can be prioritised; this may result in an extended interval strategy, where the second dose is offered beyond the minimum authorised interval of 28 days.

For post-exposure vaccination, the second dose is only administered if the person is at ongoing risk of exposure.

Imvamune® given as pre-exposure or post-exposure vaccination 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. Refer to the June 10, 2022 NACI Statement for details on co-administration guidance.

Please see the PHAC webpage: Quick reference guide on use of Imvamune® for health care professionals in the context of monkeypox outbreaks in Canada.

Additional information on Imvamune® is contained within the product monograph available through Health Canada's Drug product database.

VI. RESEARCH PRIORITIES

1. Further study of the protection offered by Imvamune® vaccine against monkeypox infection, disease and transmission (in pre-exposure and post-exposure vaccination scenarios), including:
    1. Understanding which immune responses are protective against infection and disease and defining protective thresholds, including the duration of protection
    2. Understanding how the impact of previous orthopox infection or vaccination impacts the protection offered by Imvamune®
    3. Real-world evidence on the vaccine effectiveness of Imvamune® against monkeypox when used as a single SC dose, with extended intervals, and/or in combination with fractional intradermal dosing.
2. Additional studies to further inform on the safety of Imvamune® vaccine including both clinical trials and post-market safety surveillance.
3. Further studies to assess vaccine efficacy/effectiveness and safety of Imvamune® in priority populations, including people who are pregnant or breastfeeding, children <18 years of age, and people who are immunocompromised.
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.
5. Further study into the optimal immunization strategies for outbreak control (e.g., ring vaccinations, population groups at medium/low risk of infection).
6. Further study into the optimal immunization strategies to reach and enhance vaccine acceptance and uptake in populations at highest risk of infection.

LIST OF ABBREVIATIONS

CIC	Canadian Immunization Committee
HIV	Human immunodeficiency virus
ICU	Intensive care unit
ID	Intradermal
gbMSM	Individuals who self-identified as gay, bisexual, and men who have sex with men
HCID WG	High-consequence infectious diseases working group
2SLGBTQI+	Two-Spirit, lesbian, gay, bisexual, transgender, queer, intersex +, where + is inclusive of people who identify as part of sexual and gender diverse communities, who use additional terminologies
MSM	Men who have sex with men; defined in the context of this statement as any male-identifying individual who has sex with another person who identifies as a male, including but not limited to: individuals who self-identify as trans-gender, cis-gender, Two-Spirit, gender-queer, intersex, and non-binary and who also identify as gay, bisexual, or pansexual.
MVA	Modified vaccinia Ankara
MVA-BN	Modified vaccinia Ankara - Bavarian Nordic; Imvamune®
NACI	National Advisory Committee on Immunization
PHAC	Public Health Agency of Canada
SC	Subcutaneous
WHO	World Health Organization

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APPENDIX A: EVIDENCE ON SAFETY, IMMUNOGENICITY AND EFFECTIVENESS OF MVA-BN WHEN ADMINISTERED OFF-LABEL USING FRACTIONAL DOSES OR DELAYED SECOND DOSES

Fractional Intradermal administration of MVA-BN

Safety Data on Intradermal Administration of a Fractional Dose of MVA-BN

The safety of intradermal (ID) administration of a fractional dose (1/5th of the standard dose) of MVA-BN vaccine (containing the same virus type and content as Imvamune®) was assessed in a Phase II randomized clinical trial among healthy individuals 18 years and older born after 1971. The study compared 2 doses of MVA-BN administered 28 days apart when using subcutaneous (SC) administration of a standard dose (n=167) and ID administration of a fractional dose (n=191) [(31)].

ID administration was associated with increased local reactogenicity compared to SC administration, including itchiness, erythema and induration at the infection site. Although severe (>3 cm) and long-lasting (>30 days) local reactions were more frequently reported with ID compared to SC group, there were only three (3/191; 1.6%) individuals in the ID group and none in the SC group who experienced severe local reactions (itchiness) with functional impairment. Compared to the SC group, a higher proportion of individuals in the ID group did not receive a second vaccination due to persistent local reactogenicity (mild or greater) at the time of the second vaccination (20/192 for ID administration and 3/167 for SC administration). However, most local symptoms were not deemed clinically significant by the investigators [(31)].

While the reactogenicity of both ID doses was overall similar, dose 2 ID was more reactogenic than dose 1 regarding the size of local reactions. However, the clinical significance of this difference is minimal [(31)].

Systemic reactogenicity of MVA-BN was consistent for both ID and SC administration [(31)].

Given the number of study participants, it is unlikely that rare or very rare adverse events would be detected in this clinical trial. NACI will monitor post-market safety surveillance data as it emerges and update its recommendations as needed.

Safety precaution relating to single dose vials without preservatives

Please see the PHAC webpage: Quick reference guide on use of Imvamune® for health care professionals in the context of monkeypox outbreaks in Canada.

Immunogenicity data on intradermal administration of a fractional dose of MVA-BN

MVA-BN administration at 1/5th of the standard SC dose was found to be immunologically non-inferior compared to the standard SC dose. After the receipt of the second dose, the peak geometric mean neutralization titres (GMTs) were 49.5 (95% CI: 40 to 61.3%) in the SC and 59.6 (95% CI: 48.1 to 74%) in the ID group, with 95.3% and 94.5% of study participants achieving immune response (based on peak titres) in the SC and ID group, respectively. At six months following the receipt of the second dose GMT values declined to 10.2 (95% CI: 9.4 to 11%) and 10.4 (95% CI: 9.4 to 11.5%), and only 39.2% and 35.2% of study participants remained seropositive in the SC and ID group, respectively [(31)]. These findings were in line with those previously reported from studies that evaluated the immunogenicity of influenza, rabies and hepatitis B vaccines, and which demonstrated non-inferior immune responses compared to standard dosing when 20% to 60% of antigen was administered using the ID route [(32)].

Vaccine efficacy or effectiveness data on intradermal administration of a fractional dose of MVA-BN

The relative or absolute efficacy or effectiveness of fractional doses of MVA-BN against monkeypox using an ID (versus SC) route of administration remains unknown.

Subcutaneous administration of MVA-BN using a delayed interval between first and second dose

Immunogenicity data on a single dose of MVA-BN

Immunogenicity of booster doses following a one or two dose primary vaccine schedule has been reported in one study. Up to 30 weeks following the completion of a one- or two-dose schedule, neutralizing titres were higher in study participants who received two vaccine doses, but these differences disappeared by week 108 (approaching baseline). Following the receipt of a booster dose, there were no differences observed in antibody responses (measured as neutralizing antibody titres) between those who previously received one or two doses of the vaccine when followed up to week 30 post booster immunization [(33)]. However, at this time, there is no known immunological correlate of protection for Imvamune® for any outcome associated with monkeypox infection or disease.

Effectiveness data on a single dose of Imvamune®

One of the first estimates of one-dose Imvamune® vaccine effectiveness against symptomatic monkeypox infection were reported as a pre-print by Arbel and others [(34)]. The observational study using administrative data (i.e., electronic medical records from a healthcare organization that covers approximately 52% of the entire Israeli population)

followed over 8,000 individuals who were assessed as being at moderate to high risk for infection and of whom 626 (7.7%) received one dose of the MVA vaccine. All study participants completed at least 7 days of follow-up (study period from July 31 to August 10, 2022 [last data extraction date, August 15, 2022]) during which 14 infections were confirmed only in unimmunized individuals, providing an estimated VE of 100% (95% CI: 100-100%). However, although the results of the study are encouraging, given the very short observational period (e.g., up to 10 days since vaccination, including time prior to mounting an adequate immune response), the small number of infections, and the potential biases that may be associated with the model (e.g., time-varying confounding), the GRADE assessment of the study suggests a low certainty of evidence. The results of the study remain to be validated after an anticipated peer review and the updating of the results using a longer follow-up period post vaccination.

Data from Canadian provinces and territories on breakthrough infections following a single dose of Imvamune® are emerging. While most infections have been reported during the incubation period (maximum 21 days, with the majority reporting symptoms <14 days following vaccination), there have also been cases where infections were reported beyond 21 days post vaccination (PHAC-compiled data from Alberta, British Columbia, Ontario, Saskatchewan, and the Yukon Territory) [35].

Breakthrough infections following a single dose of Imvamune® have been reported to be milder in disease severity compared to those among unvaccinated individuals. A case series analysis from Montreal among monkeypox cases confirmed that between May 12 and August 10, 2022, monkeypox cases where symptom onset occurred ≥21 days since vaccination with Imvamune® had less severe infections (lesions at fewer anatomical sites) compared to unvaccinated cases [36].

Similar to findings reported in Canada, several studies from the United States and the UK have also reported instances of breakthrough monkeypox infections following a single dose of Imvamune® at more than 25 days post vaccination [12, 27, 37]. However, these reports cannot be used to estimate the vaccine effectiveness of Imvamune® against monkeypox infection or severe disease, as they do not include a control group.

The absolute or relative efficacy or effectiveness of Imvamune® against monkeypox infection or severe disease when administered as a single-dose compared to a two-dose primary series is unknown. Considering principles of vaccinology, in general, a longer interval between the first and second doses allows maturation of the memory B cells, resulting in higher and more durable response [38].

APPENDIX B: RECOMMENDED DEFINITION OF MODERATELY TO SEVERELY IMMUNOCOMPROMISED INDIVIDUALS

Moderately to severely immunocompromised includes individuals with the following conditions:

- Immunocompromised due to solid tumour or hematologic malignancies or treatments for these conditions
- Solid-organ transplant and taking immunosuppressive therapy
- Hematopoietic stem cell transplant (within 2 years of transplantation or taking immunosuppression therapy)
- Immunocompromise due to chimeric antigen receptor (CAR) T cell therapy targeting lymphocytes
- Moderate to severe primary immunodeficiency with associated humoral and/or cell-mediated immunodeficiency or immune dysregulation
- HIV with AIDS-defining illness or TB diagnosis in last 12 months before starting vaccine series, **or** severe immune compromise with CD4<200 cells/uL **or** CD4%<15%, **or** without HIV viral suppression
- Recent treatment with the following categories of immunosuppressive therapies: anti-B cell therapies (monoclonal antibodies targeting CD19, CD20 and CD22), high-dose systemic corticosteroids, alkylating agents, antimetabolites, or tumor-necrosis factor (TNF) inhibitors and other biologic agents that are significantly immunosuppressive
- Chronic kidney disease on dialysis

For guidance on the timing of vaccination for transplant recipients and those requiring immunosuppressive therapies, for a more fulsome list of conditions leading to primary immunodeficiency, and for further information on immunosuppressive therapies, refer to Immunization of Immunocompromised Persons in the Canadian Immunization Guide (CIG), Part 3 - Vaccination of Specific Populations.