Clinical Trial Protocol

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Protocol for the Mpox Prospective Observational Cohort Study (MPOCS) among individuals with mpox in Canada

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In mid-2022, a global mpox epidemic emerged that was concentrated in gay, bisexual and other men who have sex with men, prompting the WHO to declare a public health emergency of international concern. Shortly after cases were first identified in Canada, we established the Mpox Prospective Observational Cohort Study (MPOCS) to characterize clinical, psychosocial, epidemiologic and virologic characteristics of this re-emerging infection. Community members were engaged in identifying research priorities, creating participant-facing materials, and forming a community advisory board. This article outlines the MPOCS study protocol. Although cases of mpox in Canada have rapidly declined, our research procedures may serve as a template for rapidly studying emerging infectious disease threats in the future, particularly among sexual networks.

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Mpox (formerly known as Monkeypox) is a systemic infection caused by a DNA virus in the *Orthopoxvirus* genus of the Poxviridae family. The disease is characterized by systemic flulike symptoms, and vesicular/ulcerative skin lesions that are widely disseminated across the body. The virus that causes mpox is closely related to the virus that causes smallpox, and as such has been of particular concern because of its potential use as an agent of bioterrorism [1,2]. The manifestations of mpox are typically milder than those of smallpox, and its mortality rate has historically been far lower, estimated at 6 to over 10% depending on viral clade [3,4] compared with up to 30% for smallpox caused by variola major [1,5]. During the 2022 mpox epidemic, case fatality has been lower still, at well under 1% [6].

The emergence of a global mpox epidemic in May 2022, concentrated among self-identified gay, bisexual and other men who have sex with men (GBM), sparked renewed concern [7]. Historically, cases of mpox had been largely confined to a limited number of countries in West and Central Africa, where zoonotic transmission predominated over occasional human-to-human spread [3,8–12]. Aside from a self-limited 2003 outbreak in USA related to pet

prairie dogs who had been housed in close proximity to infected animals from West Africa [13–15], only a handful of isolated, travel-associated cases had previously been reported from other regions [16]. Yet even within West and Central Africa, mpox had been re-emerging in recent years for a multitude of reasons. Deforestation, climate change, civil unrest and increased human migration have led to increased contact between humans and animal reservoirs and a wider geographic range of the infection [17]. Immunologic factors such as waning population immunity to smallpox [18], and virologic factors such as gene loss from the viral genome may also have played a role [19]. As case counts rose globally, mpox was classified as a public health emergency of international concern by the WHO on 23 July 2022 [20]. Canada was one of the first countries where cases were identified. The threat that such orthopoxviruses pose to human health, especially among historically marginalized and socially excluded groups, is particularly resonant in Canada, where there is a shameful history of colonists knowingly giving smallpox-contaminated blankets to Indigenous people as an early act of biowarfare in the 18th century [2].

The rapid rise in mpox cases among GBM in regions that had never previously been involved raised a multitude of scientific questions. What are the typical clinical manifestations and time course of infection and how do host factors (e.g., HIV and prior smallpox vaccination) alter the presentation? What are the short and longer term impacts of mpox on physical and mental health and well-being? What was the role of behavioral factors in global dissemination? Did genetic changes in the virus facilitate transmission and alter symptomatic presentation?

Introduction to the study

To address such questions, our team developed the Mpox Prospective Observational Cohort Study in June 2022, shortly after mpox cases were first detected in Canada in May 2022. This is a multicenter prospective observational cohort study of individuals with confirmed or suspected mpox infection. Our study objectives were:

- To describe the clinical manifestations of mpox infection during the Canadian outbreak;
- To assess the psychosocial impacts of mpox-related illness and isolation requirements;
- To describe the transmission-related characteristics of mpox infection; and
- To characterize virologic aspects of infection over time.

Participants consent to weekly collection of clinical, questionnaire, photographic and biospecimen data until one week after the complete clinical resolution of the acute illness (Part 1). Participants may also opt to undergo more frequent assessments three-times weekly during the acute phase. Additionally, an optional extension phase of the study (Part 2) involves ongoing data collection during the convalescent phase of illness until 12 weeks after symptom onset. The study was launched in mid-2022, but remains open to participant enrollment at the time of writing, in case future waves of the epidemic occur in the future. Accordingly, we use the present tense to describe all study procedures in this manuscript. This manuscript corresponds to version 2.0 of the protocol, dated 15 September 2023. The study is registered at www.clinicaltrials.gov.

An important aspect of our scientific approach is the engagement of community members throughout the research process, including collaboration on the identification of research priorities, co-creation of community/participant-facing study materials, and establishment of a community advisory board with evolving roles and responsibilities as the epidemic unfolds.

Design

Study setting

This multicenter study involves clinical research sites in Toronto, Montreal and Vancouver, Canada's three largest cities and the locations from which the majority of cases have been reported throughout the epidemic, with the capacity to expand to new sites if the epidemic extends into new geographic locations. Participating sites must have adequate infection prevention and control capabilities to safely evaluate patients with mpox infection (including private rooms, adequate personal protective equipment for staff, appropriate laboratory facilities to safely handle and transport study specimens).

Eligibility criteria

Individuals may be recruited into the study during either the acute or convalescent phase of their illness (Figure 1). The acute phase of illness is defined as the time from symptom onset (as identified by the participant) until the point when all lesion scabs have fallen off and new intact skin has formed below. This process varies in duration

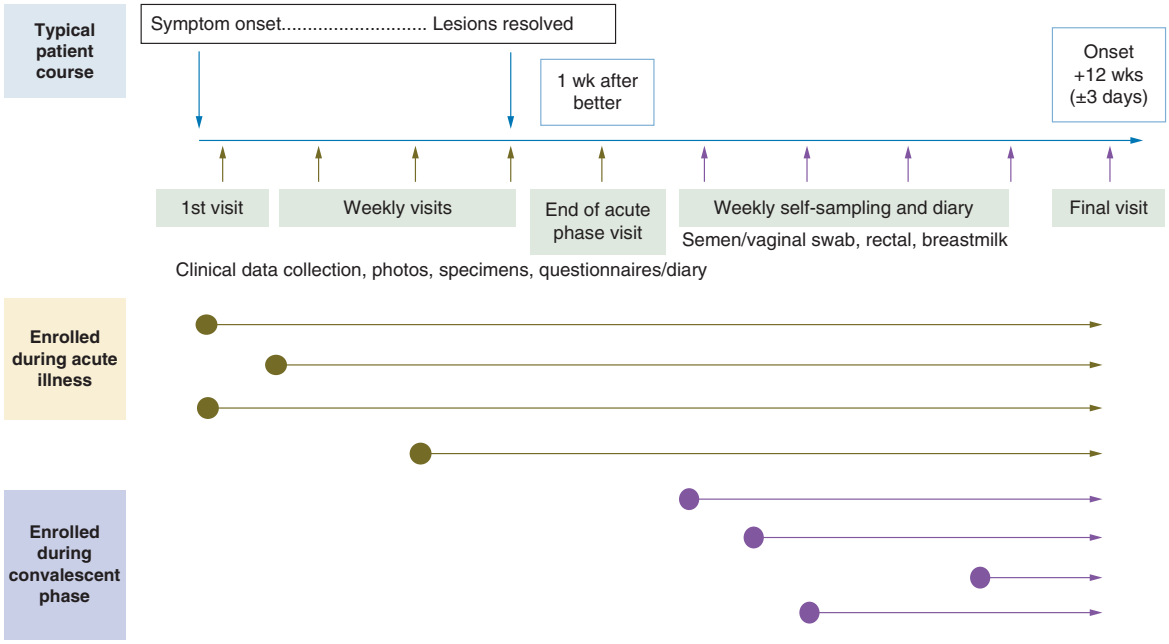

Figure 1. Study schema. Among hospitalized participants, activities labeled as weekly are performed thrice weekly (Mondays, Wednesdays, Fridays) ±1 day. Thrice weekly activities will also be done in a subset of participants (sequential enrollees to optionally participate) until n = 20.
wk: Week.

but is typically 2–4 weeks. We define the convalescent phase of illness as the period from the end of the acute phase until 12 weeks (±3 days) after symptom onset.

Individuals of any age are eligible to enroll during the acute phase of illness if they are being investigated for mpox infection by a clinician based on clinical (i.e., symptoms) and/or epidemiologic (i.e., exposure to confirmed case) grounds. Inclusion criteria during the acute phase are not contingent on microbiologic documentation of mpox infection in order to avoid delays in enrollment while awaiting confirmatory test results, and because inclusion of individuals ultimately found not to have the infection may provide a valuable comparison group.

Individuals are eligible to enroll during the convalescent phase if they: have microbiologically documented evidence of recent mpox infection (i.e., positive result on mpox polymerase chain reaction, PCR, testing) within the preceding 12 weeks; are within twelve weeks of symptom onset; and have experienced complete resolution of the acute phase of illness (i.e., all lesion scabs have fallen off and new intact skin has formed below). The decision to allow individuals who have clinically recovered from confirmed mpox infection to enroll was to afford an opportunity to study subclinical viral shedding during the convalescent period.

Potential participants not proficient in the language of the study site may join if suitable translation services are available to ensure that informed consent can be obtained and that all study activities can be performed correctly. Individuals with a poor prognosis, whether suspected to be related to mpox infection or not, are still eligible for enrollment to enable evaluation of the full spectrum of disease including severe clinical manifestations and an understanding of how mpox infection may shape severe illness. Individuals who have previously enrolled in the study but were not confirmed to have mpox at that time are eligible to re-enroll, as they are still at risk of contracting infection. Individuals who have received a smallpox vaccine, either historically (during the global smallpox eradication campaign) or in the context of evolving outbreak control vaccine efforts, are eligible, as their inclusion affords opportunities to study outcome differences by vaccine status. Similarly, individuals who enroll in interventional studies of mpox therapeutics are eligible, as their inclusion affords opportunities to study outcome differences by treatment status. Individuals with mpox re-infections are also eligible.

Outcomes

The primary objective of the study is to describe the clinical manifestations of mpox infection during the Canadian outbreak, including symptom duration and spectrum, complications, natural history and sources of variability

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in clinical manifestations. Outcome data on symptoms involve the number and proportion of participants experiencing each of: fever, chills, headache, myalgias, fatigue, sweats, sore throat, odynophagia, dysphagia, cough, backache, vomiting, diarrhea, rectal/anal pain, rectal/anal discharge, rectal/anal bleeding and eye redness. Lesion number, location and type are also recorded. Participants are also prompted to report any additional symptoms. Complication data involve the number and proportion of participants experiencing each of: secondary skin infections, bronchopneumonia, sepsis, corneal infection, encephalitis, myocarditis, proctitis and any other severe manifestations, as well as hospitalizations. To describe the natural history, we will characterize the sequence and time course of individual clinical manifestations in infected individuals. Where data allow, we will explore trends in how mpox manifestations may vary according to underlying patient characteristics, most notably HIV infection (including CD4 cell count and viral load status), gender identity and prior smallpox vaccination.

Our second objective is to describe the psychosocial impacts of mpox-related illness and isolation requirements, including financial insecurity, psychological distress and perceived and enacted stigma. Financial insecurity is measured using a self-reported questionnaire administered at the end of the study period, including items about housing, access to paid sick leave, lost employment income, difficulty covering usual household expenses and sources of income. Outcome data on psychological impacts of mpox infection is measured using the K10, a validated 10-item measure of non-specific psychological distress aligned with the structured clinical interview for DSM-IV (SCID) [21,22]. A standard cut-off score of $\geq$16 will be used to define short-term psychological distress. This instrument has been used in prior research on the psychologic impacts of epidemics including SARS and COVID-19. To gain preliminary insights into enacted and anticipated stigma, participants are asked "*Did you experience stigma from others related to monkeypox?*", and "*Do you anticipate experiencing stigma in the future related to mpox?*", and asked to describe such experiences in open-ended questions.

Our third objective is to collect data on transmission-related aspects of mpox infection. Specific outcome data include types and timing of human and animal contacts prior to mpox infection, as well as quantifying the detectability of mpox viral DNA in the immediate environment of people ultimately diagnosed with the infection, including physical surfaces and air samples.

The fourth objective of the study is to characterize virologic aspects of mpox infection over time. Key outcomes include the detectability of mpox viral DNA by polymerase chain reaction (PCR) along with the associated cycle threshold, as well as titers of infectious virus, in different anatomic compartments and examining the viral genomic sequence. Outcomes also include characterizing the host response to mpox infection including host gene and cytokine expression and antibody titers.

Participant timeline

Individuals may enroll into the study at any time during the acute (Part 1) or convalescent (Part 2) phase of illness. The frequency of follow-up visits during Part 1 is weekly, although a subset of participants may opt to be followed more intensively (thrice weekly) to generate more granular natural history and viral shedding data. All acute phase participants are followed until 1 week after all lesion scabs have fallen off and new intact skin has formed below (end of acute phase follow-up), until 12 weeks after symptom onset (end of convalescent phase follow-up for those who opt into this component), or until consent to participate in the study is withdrawn.

Sample size

The initial target sample size for this study is n = 100 confirmed mpox cases in Part 1 (including up to n = 20 intensively followed participants), based primarily on feasibility and budgetary constraints. This sample size was expected to be adequate to understand the usual clinical course of infection. Additional participants with suspected mpox who are ultimately not confirmed to have the disease may also be enrolled and followed until that information is available and an alternative diagnosis is obtained; the original target was for a similar number of these participants (n$\sim$100). However, the number of incident cases of mpox began to rapidly decline shortly after the study was launched [23], rendering the initial target sample size unfeasible unless additional epidemic waves occur in the future. Modifications were therefore made to the protocol in September 2022 to target n = 30 acute phase participants, n = 20 intensively followed acute phase participants, and n = 50 convalescent phase participants, to reflect more feasible targets.

Recruitment

Potential study participants are identified by clinicians at participating sites in Toronto, Montreal and Vancouver, Canada, who assess patients presenting with possible mpox infection. Community partners are also engaged in raising awareness about study enrollment through regular online community engagement meetings and electronic communications. Clinicians or other members of the circle of care first approach the individual to determine willingness to speak to a research coordinator. Those who agree are provided with study details by the research staff, who obtain informed consent. Non-study sites (e.g., sexual health and primary care clinics located in Toronto, Montreal and Vancouver [Canada]) may function as 'referral sites', and clinicians at these institutions are asked to refer potential participants if procedures are approved by the relevant research ethics board. Additional study sites may be opened in other cities in the future pending the evolution of the epidemic.

At study sites, individuals who are approached about the study but ultimately decline to participate for any reason are asked verbally to provide permission for the study team to document their age category (by decade), sex at birth, and reason for assessment (asymptomatic contact, systemic symptoms, and/or cutaneous symptoms), alongside the date of the assessment, in a refusal log. While it is recognized that sex assigned at birth does not adequately capture individuals' sex and gender identities, gender identity is not collected on these individuals as we feel it is not appropriate to ask about and collect this personal data on individuals who have explicitly declined to join the research study. Comparison of refusal log data with participant data will allow a crude assessment of the representativeness of the final study sample. Individuals who also refuse to have their information captured on the refusal log are simply enumerated.

Data collection methods: part 1

A full schedule of study events is presented in Table 1. At the baseline visit, study staff review the patient chart and conduct a participant interview to obtain basic information about demographics, comorbidities, medications, exposure history (timing/intensity/frequency of contact with potential cases including appropriate sexual history) and symptoms. It is anticipated that as part of the clinical standard of care, participants also undergo comprehensive HIV and bacterial sexually transmitted infection testing (syphilis serology and gonorrhea/chlamydia nucleic acid amplification testing on urine, throat swabs, vaginal swabs and rectal swabs as appropriate); those who are living with HIV would undergo CD4 cell count and viral load testing. These standard of care laboratory test results are extracted from participant charts. At weekly follow-up visits during Part 1 (the acute phase), study staff inquire about the status of ongoing symptoms, complications and health-seeking behaviors (visits to other providers, emergency department, hospital admission). At the 'end of acute phase' visit, study staff repeat chart review to ensure complete data capture regarding the final diagnosis, other diagnoses that were ruled out through standard of care clinical assessment (including laboratory test results) and complications.

Participants are asked to complete an electronic self-administered questionnaire at the baseline visit that includes demographics, a comprehensive sexual health history, animal exposure information, social/structural determinants of health and stigma. They are also asked to complete a brief (5–10 min) symptom diary three-times a week (Mondays, Wednesdays, Fridays) to document the evolution and resolution of their symptoms during Part 1. Participants are provided with a thermometer to document their temperatures as part of these brief self-assessments. Questionnaire materials were reviewed for appropriateness by community partners prior to finalization.

During weekly study visits at the study site, trained research staff take one high resolution photograph, corresponding to each of the following anatomic locations that is affected by skin lesions: oropharynx, lips, eyes, other parts of the face, head/scalp, genitalia, perianal, buttocks, chest, back, upper extremities, palms, lower extremities and soles. Participants may refuse photography at any anatomic site, or overall; they may also choose to photograph themselves and provide images to the study team instead. Staff are asked to identify prior and current lesions by body part and then photograph them at each study visit to allow an appreciation of lesion evolution. Staff receive training on how to take photographs in a respectful, non-identifiable and secure way, most notably ensuring that no identifying features (e.g., eyes, large sections of the face, tattoos, distinctive scars, etc.) are included. The participant should be shown the final photo for each site (if they wish) to confirm that they agree that they are not personally identifiable from the photo. Photos are stored on a secure hospital server.

During Part 1, the following clinical specimens are collected at each study visit for mpox PCR, viral culture, and/or genomic sequencing: blood, urine, nasopharyngeal swab, oropharyngeal swab, rectal swab, semen sample or vaginal swab (as appropriate), skin lesions (up to three) and breastmilk (if lactating). For privacy reasons, semen and breastmilk samples may be collected at home if participants prefer, double-bagged and sent back to the study

10.2217/fvl-2023-0189

Table 1. Schedule of study activities in the Mpox Prospective Observational Cohort Study (MPOCS).

Activity	Part 1				Part 2 (optional)		
	Screening	Baseline (screening ±0–2 days)	Weekly (±3 days)†,‡	End of acute phase visit	Enrollment (within 12 weeks of symptom onset)	Weekly (±3 days)	Final visit 12 weeks (±3 days) after symptom onset
Eligibility assessment	X				X		
Informed consent	X				X		
Interview by study staff		X	X	X	X		X
Chart review		X		X	X		
Participant questionnaire		X		X	X		
Acute phase participant diary		qMWF until final visit					
Convalescent phase participant diary						X	X
Skin/mucosal lesion photographs if applicable		X	X	X	X		X
Specimen collection		X§	X¶	X			
Specimen self-sampling at home						X#	X#
HIV serology data extraction††		X					
HIV viral load and CD4 count data extraction‡‡		X		X			X
Environmental specimen collection (optional)		X					
Stored blood for mpox serology		X		X			X
Participant compensation		X	X	X	X	X	X

†Weekly visits should be scheduled at 7-day intervals from the baseline date wherever possible, with the 3-day window utilized for exceptional circumstances.
‡If hospitalized and in the intensively followed subset, all activities should be performed thrice weekly (MWF ±1 day) until hospital discharge (if applicable) or resolution of the acute phase (whichever occurs first).
§Desired specimens at baseline include: blood, urine, nasopharyngeal swab, throat swab, rectal swab, semen or vaginal swab (as applicable), breastmilk (if applicable), up to 3 cutaneous specimens. Any specimens not already being collected for clinical purposes should be collected.
¶Any anatomic sites that test PCR-positive at baseline should be collected for the duration of the study. If results for baseline specimens are not yet known (likely to be the case for research specimens which will be batch tested as possible), specimen collection for these sites should be repeated at subsequent visits.
#Self-sampling during the convalescent phase will include: rectal swab, semen or vaginal swab (as applicable), breastmilk (if applicable).
††HIV serology should be done as per standard-of-care practices on patients who do not self-identify as being HIV positive upon initial suspected mpox clinical diagnosis.
‡‡HIV viral load and CD4 count should be done as per standard-of-care practices on patients who identify as being HIV positive; these tests should be repeated at the end of the convalescent phase if the viral load at the 'end of the acute phase' is detectable. If the participant is did not participate in the acute phase and is new to the study, the HIV viral load and CD4 count should be done for all HIV positive patients.
MWF: Mondays, Wednesdays, Fridays.

team within 24 h of collection. Serum samples is also collected at baseline and at the final Part 1 visit for MPXV serology.

In order to gather more granular natural history data, a subset of participants (target n = 20, and preferentially including participants hospitalized at study sites) may opt to be followed more intensively during the acute phase of illness, undergoing all study activities that are typically scheduled weekly on a thrice weekly schedule instead.

During part 1, air and surface environmental samples are collected at each study visit; participants may refuse air sampling. Air samples are collected using a high-volume air sampler (SASS 3100) with an electret filter, ideally placed between the chairs/exam tables occupied by participants and the room exhaust. Each patient area in the clinic area is characterized for its configuration (ventilation, furniture location) and space (dimensions/volume), and air exchange rates are characterized using tracer gas (SF6) decay method ASTM E741-11. Filters are removed using clean technique, and inserted into 10 ml conical tubes containing 4 ml of universal transport medium prior to transport to the study laboratory. Sampling of clinic environmental surfaces occurs after participants leave the clinic (before and after cleaning). Trained staff also collect the following surface samples: high-touch: patient examination table, patient chair; no-touch: one of top of cupboard or of a shelf above participant's height, corner of room farthest from the exam table, windowsill. For each sample collection, a dacron swab is pre-moistened and placed in a collection tube containing 1.5 ml of universal transport media (UTM). A 8.5 × 11-inch area (or the entire surface, depending on the sample) is swabbed in a continuous fashion while rotating the swab. The swab is then placed back into a collection container, refrigerated at 4°C and transported to the study laboratory for PCR testing.

Data collection methods: part 2

Those who opt into Part 2 of the study are asked to complete a brief (5 min) electronic survey each week, to document additional sexual exposures and intercurrent illnesses during this period.

They are also asked to perform limited self-sampling every week (±3 days) until the final visit, which occurs at 12 weeks (±3 days) since their symptom onset. Participants are provided with instructions on collection of: a rectal swab, semen sample/vaginal swab (as applicable), and breastmilk (if applicable). Specimens should be submitted immediately; if delayed, they must be stored at 4°C and submitted to the study site no later than within 24 h. At the final study visit, a further brief interview is conducted to capture any other major health changes, and a serum sample is collected for MPXV serology.

This study will help address key questions as to which clinical samples contain infectious viruses. For this investigation, participant samples will be overlayed on appropriate cell lines (eg. Vero E6) and monitored for cytopathic effect for 72 h. Where required, titers will be performed using established $TCID_{50}$ method. Additionally, titers of neutralizing antibody will be determined from patient serum through the plaque reduction neutralization assay as a means of correlating this data with reductions in patient shedding. All work will be performed in a CL3 laboratory. Whole genome sequencing will also be done on viral samples using either a metagenomic or amplicon-based approach, this information will complement epidemiological investigations outlined above, and will help further characterize transmission. Additionally, RNAseq will be performed on patient samples as a mean of identifying host genes that are dysregulated during the course of disease as a means of identifying potential prognostic biomarkers.

For participants who consent, all biological specimens collected are stored in a biobank for potential future testing related to mpox virus (e.g., PCR testing using additional primers/ platforms, whole genome sequencing, RNAseq), co-infections (e.g., herpes simplex virus, varicella zoster virus serology), and the host response to mpox infection (e.g., inflammatory biomarkers). Requests for access to the biobank samples/data will be reviewed by a steering committee and provided based on scientific merit of the proposed testing.

Participant retention is encouraged by offering flexibility in visit scheduling, by providing ample compensation for study visits using amounts agreed to by community partners, and by obtaining multiple types of contact information for each participant.

Data management

Study investigators must maintain detailed records on all study participants. Data for this study must be recorded into electronic case report forms (CRFs), within a Research Electronic Data Capture (REDCap) database. Investigators must maintain adequate and accurate source documents upon which CRFs for each participant are based. The Investigator will maintain all study records according to ICH-GCP requirements. Records will be retained for 7 years by the study team, led by the Principal Investigator. Upon request, participant records will be made available to monitoring groups representative of the study Sponsor-Investigator, funders, and relevant regulatory agencies for the verification of clinical research procedures and/or data, as legally permissible. Data management responsibilities for this study are assumed by the Applied Health Research Centre at St. Michael's Hospital, Toronto, Canada. Because this study is non-interventional, no data monitoring committee or trial auditing plan was instituted.

Ethics & dissemination

This study is conducted in accordance with the ICH-GCP Guidelines and the principles in the Declaration of Helsinki. The relevant Research Ethics Board (REB) of all participating institutions must review all study documentation in order to safeguard the rights, safety and well-being of study participants. Ethics approval must be obtained prior to study initiation at any site. A copy of all relevant study documents including the protocol, protocol amendments, informed consent forms, survey instruments, and recruitment materials must be reviewed and approved by the REB of each participating center. The investigator is responsible for obtaining REB approvals throughout the duration of the study, including communicating and seeking ethical approval for any protocol modifications. The investigator must seek prior ethics approval for any protocol deviations unless intended to eliminate an immediate safety concern for participants, in which case deviations must be promptly reported. All participant-related information including Case Report Forms, laboratory specimens, evaluation forms, reports, etc. will be kept strictly confidential. Participants will be identified only by means of a coded number specific to each participant.

10.2217/fvl-2023-0189

All participants in the study must provide written informed consent prior to the initiation of study activities, in accordance with principles outlined in the 2nd edition of the Tri-Council Policy Statement on Ethical Conduct of Research Involving Humans (TCPS2) [24]. Each participant should have sufficient opportunity to discuss the study, have all of their questions addressed and consider the information in the consent process prior to agreeing to participate. A separate consent form should be used for each of Part 1, Part 2, and the biobanking procedures, and sites enrolling pediatric participants will have an assent form along with procedures for documenting capacity to consent. Informed consent to participate in research is an ongoing process and should be re-confirmed with study participants at each study visit. Participants may withdraw consent at any time during the course of the study without prejudice. Consent activities are led by trained research coordinators at each study site.

Findings from this study will be disseminated through peer-reviewed presentations at suitable academic conferences and manuscripts submitted to peer-reviewed scientific journals. Dissemination of results with the broader GBM community will be achieved through lay reports and presentations to community audiences, to be planned in conjunction with community partners.

Data analysis

Analyses will primarily be descriptive. First, the characteristics of the enrolled study participants will be described using measures of central tendency and dispersion for continuous variables and frequencies/proportions for categorical variables. To help assess for selection bias, the age category, assigned sex at birth and reason for assessment (asymptomatic contact, systemic symptoms, and/or cutaneous symptoms) for the enrolled participants will be compared with those on the refusal log.

To achieve Objective 1, we will use descriptive statistics to characterize the clinical manifestations of enrolled participants with mpox infection, calculate the proportion who experience our symptoms and complications of interest (including hospitalization or death), and characterize the natural history of infection by describing the evolution of symptoms over repeated visits. To assess preliminary trends in how mpox manifestations may vary according to underlying patient characteristics, where numbers permit, we will compare these clinical outcomes according to key characteristics of participants, including: HIV serostatus (including CD4 cell count and viral load) and receipt of smallpox vaccine (both prior to and during the current epidemic), sex assigned at birth and gender identity.

To achieve Objective 2, we will summarize the proportions of participants reporting each manifestation of financial insecurity, and quantify the degree of short-term psychological distress reported by participants by calculating the proportion scoring $\geq$16 on the K10 at the final study visit [21,22]. Finally, we will analyze any qualitative responses regarding perceived and enacted stigma provided by participants using content analysis.

To assess transmission potential and transmission dynamics (Objective 3), we will first describe the types and timing of human and animal contacts reported by participants. If participant numbers are sufficient, we will conduct a test-negative cross-sectional analysis comparing those who test negative versus positive for mpox by PCR. We will focus on exposures related to sexual activities, travel-related sexual activities, event/venue-related sexual activities, and non-sexual exposures (household contact); and conduct univariable, modified Poisson regression and report relative risks of each type of exposure. Based on the sample size, we do not expect to conduct multivariable regression; but will conduct stratified analyses if sufficient sample size is accrued (minimum 10) by sex assigned at birth and gender identity. We will conduct sensitivity analyses with serology positive or PCR positive versus serology-negative and PCR-negative.

Among participants for whom environmental surface and/or air samples are available, we will correlate the result (positive/negative) and viral load (Ct value) from each sample with participant and lesion characteristics, including symptoms (systemic vs lesions only); lesion numbers (numerous >10; 3–10; 1–2), lesion characteristics (exposed/covered and unexposed/covered); and lesion stage (maculo-papular; pustule-vesicle; ulcerative; crusted/scab; healed with new skin covering).

To achieve Objective 4, we will first determine the proportion of specimen types in which mpox viral DNA is detectable by PCR at the baseline visit, and at the final Part 1 visit (i.e., 1 week after complete clinical resolution of symptoms). To determine the rate at which DNA detectability recedes, and the time until complete resolution of DNA detectability, we will then model exponential decay in the Ct value as a function of time (day since symptom onset) for each specimen type using linear mixed effects regression models, after censoring out any specimens collected while the participant is exposed to antiviral therapy (e.g., tecovirimat).To determine titers of infectious virus, participant samples will be diluted in MEM media and used to inoculate Vero E6 cells, which will be

monitored for cytopathic effect [25]. Viral loads will be determined using 50% tissue culture infectious dose method and quantified as $TCID_{50}$/ml.

Discussion

The 2022 global mpox epidemic is representative of the ongoing possibility of emerging and re-emerging zoonotic infectious threats to human health. When such new epidemics occur, it is vital that data on relevant clinical, psychosocial, epidemiologic and microbiologic aspects be rapidly collected and disseminated. Our team designed the Mpox Prospective Observational Cohort Study for this reason, and collaborated closely with a wide array of stakeholders including front-line clinicians; national, regional and local public health authorities; scientists from diverse disciplines, and community members.

Shortly after the launch of this cohort study, case counts of mpox began to decline precipitously in Canada [23], for a variety of reasons. Most importantly, extensive education efforts spearheaded by regional and local community organizations, primarily those serving gay, bisexual and other men who have sex with men, led to widespread behavior change that likely played an important role. In the USA, for instance, the American Men's Internet Survey documented that roughly 50% of a national convenience sample of GBM were reporting decreases in numbers of sexual partners, fewer one-time sexual partners, fewer partners met on dating apps or sex venues, less group sex and other relevant alterations in behavior by early August 2022, only weeks after the epidemic emerged in North America [26]. These efforts underscore the critical importance of community leadership and engagement during a rapidly evolving health crisis, because the dissemination of reliable health information by trusted community stakeholders is essential.

Another major contributor to declining case counts was the rapid deployment of a vaccine. Cessation of the worldwide smallpox immunization campaign after the eradication of smallpox is widely believed to have increased global vulnerability to mpox [27]. Fortunately for Canada, a 3rd generation live non-replicating smallpox vaccine containing Modified Vaccinia Ankara-Bavarian Nordic (Imvamune®, also known as Jynneos® and Imvanex® in other jurisdictions) already had regulatory approval for the prevention of mpox at the time of the global outbreak. Canada's National Advisory Committee on Immunization issued interim guidance recommending two Imvamune® doses 28 days apart as mpox post-exposure prophylaxis in adults with high-risk exposures, and as mpox pre-exposure prophylaxis for adults at high occupational risk in research laboratories [28]. Based on these recommendations, and buttressed by safety data from 20 trials [28], provincial authorities in Canada began recommending this product as pre-exposure prophylaxis for sexually active GBM in June 2022, although most jurisdictions initially restricted use to only a single dose given uncertainties regarding vaccine supply [29]. Subsequent observational studies from Israel [30], the US [31–33], the UK [34], Spain [35], Canada [36,37] and other jurisdictions have suggested that a single dose offers 36–68% risk reduction, likely further contributing to local epidemic control across these settings.

Other potential explanations for the rapid decline in mpox cases by late 2022 in Canada include herd immunity effects, saturation of the pool of individuals at highest risk, and as-yet-unidentified genomic changes in the virus conferring reduced transmissibility. As a result of these dynamic factors, incident cases of mpox had stabilized at only one or two cases per week by October 2022 [23], a triumph for public health but an impediment to timely recruitment of individuals into this study.

Our team mobilized rapidly to launch this study; the first version of our study protocol was finalized on 30 May 2022, ten days after the first case of mpox in Toronto was clinically suspected, and ethical approval was granted relatively soon thereafter, on 14 June 2022. Our ability to rapidly develop study tools was in part helped by the existence of related protocols on characterizing emerging infectious diseases by the WHO [38], and could be emulated by others using tools such as the open-source International Severe Acute Respiratory and emerging Infection Consortium (ISARIC) Clinical Characterization protocol [39].

However, the MPOCS study enrolled 26 individuals during the primary wave of the epidemic, considerably short of our initial target of 100. Several factors contributed to this shortfall, highlighting some of the challenges to conducting rigorous scientific research during an evolving outbreak and offering lessons for future epidemic preparedness. A major challenge was the protracted time taken for finalizing research contracts for this multi-centre study, the shortest of which required 111 days. As a result, virtually all of the currently enrolled participants were from the lead study site, despite dozens of eligible patients receiving care during the initial study period by our investigators at collaborating sites. This experience mirrors that seen while launching the Canadian arm of the SOLIDARITY trial during the COVID-19 pandemic, during which the median time between protocol receipt and site initiation was 111 (interquartile range, 39–189) days [40]. Accelerating this process remains a priority for

10.2217/fvl-2023-0189

the Canadian health research community and will require collaboration between legal teams, research institutes and clinical trialists.

Human resource constraints posed another barrier to more rapid recruitment, with the number of eligible patients at times exceeding sites' capacity to enroll. The mpox epidemic also occurred on the heels of the global COVID-19 pandemic, disproportionately impacting the field of infectious diseases where burnout has been high and recruitment of new trainees has been challenging [41]. Building capacity to conduct high quality research during infectious diseases outbreaks in the future will require increased investment of financial and human resources, to ensure adequate 'surge capacity'.

Finally, although the original ethical approval was rapid, approval for amendments was relatively delayed, making it difficult to achieve all our scientific objectives. For instance, although the protocol encourages the same individuals to participate in both the acute and convalescent phases of the study whenever possible, to facilitate intra-individual comparisons, the convalescent phase of the study was conceived and submitted for ethical approval on 28 June 2022, weeks after the Canadian mpox outbreak began, and ultimately approved only on 17 October 2022, after the primary wave of the epidemic was already over. Research ethics boards and the institutional administrations that support them should be encouraged to implement strategies to prioritize time-sensitive outbreak-related research throughout the lifetime of the project.

Despite these challenges, recent events in the evolution of the global mpox epidemic underscore the need for continued vigilance, and the importance of keeping the MPOCS protocol active. For instance, although other orthopoxviruses such as variola virus confer lifelong immunity, mpox re-infection and mpox infection after a two-dose Modified Vaccinia Ankara-Bavarian Nordic vaccine series still occur [42]; ongoing study may elucidate clinical, virological and epidemiologic differences between these infections and those occurring in naive hosts. A recent outbreak of travel-related clade I mpox infection in the Democratic Republic of Congo that includes heterosexual transmission has raised further uncertainties [43]. However, keeping our protocol active may introduce new challenges, related to the time-limited nature of study funding and the difficulty of detecting rare, and potentially less symptomatic cases [42].

Strengths of our approach include our inclusion of multiple clinical, psychosocial, epidemiologic and virologic outcomes, our engagement of community partners in multiple aspects of study planning and implementation, and our rapid initiation of the study within weeks of the first case of mpox being detected in Canada. Important limitations include the restrictions on enrollment imposed by the rapid changes in case counts as described above, and the observational nature of the study which limits our ability to infer causality in our analyses on the impact of clinical covariates. Conducting clinical research during an evolving outbreak also introduced challenges related to the rapid identification of cases, need for isolation facilities, safe handling of specimens, and intensive study requirements. We also encountered difficulties finalizing ethical reviews and research contracts in a timely enough way. These experiences underscore the potential value of developing research protocols and finalizing approvals in advance, to prepare for future outbreaks, and emphasize the importance of ongoing community engagement.

Conclusion

Despite the limitations on enrollment into this cohort imposed by the dynamic nature of the global mpox epidemic, we believe that our protocol and study documents can serve as a useful template for similar research protocols aimed at characterizing future emerging infections.

Key to the success of such efforts in the future include a multidisciplinary approach to considering relevant study outcomes, rapid protocol activation in the face of early warnings regarding epidemic emergence, and the engagement of community partners in as many aspects of the study as possible.

Executive summary

Introduction

- Mpox is a systemic orthopoxvirus infection characterized by systemic flulike symptoms, and widely disseminated vesicular/ulcerative skin lesions.
- A global mpox epidemic emerged in May 2022, concentrated among self-identified gay, bisexual and other men who have sex with men (GBM).
- Mpox was classified as a public health emergency of international concern by the WHO.

Introduction to the study

- The Mpox Prospective Observational Cohort Study (MPOCS) is a multicentre non-interventional study of individuals in Canada with confirmed or suspected mpox infection.
- Study objectives are:
  To describe the clinical manifestations of mpox infection during the Canadian outbreak;
  To assess the psychosocial impacts of mpox-related illness and isolation requirements;
  To describe the transmission-related characteristics of mpox infection; and
  To characterize virologic aspects of infection over time.
- The study was designed in collaboration with stakeholders including front-line clinicians; national, regional and local public health authorities; scientists from diverse disciplines, and community members.

Design

- Participants are individuals of any age with suspected or confirmed mpox infection, who consent to weekly collection of clinical data, questionnaires, photographs and biospecimens (blood, urine, nasopharyngeal swabs, oropharyngeal swabs, rectal swabs, semen samples or vaginal swabs as appropriate, up to three skin lesions and breastmilk if lactating) until one week after the complete clinical resolution of the acute illness (Part 1).
- An optional extension phase of the study (Part 2) involves ongoing data collection during the convalescent phase of illness until twelve weeks after symptom onset.
- Initial target sample size is n = 100 confirmed mpox cases in Part 1.

Data analysis

- Data on the clinical manifestations, psychosocial impacts and epidemiologic aspects of mpox will be analyzed descriptively, including exploration of variation related to HIV infection, gender identity and prior smallpox vaccination.
- The key virologic outcome is detectability of mpox viral DNA by polymerase chain reaction (PCR) along with the associated cycle threshold, as well as titres of infectious virus, in different anatomic compartments and examining the viral genomic sequence.
- We will estimate the time until complete resolution of DNA detectability for each specimen type by modeling exponential decay in cycle threshold value as a function of time (day since symptom onset) using linear mixed effects regression models.

Discussion

- Shortly after study launch, mpox case counts declined rapidly in Canada, in conjunction with the deployment of a 3rd generation live non-replicating smallpox vaccine and extensive behavior change within GBM communities.
- The MPOCS study enrolled 26 individuals during the primary wave of the epidemic, considerably short of our initial target of 100; factors contributing to the shortfall include the protracted time taken for finalizing research contracts, delays in securing ethical approvals for protocol amendments, and limited human resources.
- The study remains open to enrollment in hopes of recruiting participants during potential future waves of the epidemic in Canada.

Conclusion

- The 2022 global mpox epidemic is representative of the ongoing possibility of emerging/ re-emerging zoonotic infectious threats to human health, and our protocol may be a useful template for similar studies of future emerging infections.

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10.2217/fvl-2023-0189

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Competing interests disclosure

DHS Tan's institution has received support from Abbvie and Gilead for investigator-initiated research studies and support from Glaxo Smith Kline for participation in industry-sponsored clinical trials. SL Walmsley has served on advisory boards, speaking engagements, CME events, symposiums, and conduct clinical studies for ViiV Health Care, GSK, Merck, and Gilead Sciences. MB Klein reports grants for investigator-initiated studies from ViiV Healthcare, AbbVie, and Gilead; and consulting fees from ViiV Healthcare, Merck, AbbVie, and Gilead. The authors have no other competing interests or relevant affiliations with any organization or entity with the subject matter or materials discussed in the manuscript apart from those disclosed.

Writing disclosure

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

This study is conducted in accordance with the ICH-GCP Guidelines and the principles in the Declaration of Helsinki. The relevant Research Ethics Board (REB) of all participating institutions must review all study documentation in order to safeguard the rights, safety, and well-being of study participants. All participants in the study must provide written informed consent prior to the initiation of study activities, in accordance with principles outlined in the 2nd edition of the Tri-Council Policy Statement on Ethical Conduct of Research Involving Humans (TCPS2).

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