Characteristics of the sexual networks of gay, bisexual, and other men who have sex with men and impact of past interventions on mpox transmission during the 2022 outbreak in Montréal, Toronto, and Vancouver (Canada)

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Abstract

Background: The 2022-2023 global mpox outbreak affected more than 90,000 people in 110 historically non-endemic countries, including Canada. Almost all reported Canadian cases were among gay, bisexual, and other men who have sex with men (GBM) and 70% of the cases occurred in the country's three largest cities: Montréal, Toronto, and Vancouver. It remains unknown how characteristics of GBM sexual networks and public health interventions shaped mpox's transmission dynamics in the three cities.

Objectives: My thesis aims to understand mpox outbreaks and inform preparedness and response to re-emerging threats through data-driven statistical and mathematical modeling. Specifically, I addressed two main research questions:

1) How did GBM's sexual networks affect mpox's transmission potential in Montréal, Toronto, and Vancouver?
2) What is the relative contribution of changes in sexual partner numbers, contact tracing/isolation, and first-dose vaccination to the epidemic downturn of the 2022-2023 mpox outbreak?

Methods: For 1), I leveraged the *Engage Cohort Study* (2017-present), which recruited self-identified GBM in Montréal, Toronto, or Vancouver via respondent-driven sampling (RDS). Using this data, I compared GBM's self-reported number of sexual partners in the past 6 months (P6M) across cities and by time periods (i.e., pre-COVID-19 pandemic, pandemic, and after lifting travel restrictions). I modeled the distributions of sexual partners using Bayesian negative binomial regressions, adjusting for key correlates, survey weights, and loss to follow-up. I then developed a deterministic mathematical model to estimate mpox's city-specific basic reproduction number (R_0). For 2), I examined if GBM's number of sexual partners changed during the peak of the mpox outbreak in Canada (May–August 2022) compared to the rest of 2022 using a negative binomial regression model. I expanded the deterministic mathematical model to estimate the averted fraction of new infections (AF) in the first 150 days of the outbreak through the three interventions separately, as compared to the counterfactual scenario of an unmitigated epidemics.

Results: A total of 2,449 GBM participated in *Engage* (Montréal: 1,179; Toronto: 517; Vancouver: 753). The pre-COVID-19 pandemic distribution of sexual partner numbers (P6M) was similar across cities: participants' mean number of partners was 10.4 (95% credible interval [CrI]: 9.4-11.5) in Montréal, 13.1 (11.3-15.1) in Toronto, and 10.7 (9.5-12.1) in Vancouver. Partner numbers decreased greatly during the COVID-19 pandemic in all cities: 4.7 (4.0-5.5) in Montréal, 4.3 (3.3-5.8) in Toronto, and 5.5 (4.3-7.3) in Vancouver. Post-travel-restrictions, sexual partner numbers increased but remained well below pre-pandemic levels: 5.5 (4.7-6.4) in Montréal, 7.2 (5.7-9.1) in Toronto, and 6.7 (5.3-8.4) in Vancouver. The estimated R_0 for mpox varied from 2.4 to 2.7 between cities.

During the peak of the mpox outbreak, GBM might have had fewer sexual partners compared to the rest of 2022, but the estimates were imprecise. A larger decline was observed among GBM with >7 sexual partners (P6M) before 2022 (rate ratio [RR]: 0.67, 95%CrI: 0.31-1.43), as compared to 0.80 (0.47-1.36) among those with ≤ 7 sexual partner, but credible intervals were overlapping and very wide. Cases prevented by changes in sexual partner numbers and contact tracing/isolation were around 12% and 14% in the cities, respectively. Vaccination averted most cases in all cities, contributing to 21% (16%-33%), 22% (16%-41%), and 39% (35%-48%) of infections prevented in Montréal, Toronto, and Vancouver, respectively.

Conclusions: The 2022-23 mpox outbreak in Canada occurred while sexual activity had not yet recovered to pre-pandemic levels and ongoing surveillance is warranted. In case of mpox resurgence, ensuring contact tracing/isolation, as well as increasing vaccination coverage among individuals with high numbers of sexual partners, should be prioritized.

Résumé

Contexte : L'épidémie mondiale de mpox de 2022-2023 a touché plus de 90 000 personnes dans 110 régions historiquement non endémiques, y compris le Canada. Presque tous les cas signalés au Canada concernaient des hommes gais, bisexuels et autres hommes ayant des relations sexuelles avec des hommes (GBM) et 70 % des cas sont survenus dans les trois plus grandes villes du pays: Montréal, Toronto et Vancouver. On ignore comment les caractéristiques des réseaux sexuels de GBM et les interventions de santé publique ont façonné la dynamique de transmission du mpox dans les trois villes.

Objectifs : Ma thèse vise à comprendre les épidémies de mpox et à éclairer la préparation et la réponse aux menaces ré-émergentes grâce à une modélisation statistique et mathématique, basée sur les données. Concrètement, je réponds à deux questions de recherche:

1) Comment les réseaux sexuels de GBM sont associés au potentiel de transmission du mpox à Montréal, Toronto et Vancouver?

2) Quelle est la contribution relative des changements dans le nombre de partenaires sexuels, le traçage des contacts/isolation, et la vaccination (1 dose) sur le nombre de cas de mpox?

Méthodes : Pour 1), j'ai utilisé l'étude de *Cohorte Engage* (2017-présent), qui a recruté des GBM auto-identifiés à Montréal, Toronto et Vancouver via un échantillonnage axé sur les répondants (RDS). À l'aide de ces données, j'ai comparé le nombre de partenaires sexuels autodéclaré au cours des 6 derniers mois par villes et périodes (c.-à-d., avant la pandémie de COVID-19, durant la pandémie et après la levée des restrictions de voyage). J'ai modélisé les distributions des partenaires sexuels à l'aide de régressions binomiales négatives bayésiennes, en ajustant pour les corrélats clés, les poids d'enquête et les poids de pertes au suivi. J'ai ensuite développé, paramétré et calibré un modèle mathématique déterministe pour estimer le taux reproduction de base ($\mathcal{R}_0$) du mpox spécifique à chaque ville. Pour la question 2), j'ai examiné si le nombre de partenaires sexuels de GBM avait changé pendant le pic de l'épidémie de mpox (mai-août 2022) par rapport au reste de 2022 en utilisant un modèle de régression binomiale négative. J'ai adapté le modèle mathématique déterministe pour estimer la fraction évitée des nouvelles infections (FA) au cours des 150 premiers jours de l'épidémie grâce aux trois interventions

séparément. La contribution relative de ces interventions a été estimée séparément pour ces trois interventions et comparée à un scénario contrefactuel sans intervention.

Résultats : Au total, 2 449 GBM ont participé à *Engage* (Montréal : 1 179; Toronto : 517; Vancouver : 753). La répartition du nombre de partenaires sexuels avant la pandémie de COVID-19 était similaire dans toutes les villes : le nombre moyen de partenaires des participants au cours des 6 derniers mois était de 10,4 (intervalle de crédibilité [ICr] à 95% : 9,4-11,5) à Montréal, 13,1 (11,3-15,1) à Toronto, et 10,7 (9,5-12,1) à Vancouver. Le nombre de partenaires a considérablement diminué pendant la pandémie de COVID-19 dans toutes les villes : 4,7 (4,0-5,5) à Montréal, 4,3 (3,3-5,8) à Toronto et 5,5 (4,3-7,3) à Vancouver. Après la levée des restrictions de voyage, le nombre de partenaires sexuels a augmenté, mais est resté bien inférieur aux niveaux d'avant la pandémie : 5,5 (4,7-6,4) à Montréal, 7,2 (5,7-9,1) à Toronto et 6,7 (5,3-8,4) à Vancouver. Le $\mathcal{R}_0$ du mpox estimé varie de 2,4 à 2,7 selon les villes.

Les GBM pourraient avoir eu moins de partenaires sexuels pendant le pic de l'épidémie de mpox par rapport au reste de l'année 2022, mais les estimés sont imprécis. Une baisse plus importante a été observée parmi les GBM avec >7 partenaires sexuels avant 2022 (rapport de taux [RR] : 0,67; 95%CrI : 0,31-1,43), contre 0,80 (0,47-1,36) chez les personnes ayant ≤7 partenaires sexuels. Cependant les intervalles de crédibilité se chevauchent et sont larges. Les cas évités grâce à la modification du nombre de partenaires sexuels et à la recherche des contacts/isolation représentaient tous deux environ 12% et 14% dans les villes, respectivement. La vaccination a évité 21% (16%-33%), 22% (16%-41%) et 39% (35%-48%) des infections à Montréal et Toronto et Vancouver, respectivement.

Conclusions : L'épidémie de mpox de 2022-23 au Canada s'est déroulée dans un contexte où l'activité sexuelle n'était pas revenue à son niveau prépandémique. En cas de résurgence, tracer les contacts et accroître la couverture vaccinale parmi les personnes ayant un nombre élevé de partenaires sexuels devraient être priorisés.

Preface

This thesis focuses on the 2022-2023 mpox outbreak in Canada, which primarily affected gay, bisexual, and other men who have sex with men (GBM) in Montréal, Toronto, and Vancouver. Throughout this thesis, I use the term *men* to refer to individuals who self-identify as cisgender or transgender men. The thesis starts with an introduction to provide context to the 2022-2023 global mpox outbreak, the epidemics in Canada, and the main public health interventions. In Chapter 1, I review the literature on mpox, including its epidemiology, spread among GBM sexual networks, and treatment and prevention strategies. Chapter 2 presents the objectives of this thesis. Chapter 3 describes the study population and the methodology. Analyses and results for the two objectives are presented in the form of two manuscripts in Chapter 4 and 5, respectively. In Chapter 6, I discuss the implications of my results within the context of mpox prevention and control efforts. Finally, I provide concluding remarks in Chapter 7.

This thesis was prepared according to the guidelines for a Manuscript-Based Thesis. The results are given in the following manuscripts:

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Contribution of Authors

FX, JLFA, SM, MI, and MM-G conceptualized the project. FX conducted the literature review.

For the 1st manuscript, FX and JLFA cleaned the data and drafted the initial version of the manuscript (Chapter 4). JLFA conceived and optimized the regression and post-stratification. MM-G, JFLA, and FX developed the mathematical model in Chapter 4. FX performed sensitivity analyses adapting the regression, estimated the basic reproduction number from the next-generation matrix, and computed attrition weights. FX and JLFA revised Chapter 4 based on suggestions from MM-G, JC, SM, MI, JK, LW, HS, OG, SS-S, MD, DG, TH, EC and TZ. All authors contributed intellectual content and edited the manuscript.

For the 2nd manuscript, FX, MM-G, and CD conceived the study (Chapter 5). FX developed the regression model for the first objective and the mathematical model of mpox transmission and control for the second objective. FX performed the regression and modeling analyses with guidance from CD, JLFA, MM-G, SM, and MI. JK and LW developed and coded the methodology to balance sexual partnerships. FX conducted all sensitivity analyses. FX drafted the initial version of the manuscript. FX revised Chapter 5 based on suggestions from MM-G, CD, and JLFA.

All authors contributed intellectual content and edited the manuscripts. This thesis was written by FX.

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List of Acronyms and Abbreviations

AF	Averted fraction of new infections
ART	Antiretroviral therapy
BFGS	Broyden-Fletcher-Goldfarb-Shanno
CAD	Canadian dollar
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CrI	Credible interval
DRC	Democratic Republic of Congo
EC	Emergency Committee
ESS	Effective sample size
GBM	Gay, bisexual, and other men who have sex with men
HIV	Human immunodeficiency virus
IPC	Inverse probability of censoring
IPCW	Inverse probability of censoring weights
LTFU	Loss to follow-up
MPXV	Human monkeypox virus
MVA-BN	Modified Vaccinia Ankara-Bavarian Nordic
NAAT	Nuclear acid amplification test
NB	Negative binomial
NGM	Next-generation matrix
P6M	Past 6 months
PEP	Post-exposure prophylaxis
PHEIC	Public health emergency of international concern
PLHIV	People living with HIV
PrEP	Pre-exposure prophylaxis
RDS	Respondent-driven sampling
REB	Research ethics board
REF	Reference
$\mathcal{R}_e$	Effective reproduction number
RR	Rate ratio
$\mathcal{R}_0$	Basic reproduction number
SD	Standard deviation
SE	Standard error
SEIR	Susceptible-Exposed-Infectious-Recovered
SIR	Sampling importance resampling
SMD	Standardized mean differences
STI	Sexually transmitted infection
SVEIJR	Susceptible-Vaccinated-Exposed-Infectious-Isolated-Removed
U.S.	United States of America
UK	United Kingdom
VE	Vaccine effectiveness
WHO	World Health Organization

Introduction

Mpox is an infectious disease caused by a zoonotic orthopoxvirus endemic in rural, forested areas of Central and West Africa [1]. In 2022-2023, an unprecedented global mpox outbreak driven by rapid human-to-human transmission via close and often sexual contacts led to over 90,000 confirmed cases in 116 countries [2]. On July 23rd, 2022, the Director-General of the World Health Organization (WHO) declared the mpox outbreak a *public health emergency of international concern* (PHEIC), which remained in effect until May 2023 [3].

Gay, bisexual, and other men who have sex with men (GBM) were disproportionately affected by the 2022-2023 mpox outbreak [4]. As of October 2023, most of the 1,443 Canadian cases with available data self-identified as GBM [5]. Further, more than 70% of all reported cases were concentrated in the country's three largest cities: Montréal, Toronto, and Vancouver [6–9].

The structure of the GBM sexual networks was an important factor in shaping local mpox outbreaks in Europe and the U.S. [10–14]. The mpox outbreaks took place in the aftermath of the COVID-19 pandemic, and the added disruptions from the pandemic contributed uncertainty to our understanding of the sexual behaviours and how that could have shaped mpox's transmission potential in Canada.

In Canada, the local outbreaks were met with swift responses from public health actors, including case management, contact tracing/isolation, and vaccination. The number of confirmed mpox cases in the three cities peaked from late-June to mid-July 2022, declined thereafter, and has been sporadic since mid-November 2022 [6–8]. Although the mpox epidemics have waned in Canada, the role played by potential changes in sexual behaviours, contact tracing/isolation, and vaccination in curbing transmission remains uncertain. These are important to understand for ensuring future preparedness and serve as a starting point of developing a comprehensive mpox outbreak response strategy.

Objectives

This thesis aims to improve our understanding of mpox and its transmission among GBM sexual networks in the three major urban centers of the country. Using data from a large, population-based prospective cohort of GBM in Montréal, Toronto, and Vancouver, I describe the

association between GBM sexual networks and mpox transmission potential and examine the impact of public health interventions on controlling the mpox outbreaks.

Chapter 1

Literature Review

This chapter starts by reviewing the epidemiology of mpox in historically endemic countries. I then describe the 2022-2023 global mpox outbreak and its spread among the sexual networks of gay, bisexual, and other men who have sex with men (GBM), as well as the community and public health responses in the affected countries. Lastly, I highlight knowledge gaps on the impact of sexual networks and public health interventions on mpox outbreaks in Canada.

1.1 Epidemiology and transmission of mpox

1.1.1 Epidemiology of mpox in endemic countries

History and burden of mpox

Mpox is formerly known as "monkeypox". It is an infectious disease caused by the human monkeypox virus (MPXV), a zoonotic orthopoxvirus first identified in 1958 among captive monkeys in Denmark [15]. The first human case was reported in 1970 in a child in the Democratic Republic of Congo (DRC) [15,16]. Since then, human cases have been reported from 10 West and Central African countries, with most cases concentrated in the DRC [15,17].

In the last two decades, endemic countries have faced a growing burden from mpox, a challenge largely ignored by the global community [18,19]. In the most affected country, the DRC, case numbers jumped to more than 18,000 between 2010-2019, as compared to over 10,000 in 2000-2009 [17]. Historically, the disease primarily affected children. In more recent times, it has affected individuals from a broader age range: the age of cases in endemic countries rose from a median of 4 years in the 1970s to 21 years in the 2010s [17]. More than 80% of the cases reported in the DRC occurred among individuals without prior smallpox vaccination [17], which could offer cross-protection against MPXV [20]. These age and vaccination patterns suggest that the rising incidence could be attributed to cessation of smallpox mass vaccination in 1980, after its eradication [18,19,21].

Transmission

The definitive natural reservoir of MPXV remains unknown. However, available evidence points to African rodents as the animal reservoir [15,22,23]. Rats, mice, squirrels, monkeys, prairie dogs, and humans have been identified as hosts of the disease based on existing reports [24].

MPVX can be acquired through animal-to-human and human-to-human transmission [24]. Animal-to-human infections are associated with direct and indirect contact with rodents and primates, including handling infected animals and exposure to their blood and bushmeat [15,25]. Human-to-human transmission can occur through close contact with mpox rash and scabs from an infected person, saliva and large respiratory droplets, and contaminated fomites [15,24,25]. It remains uncertain whether MPVX can spread through airborne particles or seminal or vaginal fluids [26,27]. In a 2017 outbreak in Nigeria, one of the historically endemic countries, sexual transmission between humans was hypothesized [28]

Clinical course

Two distinct clades of MPXV have been identified: Clade I (also known as the Central African or Congo Basin clade) and Clade II (known as the West African clade). Clade I is reported more often in endemic countries, with a case fatality rate of 10% [29]. It has instances of human-to-human transmission before the 2022-2023 global outbreak [22]. Compared to Clade I, Clade II is associated with less severe symptoms and better prognosis [18,29,30], with a case fatality rate of around 3-6% [29] and no reported human-to-human transmission prior to the 2022-2023 global outbreak [22]. Overall, the case fatality rate was 8.7% in endemic countries from 1970 to 2019 [17].

Typical prodromes of MPXV infections are headache, fever, fatigue, sore throat, and muscle aches, followed by symptoms including swollen lymph nodes, and skin and mucosal rash on hands, feet, face, mouth, chest and genital areas [15]. Occasionally, secondary bacterial infections occur on affected skin or lesions, but these infections are generally mild [31]. Mpox is usually self-limited, with most people recovering within 2-4 weeks [20], but can be severe or lethal among children, pregnant or immunocompromised people [15,18].

Treatment

There is no specific treatment for mpox. Clinical professionals often focus on symptomatic management, wound care, pain control, and treatment of secondary bacterial infections [25]. These measures are usually sufficient for people who are not immunocompromised [32]. Several antiviral therapeutics, including tecovirimat, brincidofovir, and cidofovir, showed activity against orthopoxviruses [32], but may present risk of drug resistance and adverse events [33]. Hence, they are only recommended for people living with HIV (PLHIV) or at high risk of severe mpox [32,33]. Developed for smallpox, clinical trials of tecovirimat for mpox treatment are currently underway in Europe (Phase 4), the U.S. (Phase 3), Canada (Phase 3), and the DRC (Phase 2) [32,34–36].

Prevention

Mpox prevention in endemic areas has been largely ignored before the 2022-2023 global mpox outbreak [37]. In these areas, reliance on bushmeats as local protein sources, along with a lack of identification methods for infected animals, make it challenging to avoid both direct and indirect contact with infected rodents and primates [25].

Smallpox vaccination offers cross-protection against all orthopoxviruses and was authorized to use for people at high risk of mpox in November 2020 in Canada [20,23,38,39]. Post-exposure prophylaxis (PEP) vaccines are given to people within 14 days of a presumed or known MPXV exposure to prevent acquisition or decrease severity [40]. Pre-exposure prophylaxis (PrEP) vaccines are offered prophylactically to people at high risk of MPXV exposure. Smallpox vaccines have evolved through three generations: 1st and 2nd generation vaccines were historically used for smallpox vaccination and contained live and replicative virus, thus possessing risk of life-threatening adverse infections [23]. 3rd generation vaccines use attenuated viruses and no longer presents risks of inadvertent transmission [23].

Modified Vaccinia Ankara-Bavarian Nordic [MVA-BN] is a 3rd generation vaccine derived from replication-deficient virus and was approved to be administered as two doses, separated by 28 days for protecting against MPXV. The registered trademark of MVA-BN is *Imvamune*® in Canada, *Jynneos*® in the U.S., and *Imvanex*® in the European Union. In this thesis, I refer to MVA-BN as *Imvamune*®. *Imvamune*® has shown a favorable safety profile across 22 clinical trials in all populations, including PLHIV [41]. Studies have revealed that *Imvamune*® is immunogenic

against MPXV in humans and antibody responses were comparable between PLHIV and those not living with HIV [42]. The administration of a two-dose PrEP regimen is more effective [41,43]: vaccine effectiveness [VE] for two-dose *Imvamune*® against MPXV varies from 66%-89% across studies [44–46], and VE for one-dose PrEP was estimated around 36%-86% [44–50]. In a Spanish cohort of PLHIV, the VE for one-dose *Imvamune*® against MPXV was 79%, 14 days after vaccination [51]. Duration of MPXV protection for *Imvamune*® remains unclear [5,39].

Despite their effectiveness, mpox vaccines have not been available in endemic countries except sporadically as part of research studies [33,38,52]. Previous vaccinations against smallpox during the global smallpox eradication programme (1966-1980) could provide some level of cross-protection for MPXV [20,53]. Nevertheless, the immunity against MPXV among vaccinated individuals decreased over time [53] and it is challenging to quantify how much residual protection remains in different populations.

1.1.2 Mpox outbreaks in non-endemic countries before 2022

Sporadic clusters of human mpox cases outside of Africa have been documented. In 2003, Gambian giant rats imported from Ghana infected cohabiting pet prairie dogs in the U.S. [54]. This resulted in 53 human cases of mpox (Clade-II) in Illinois, Indiana, and Wisconsin. It represented the first mpox outbreak outside Africa [22]. Investigations indicated that the primary route of transmission was from close contact to infected prairie dogs, but the possibility of human-to-human transmission could not be ruled out [54]. In October 2018 and May 2019, two cases occurred respectively in Israel and Singapore, both with travel history to Nigeria [55,56]. In May 2021, mpox (Clade-II) developed in a man who returned with their family to the United Kingdom after living and working in Nigeria. Two family members respectively showed mpox symptoms 19 and 33 days after the man's symptoms' onset, suggesting possible human-to-human transmission [57]. In July and November 2021, two cases occurred in the U.S., both with a travel history to Nigeria [58,59].

The outbreaks in the non-endemic countries demonstrated mpox's capacity to circulate in a globalizing world. This has been cautioned as a potential global health security risk, but was largely ignored until the 2022-2023 global outbreak [17,18,37].

1.2 The global mpox outbreak of 2022-2023

1.2.1 Origins of the outbreak

In 2022, non-endemic countries began reporting Clade-II mpox cases. The first confirmed case was reported in the UK on May 6th 2022, involving a man with a travel history to Nigeria [60]. Identification of confirmed cases rapidly expanded to people without direct travel links to historically endemic areas or imported animals, which was considered highly unusual [4,15]. By May 21st, 2022, more than 90 cases were confirmed in 13 historically non-endemic European and North American countries [60].

1.2.2 WHO's declaration of PHEIC

On July 23rd, 2022, mpox was declared a PHEIC by the WHO Director-General, overruling the opposite assessment by WHO's *Emergency Committee* (EC) [3]. The declaration represented the first time that the Director-General deviated from the decision of the EC in declaring a PHEIC [61]. The PHEIC declaration signaled that the mpox outbreak was unprecedented, posed a global public health risk, and required organized international response [62]. The decision also demonstrated WHO's growing commitment to ensuring health and rights among traditionally marginalized populations, including GBM, which might not be as prioritized by a technical committee like EC [61]. On May 11th, 2023, after a steady decline in the reported global case numbers, WHO Director-General declared end of mpox PHEIC [63].

1.2.3 Chronology of spread

Although the phylogenetic origin of the 2022-2023 global mpox outbreak is not definitive [64,65], studies showed its linkage to the 2017-2018 outbreak in Nigeria [66–69]. Based on an analysis of phylogenetic trees, two lineages of Clade-II MPXV among cases in non-endemic countries were identified: B.1 and A.2. A descendent of lineage A, lineage B.1 was the primary variant that caused the 2022-2023 global outbreak [67,68]. Lineage B.1 has a higher number of mutations than any lineage A variant, which could be attributable to its exposure to diverse demographic profiles [68,70].

On the other hand, lineage A.2 was only linked to a few cases in the U.S., Thailand, and India in 2021 and 2022 [71,72]. Yet, it might have circulated in humans and remained undetected for years before its last recorded exportation to other countries [68,70,71]. Three U.S. genomes

(July 2021-May 2022) of A.2 lineage were found to be on the same branch of the phylogenetic tree with three Nigerian genomes (December 2019-Januagry 2020) [68]. Since these importations occurred prior to the 2022-2023 outbreak, researchers proposed that the A.2 the lineage has spread independently of the one that caused the global outbreak [68,70].

The path of divergence between the two lineages remains unclear, but the observed phylogenetic differences and the number of cases associated suggest microevolution of MPXV as opposed to a recent diversification during the 2022-2023 outbreak [65,67,69].

1.2.4 Epidemiological features

Geographical spread

As of October 31st, 2023, a total of 91,788 cases from 116 countries were reported [2], 98% of which were from 110 non-endemic countries [73]. The five most affected countries by cumulative number of confirmed cases were the U.S. (n=30,771), Brazil (n=10,967), Spain (n=7,647), France (n=4,161), and Colombia (n=4,090) [2]. In Canada, most of the 1,515 mpox cases (May 19th, 2022-September 29th, 2023) were concentrated in the country's three largest cities: Montréal, Toronto, and Vancouver [6–9]. At least 98% of confirmed mpox cases in Canada with available data (n=1,443) were among self-identified men, most of whom reported sex with other men [30].

Clinical course of mpox during the 2022-2023 outbreak

The 2022-2023 outbreak is characterized by milder clinical manifestations, as compared to outbreaks in endemic countries [74,75]. With 170 confirmed deaths, the case fatality rate of 0.02% [73] was remarkably lower than that for Clade-I (10%) and II (3%-6%) in endemic countries [29,76]. The hospitalization rate was 7% in the 2022-2023 outbreak [74]. In Canada, 3% of all confirmed cases were hospitalized [9]. These proportions are much lower than the 35% hospitalization rates recorded in previous outbreaks in endemic countries [77].

Lesions found in genital or perianal areas were reported in >50% of all cases in the 2022-2023 outbreak [2], but was not commonly documented from previous outbreaks [22,39,78–80]. Prodromal symptoms were less often reported, which was a challenge to timely diagnosis and isolation [33].

Gay, bisexual, and other men who have sex with men (GBM)

This 2022-2023 outbreak was also differentiated by the outsized impact on GBM. Global cases with available data were predominantly male (>96%, as compared to 50%-60% in endemic countries) and were slightly older, with a median age of 34 years, as of October 31st, 2023 [2,17,81]. Sexual encounters comprised more than 80% of all reported transmission events [2,4]. The rapid, sustained human-to-human transmission through sexual networks had never been this salient prior to this outbreak.

People living with HIV (PLHIV)

The transmission of MPXV through dense sexual networks entailed that PLHIV and people with recent sexually transmitted infections (STI) could be disproportionally affected. Indeed, more than half (52%) of the global cases with available data were among PLHIV (as of October 31st, 2023) [2]. Among 1,969 mpox cases in a U.S. study, 38% were PLHIV, and 41% had an STI in the past year [82]. In the U.S., hospitalization rates among mpox cases were 5% higher for PLHIV (8%) than for people without HIV (3%) [82]. Most reported cases among PLHIV had similar outcomes to those without HIV. However, deaths occurred predominantly among those with low CD4 counts and high HIV viral load [83]. The specifics impacts of antiretroviral therapy (ART) for HIV treatment on the health outcomes of mpox cases remain unknown [84].

1.3 Mpox's spread among GBM's sexual networks

1.3.1 GBM sexual behaviours and risk factors

It is essential to understand how GBM sexual behaviours were associated with mpox transmission. In the UK, at least 80% of mpox cases resulted from partnerships with GBM with ≥10 anal sex partners in the past four months [85]. Studies also suggested that a densely connected core group of GBM with high sexual partner numbers likely sustained local outbreaks in many non-endemic countries [12,13,86].

Case interviews and modeling studies have identified a higher risk of mpox acquisition among GBM with multiple one-time sexual partnerships, those engaging in anal intercourse, condomless sex, meeting sexual partners through geospatial dating apps, or having sex on sex-on-premises venues (e.g., bathhouses and sex clubs) [13,87,88]. There is no clear clinical evidence

that anal intercourse poses a higher risk of mpox transmission compared to other types of sexual acts (e.g., oral sex). Wearing a condom does not provide complete protection from mpox but could reduce the risk of transmission [89]. Other risk factors included attending sex parties, group sex, and sexualized substance use (i.e., "chemsex") [14,90–92].

1.3.2 GBM community responses

Community advocacy

In most high-income countries, including Canada, health agencies and LGBTQ2S+ community organizations shared epidemiological updates, raised community awareness, and worked jointly to reduce mpox-related stigma [93–95]. In countries where GBM are traditionally marginalized, activism spearheaded by LGBTQ2S+ groups often faced difficulties due to the prevailing sociopolitical circumstances [96,97].

In Canada, GBM communities and LGBTQ2S+ advocacy groups disseminated evidence-based information on mpox through newsletters, workshops, and social media [96]. Community organizations worked with public health authorities and owners of sex-on-premises venues to improve access to diagnosis and information on vaccination [98,99].

Behavioural adaptations

Studies in various affected countries have shed light on behavioural adaptations among GBM in response to the mpox outbreak. A study in the Netherlands estimated a >10% decline in GBM's number of casual partners, with a higher decrease among those with high sexual activity levels [100]. A large online survey of GBM in the UK showed that over half of respondents reported behavioural adaptations to avoid mpox exposure [101]. Among those, reducing numbers of male sexual partners was most frequently reported [101]. Similarly, online surveys of GBM in the U.S. and Brazil found that around half of participants reported reducing their numbers of sexual partners after the onset of mpox outbreak [102,103].

The GBM community generally had a good understanding of mpox transmission and exhibited willingness to be vaccinated [103–105]. In a UK study, vaccination uptake was 90% among GBM offered a vaccine [101]. More than 80% of surveyed GBM in the Netherlands were willing to accept vaccination [106]. Higher acceptance was associated with living in urban areas,

connection to the GBM community, self-identifying as gay or homosexual (as opposed to bisexual), higher education level, being employed, and reporting their relationship status as single [101,106].

1.3.3 Public health responses

After the declaration of the PHEIC, the WHO issued comprehensive guidance on diagnosis, case investigations, contact tracing, vaccines and immunization for mpox [107]. Most affected countries, including Canada [5], followed these recommendations, actively ensuring surveillance and adopting prevention and control strategies [108]. Specifically, case surveillance, diagnosis, detection, isolation, and contact tracing were introduced in most non-endemic countries. However, comprehensive risk communication, community engagement, and mass immunization programs targeting at-risk populations were implemented mostly in high-income countries [33,108].

In Canada, local provincial and territorial public health authorities managed the responses to outbreaks [5]. Local public health authorities were responsible for contact tracing and administration of the *Imvamune*® vaccine to groups at risk of mpox [5,109].

Contact tracing

Contact tracing was implemented early in Montréal, where the first Canadian case was recorded. During the first four months of the epidemic, over 350 contact surveys were collected in that city [6]. An analysis showed that early in the outbreak, over half of the cases in Montréal mentioned visiting a sex-on-premises venue or participation in group sex, whereas in September, 2022, only 21% and 9% of cases mentioned those sources, respectively [6]. About 80% of contacts from cases were anonymous or non-traceable [6,109]. Contact tracing information for the other two cities was not available.

Vaccination

As of May 27th, 2022, PEP vaccination was offered to people with high-risk exposures to a suspected or confirmed mpox case in Montréal by the *Comité sur l'immunisation du Québec* (Québec Immunization Committee) [20,109]. Shortly thereafter, on June 3rd, 2022, one-dose PrEP vaccination was offered to sex workers, staff working in sex-on-premises venues, and GBM who met at least one of the following criteria: having at least two sexual partners where at least one has other sexual partners, having had an STI in the last year, or engaging in sexual activities in sex-

on-premises venues [20]. Given limited vaccine supply, the *Comité sur l'immunisation du Québec* delayed the administration of a second dose to maximize vaccine coverage [109,110]. The decision was quickly followed by other provinces [7,111]. Toronto and Vancouver respectively started one-dose PrEP vaccination on June 12th and June 20th, 2022 [7,111]. Second-dose vaccines became available in Montréal on October 6th, 2022 [109], followed by the other two cites [7,111]. Vaccination was administered at sexual health clinics, pop-up mobile clinics, and mass vaccination sites accessible to the GBM community [6,109,112,113].

As of mid-October 2022, about five months after the first reported mpox case in Canada, around 24,000 and 1,300 people in Montréal received first and second doses, respectively [109]. More than 35,000 first and 1,900 second doses were administered in Toronto [111]. In British Columbia, a total of over 18,000 doses (first- and second-doses combined) were offered by that time [7].

1.3.4 Impacts of GBM behaviour changes and public health responses on cases averted

Modeling studies have evaluated the contribution of behaviour changes to reducing mpox infections in different non-endemic countries. Based on a large GBM survey [13], Lin et al. estimated that reducing sexual behaviours with a higher risk (including number of sexual partners, one-time sexual encounters, participation of group sex, and/or visits to sex-on-premises venues) within high-activity groups alone would prevent 15% of the cases in the U.S. [114]. Clay et al. estimated that behavioural adaptation would have averted 25% of mpox cases in Washington DC (U.S.), primarily by contributing to the initial case reductions [115].

When the proportion of contacts traced and isolated was high, such measures could be more effective than behavioural adaptation. Ko et al. found that primary case detection followed by contact tracing and isolation was more impactful than reducing the number of close contacts among primary cases [116]. Chitwood et al. and Yuan et al. projected that tracing 50% and 65% of contacts can contain mpox transmission among GBM in the U.S. and a hypothetical metropolitan area, respectively [117,118].

In European countries and the U.S., vaccination was estimated to have averted a high percentage of new mpox infections. A network model of GBM in Belgium suggested that PrEP vaccination among half of GBM with a high partner change rate (30% of the population) could

contribute to a 95% reduction in case numbers [119]. Lin et al. estimated that two-dose vaccination alone prevented 21% of cases in the U.S., and 64% when combined with behaviour changes, compared to the absence of both measures [114]. The impact of those public health interventions has not been assessed in Canada yet.

1.4 Concluding remarks

Mpox has been a neglected tropical disease endemic to Central and West Africa that recently caused a major global outbreak [120], disproportionately affecting GBM. Although the WHO declared the end of the mpox PHEIC, it still poses a re-emerging global health threat. Given the unprecedented dominance of sexual human-to-human transmission, understanding the transmission and prevention impacts of the 2022-2023 outbreak are necessary. Because GBM were predominantly affected, quantifying how their sexual networks shaped outbreaks using population-based data will be key to understanding mpox's transmission potential. Despite growing evidence from other countries, it remains unknown whether GBM in Canada adopted similar behaviour changes during mpox and, if so, its impact on mpox's epidemic downturn. In this context, the relative contributions of vaccination and contact tracing is not known. Answering these questions will help improve Canadian preparedness to future outbreaks and the local public health responses.

Chapter 2

Study Objectives

The overarching aim of this thesis is to understand mpox outbreaks and inform preparedness and response to re-emerging threats through data-driven statistical and mathematical modeling. This was achieved through two specific objectives:

1) **Objective 1**: examine how GBM sexual networks were associated with mpox's transmission potential in Montréal, Toronto, and Vancouver, and

2) **Objective 2**: evaluate the relative contribution of changes in sexual behaviours, contact tracing/isolation, and first-dose vaccination on mpox outbreak dynamics.

Chapter 3

Study Methodology

Understanding the transmission dynamics of infectious diseases requires the use of quantitative tools that consider the various factors affecting the dynamics of outbreaks, from population sizes, heterogeneity in contact rates, latency and incubation periods, and transmission probabilities, to the direct and indirect benefits of interventions. Transmission-dynamics mathematical models allow for the integration and interpretation of diverse data sources to improve our understanding of infectious diseases.

Mathematical models of disease transmission can be roughly divided into static and dynamic models. In contrast with static models, which fixes the per subject disease acquisition rate ("*force of infection*") across time, dynamic models allow a force of infection depending on time-varying prevalence of the disease, as well as other behavioural and policy-level factors [121]. Dynamic models consider the interplays between disease transmission, interventions and risk factors and are therefore instrumental in providing reliable assessments of public health interventions. Dynamic models can further be categorized into network and compartmental models. Network models, a type of agent-based models, are simulation-based models that represents each agent separately, meaning that each can have heterogenous disease-related characteristics and interact with their neighbouring agents differently [122]. In contrast, compartmental models rely on differential equations and group individuals into states ("compartments") based on their characteristics [122]. They assume that individuals in one compartment behave in the same fashion. Although compartmental models cannot track each agent's disease trajectory, they can be sufficient for providing insight into infectious disease dynamics, are usually more computationally efficient, and require less data [122,123]. Most of the models used to study the 2022-2023 mpox outbreak were compartmental models [124].

This chapter describes the main data sources used in my thesis and the mathematical tools I employed, including compartmental models.

3.1 Data Sources

3.1.1 Engage Cohort Study

For both of my objectives, I leveraged data from the *Engage Cohort Study* (*Engage*; 2017-2023), a multi-site, prospective cohort study on the sexual health of gay, bisexual, and other men who have sex with men (GBM) in Montréal, Toronto, and Vancouver. Eligible participants resided in one of the three cities, identified as a cisgender or transgender man, were aged 16 years or older, reported sex with a man in the past six months (P6M), read English and/or French, and provided informed consent [125]. *Engage* participants completed questionnaires that captured various determinants related to sexual health outcomes, including socio-demographic characteristics and sexual behaviours. The questionnaires were developed based on scientific frameworks including Ivankovich's Model of Sexual Health [126], the access to health care framework [127], and syndemic theory [128].

Due to a lack of sampling frame for GBM, *Engage* utilized respondent-driven sampling (RDS) to recruit a representative sample of GBM. RDS is a type of chain referral sampling technique that aims to reach hidden, hard-to-reach populations through individuals' social networks [129]. The RDS approach used by *Engage* has been described previously [129–131]. Briefly, recruitment was initiated with a convenience sample of 27 (Montréal), 96 (Toronto), and 117 (Vancouver) initial recruits (i.e., "seeds") chosen to represent diverse characteristics of the GBM communities [129,132]. Each seed was given six coupons to distribute among their GBM peers. Participants received a compensation of $50 CAD for each visit and $15 CAD for each eligible recruit who completed a visit [133]. The study recruited a total of 2,449 GBM (Montréal: 1,179, Toronto: 517, and Vancouver: 753) over February 2017-August 2019. Follow-up visits were scheduled semi-annually, except annually in the first two years in Montréal and Toronto.

By leveraging this large, longitudinal dataset of GBM in the three cities, I was able to examine characteristics of GBM's sexual networks across cities and time for objective 1 and investigate potential change in partner numbers during the mpox outbreak for objective 2. Further, information from *Engage* was used to parameterize the mathematical models of mpox transmission used in my thesis.

In terms of study population, I included all *Engage* participants' baseline and follow-up visits from February 2017 to February 2023 for Objective 1, the latest data available at the time of analysis. For objective 2, I included participants with at least one visit during 2022, when the recent mpox outbreak primarily took place in Canada [9]. This restriction enabled me to compare the short-term change in sexual partner numbers during versus before the mpox outbreak, while avoiding potential confounding from disruption of sexual activities from the fifth wave of the COVID-19 pandemic [134].

3.1.2 Surveillance data on reported mpox cases

For both of my objectives, I utilized data on mpox reported to public health agencies (referred to as "reported cases" throughout the thesis). These included daily confirmed and probable mpox cases. The definition of a confirmed mpox case is a person detected with MPXV DNA by a nuclear acid amplification test (NAAT). A suspect case is a person with cutaneous lesions or at least one systemic symptom of mpox (not caused by another disease). A probable case is a person detected of *Orthopoxvirus* by NAAT, a suspect case with extensive recent exposure to a confirmed mpox case, or a suspect case who was male and recently had sex with a man [109].

For objective 1, I used provincial daily cases for Québec, Ontario, and British Columbia, as reported to the *Public Health Agency of Canada* [9]. The provincial cases were used since city-level data were not available at the time of analysis and most provincial cases were concentrated in these cities during the early phases of the outbreaks [6–8]. For Québec, only the total (confirmed and probable) cases counts were available.

For objective 2, I used surveillance reports published by the *Direction régionale de santé publique de Montréal* [6,109], *Public Health Ontario* [8,135], and the *British Columbia Centre for Disease Control* [7] to infer the confirmed fractions of total cases and the weekly-varying city fractions of provincial cases. Using these quantities, I estimated daily number of confirmed cases for each city.

3.1.3 First-dose vaccination

For Objective 2, I utilized reported data on the numbers of weekly vaccines administered, as published by the *Direction régionale de santé publique de Montréal* [109], *Public Health Ontario* [111], and the *British Columbia Centre for Disease Control* [7], all of which were assumed to be first-dose only –a reasonable assumption since second doses were largely available in

October 2022, after the epidemic downturn. The data was city-specific for Montréal and Vancouver. For Toronto, only provincial administered doses were available.

3.2 Statistical analyses

3.2.1 Characteristics of sexual networks across cities and time (objective 1)

Outcome

The primary outcome was the self-reported number of sexual partners in the P6M, measured through the question:

> "*During the PAST 6 MONTHS, with how many guys have you had any kind of sex (anal, oral, mutual masturbation, rimming, frontal/vaginal, etc.)?*".

As part of the sensitivity analyses, I also used the self-reported number of anal sexual partners in the P6M, measured from:

> *"During the past 6 months, how many guys have you had anal sex with (as top or bottom)?"*.

Time period definitions

To investigate changes in sexual partner numbers related to the COVID-19 pandemic in the cities, I defined three time periods as the following.

Table 1. Definition of time periods related to the COVID-19 pandemic.

Period	Definition
Pre-pandemic period	Participants' baseline visit (February 2017–August 2019)
Pandemic period†	Participants' earliest follow-up visit that occurred between June 2020–November 2021, when the first four waves of COVID-19 and physical distancing measures mainly took place in Canada
Post-restrictions period†	Participants' latest follow-up visit that occurred between December 2021–February 2023. To have a consistent time period across the three cities, I defined the start of this period with the easing of entry requirements for non-essential travel into Canada (September 3rd, 2021) [136]

†The start date for pandemic and post-restrictions period were shifted forward three months to account for the 6-month recall period in the *Engage* questionnaire.

Covariates

Informed by epidemiological data on the mpox epidemics, I identified the following correlates of the outcome (sexual partner numbers in P6M):

- Age (16-29, 30-39, 40-49, 50-59, ≥60 years);
- Relationship status (single, exclusive relationship, open relationship, unclear);
- HIV status (binary);
- Visit to bathhouses and/or sex clubs at least once in the P6M (binary);
- Attendance of group sex events at least once in the P6M (binary);
- Use of dating apps to find partners at least once in the P6M (binary); and
- Participation in transactional sex at least once in the P6M (i.e., received money and/or goods in exchange for sex; binary).

Age was categorized as mentioned above to ensure similarly sized groups and intervals. The relationship status variable was categorized into four groups to ensure adequate sample size. Specifically, various types of non-monogamous sexual arrangements were combined into the "*open relationship*" group and free text answers were examined and categorized into the most fitting group. An "*unclear"* relationship status refers to the situation where a couple did not have a conversation on only having sex with each other or not, or a participant did not enter a response to this question. HIV status was determined using 4th generation tests with a confirmatory assay. However, I used the self-reported HIV status for the 4% of baseline participants with unavailable testing data. The first three variables had complete data. I handled the missing values for the last four variables (1%, 1%, 9%, and 2% missing at baseline, respectively) using the missing indicator method [137]. Furthermore, an interaction between age and HIV status was included to reflect the heterogenous effect of age by HIV status on sexual partner numbers and to improve model fit.

Analyses

I modeled the observed distributions using a Bayesian negative binomial model. The goal of this model is twofold: to evaluate effect of covariates on sexual partner numbers, and to estimate the distribution of sexual partner numbers in each city at each period. The Bayesian approach was preferred over the Frequentist approach due to its ability to incorporate prior knowledge and uncertainty of results is easier to interpret.

To incorporate RDS-II and IPC weights (see next section) on fitted partner number distributions, I applied a post-stratification approach, a technique for adjusting a non-

representative sample after model fit, as the Bayesian framework does not allow for adding weights while fitting the model. I then compared the distribution of sexual partner numbers between a pair of cities or time periods by computing the proportion of post-stratified samples that had greater cumulative density for ≥25 and ≥100 partners. These thresholds were chosen based on previous literature [100].

3.2.2 Respondent-driven sampling weights

When using an RDS design, respondents with a larger social network are more likely to be sampled. RDS-II weights are inversely proportional to the respondent self-reported network size. They are assigned to every participant to compensate for the unequal selection probability [138]. In Engage, the network size was measured using the following question:

> "*How many men who have sex with men aged 16 years or older, including trans men, do you know who live or work in the [Metro Vancouver/Greater Toronto/Metro Montreal depending on site] area (whether they identify as gay or otherwise)? This includes gay/bi guys you see or speak to regularly; e.g., close friends, boyfriends, spouses, regular sex partners, roommates, relatives, people you regularly hang out with, etc.*".

Consistent with the recruitment process, I computed RDS-II weights for each city separately. The self-reported network size was capped at 150, in line with previous *Engage* analyses, to avoid undue influence of outliers. To ensure that the weights sum to the sample size in each city, I normalized the RDS-II weights. Specifically, for a participant i in city c, the RDS-II weight was:

$$\widetilde{w}_{RDS}^{ic} = \left(\frac{\sum_{i=1}^{n_c} network\ size_i}{n_c}\right)\left(\frac{1}{network\ size_i}\right).$$

The normalized RDS-II weight was:

$$w_{RDS}^{ic} = \widetilde{w}_{RDS}^{ic}\frac{n_c}{\sum_{i=1}^{n_c}\widetilde{w}_{RDS}^{ic}}$$

where $c \in \{Montréal, Toronto, Vancouver\}$ and n_c is the sample size for city c.

3.2.3 Inverse probability of censoring weights

To account for potential differential loss to follow-up (LTFU) in the *Engage* cohort, I calculated and included inverse probability of censoring weights (IPCW) in my analyses [139]. I

first determined potential predictors of LTFU. This was achieved through computing RDS-weighted standardized mean differences (SMD) to examine the imbalance in the predictors (all measured at baseline) between LTFU and retained participants. The predictors selected were all the covariates defined in 3.2.1 and four additional variables:

- Highest education being a bachelor's degree or higher (binary);
- Income (<20,000 annually, 20,000-40,000 annually, >40,000 annually);
- Self-identification as an ethnic minority (binary); and
- Greater than 5 sexual partners in the P6M (binary);

Income, ethnicity, and sexual partner numbers were categorized as mentioned above to account for potential non-linear relationships and ensure similarly sized groups. All four variables had complete data.

All selected predictors were included as covariates in matrix Z_{ij}. I then estimated the probability of LTFU given the selected predictors, referred to as $P(LTFU = 1|Z_{ij})$ for participant i in a combination of city and period j, using a binomial regression model. Specifically, the model is the following:

$$logit(LTFU_{ij}) = \alpha'_j + \beta'_j Z_{ij}$$

where α'_j is the model intercept for city-time period j and β'_j is the regression coefficients for city-time period j, for set of covariates Z_j.

The model estimates of $P(LTFU = 1|Z_{ij})$ are referred to as $\widehat{ps_{ij}}$ for participant i being LTFU in city-time period j. The IPCW are estimated as the multiplicative inverse of the probability of being LTFU:

$$\widehat{IPCW_{ij}} = \begin{cases} 1 \text{ if j} = \text{pre} - \text{pandemic period (i.e. } Engage \text{ baseline)} \\ \dfrac{1}{\widehat{ps_{ij}}} \text{ if participant i was LTFU at time period j} \\ \dfrac{1}{1 - \widehat{ps_{ij}}} \text{ otherwise} \end{cases}$$

For each city-time period j, the index c refers to the corresponding city. Combined with derived normalized RDS-II weights from 3.2.2, the derived RDS-IPC weight for participant i in city-time period j is the following [140]:

$$w_{ij} = \begin{cases} w_{RDS}^{ic} & \text{if j} = \text{pre} - \text{pandemic period (i. e. } Engage \text{ baseline)} \\ w_{RDS}^{ic}\left(\frac{1}{\widehat{ps_{ij}}}\right)(pr_j) & \text{if participant i was LTFU at time period j} \\ w_{RDS}^{ic}\left(\frac{1}{1-\widehat{ps_{ij}}}\right)(1-pr_j) & \text{otherwise} \end{cases}$$

Here, pr_j is the weighted proportion of participants LTFU in city-time period *j* and was included to make the RDS-IPC weights sum to the RDS-weighted sample sizes in city *c*, i.e., $\sum_{i=1}^{n_j} w_{ij} = \sum_{i=1}^{n_j} w_{RDS}^{ic}$.

$$pr_j = \frac{\sum_{i=1}^{n_c} w_{RDS}^{ic} I\left(LTFU_{ij} = 1\right)}{\sum_{i=1}^{n_c} w_{RDS}^{ic}}$$

3.2.4 Transmission potential of mpox (objective 1)

Rationale

To estimate the transmission potential of mpox among GBM in the three cities, the basic reproduction number was computed ($\mathcal{R}_0$). $\mathcal{R}_0$ is defined as the expected number of secondary cases arising from an initial case in an entirely susceptible population. We developed, parametrized, and calibrated a dynamic transmission model to compute $\mathcal{R}_0$ using the next-generation matrix (NGM) approach [141,142]. The NGM describes the transmission events across disease states and sexual activity groups.

Compared to estimating $\mathcal{R}_0$ from reported case counts [142], our modeling approach accounted for heterogeneity in sexual activity among GBM by including 20 sexual activity groups. Further, unlike a static model, a dynamic model allows the force of infection to depend on time-varying prevalence of individuals infectious for mpox, which ensured the $\mathcal{R}_0$ was computed as defined –before any GBM acquired immunity from mpox infections. Finally, the modeling approach accounted for the uncertainty of key natural history parameters.

Model Assumptions

The model assumed that all GBM were fully susceptible to mpox at the beginning of the outbreak. Given the short timeframe of the mpox epidemics, we modeled a closed population (i.e. no births or deaths). The exposed and infectious durations followed an Erlang-2 distribution. We only modeled the first 4-8 weeks of the outbreaks, prior to scale-up of vaccination in each city

(June 14th for Montréal and July 10th, 2022 for Toronto and Vancouver) [7,109,111,143]. The beginning of the vaccination scale-up was defined using the implementation date of a one-dose PrEP vaccination campaign among GBM [109] or, if unavailable, when first-dose vaccination coverage reached approximatively 10% [7,111]. GBM contact rates were assumed to be constant over the modeled period. Given reports of asymptomatic cases in the recent outbreak [144], we assumed that some infections were not reported to the surveillance databases, either because they were asymptomatic or the individual did not seek testing. Finally, we assumed an average 2-day delay between symptom onset and case confirmation.

Model Structure

We developed a risk-stratified *Susceptible-Exposed-Infectious-Recovered* (SEIR) model of mpox transmission among GBM (Figure 3.1). The model captured mpox's natural history and mixing between sexual activity groups, which means it considered the probability of sexual partnership formation between GBM with various levels of sexual activity. The categorization of the population into 20 sexual activity groups was chosen to capture GBM with highest contact rates, who were hypothesized to have primarily sustained the 2022-2023 mpox outbreak in the UK and the U.S. [13,86]. As we calibrated the model to the period before vaccination was scaled-up, the latter was not included. Further, we did not model contact tracing/isolation directly. Instead, we modeled the effective duration of the infectious period. That is, the average time between when people start being infectious and the time they isolate, stop having sexual contacts, or recover from the infection.

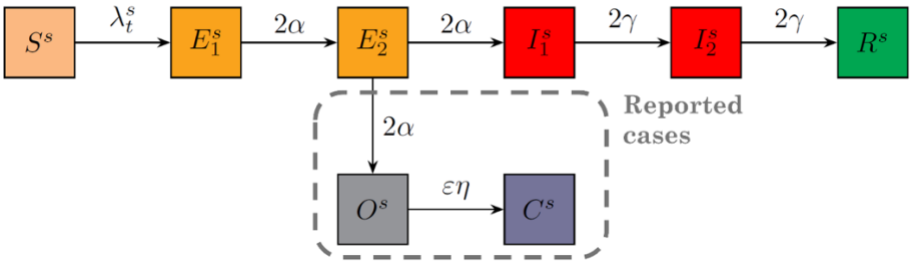

Figure 1. Diagram of the compartmental flows of the deterministic SEIR model of mpox virus transmission among gay, bisexual, and other men who have sex with men. The durations of the latent and infectious period are assumed to follow an Erlang-2 distribution. The gray box indicates compartments used to track the number of reported mpox cases, accounting for the delay between symptom onset and case confirmation and for the reporting fraction. S: number of susceptible; E: number of exposed; I: number of infectious; R: number of recovered, referring to

the state where GBM were no longer infectious or stopped having sex. $\boldsymbol{\lambda_t^s}$: force of infection specific to sexual activity group s at time t; $\boldsymbol{\alpha}$: rate of symptom onset among exposed = (latent period)$^{-1}$; $\boldsymbol{\gamma}$: rate of recovery among infectious individuals = (effective infectious period)$^{-1}$, calibrated parameter; $\boldsymbol{\varepsilon}$: the reporting fraction (proportion of cases that are reported, calibrated parameter); $\boldsymbol{\eta}$: reporting delay (rate at which cases are reported = 1/2 days).

Model Parametrization

Model parametrization is the process of assigning values or ranges to the model parameters, often informed by empirical data or previous research.

Contact rates for the SEIR model were informed by the sexual partner distributions of GBM from *Engage*. Specifically, we estimated the contact rates following 3.4.3, using the post-stratified samples of partner numbers in the post-restriction period defined in 3.2.1. We partitioned the city-specific GBM population into 20 groups to capture the tail of the distribution while ensuring that the smallest group size in that upper tail was realistic (>30 GBM). Natural history parameters were informed by the scientific literature.

Model Calibration

The objective of model calibration is to reproduce epidemiological outcomes of interest by statistically selecting parameters. We calibrated the SEIR model independently for each city to the daily reported mpox cases in their respective provinces, as described in 3.1.2.

We calibrated five parameters: 1) the number of imported cases, 2) the probability of transmission per effective contact, 3) the mixing parameter (between assortative by sexual activity group and proportional), 4) the duration of the infectious period, and 5) the fraction of all cases reported in the surveillance data.

Given its computational efficiency and flexibility, sampling importance resampling (SIR) was adopted for model calibration. Prior distributions for the infectious duration were derived from literature, and weakly informative priors were used for the other four parameters. We assumed a Poisson likelihood for the observed daily mpox cases. The posterior modes of the parameters were first obtained using nonlinear optimization via the *Broyden-Fletcher-Goldfarb-Shanno* (BFGS) algorithm. The proposal distribution for parameter sets was sampled 15,000 times from a multivariate *t*-distribution with 2 degrees of freedom, which has a thick tail and is more likely to

capture the characteristics of the target distribution. Then, we estimated the posterior distributions of the parameters by sampling 1,000 sets without replacement from the proposal distribution.

Estimation of $\mathcal{R}_0$ from NGM

Using the calibrated transmission probability and mixing parameter specific to each city, we estimated $\mathcal{R}_0$ for mpox by constructing the NGM. $\mathcal{R}_0$ can be computed as the largest non-zero eigenvalue of the NGM [141,142]. We repeated this computation for all posterior parameter sets to obtain the 95% credible intervals for the $\mathcal{R}_0$.

3.2.5 Change in sexual partner number during mpox outbreak (objective 2)

Outcome

The primary outcome was the self-reported number of sexual partners in the P6M as defined in 3.3.1. As part of sensitivity analyses, I also used visit to bathhouses and/or sex clubs and attendance of group sex events (as defined in 3.2.1) as outcomes.

Exposure

I defined the period of potential mpox-driven behaviour changes as May 19th, 2022—August 14th, 2022. The start of the period was the date of first mpox case in Canada, and the end was vaccination coverage reached >30% in the three cities, while ensuring a reasonable sample size.

Then, I defined the exposure variable ($\boldsymbol{x}$) as a visit's 6-month recall period coverage (in percentage) of the period of mpox-driven behaviour changes. This was done to account for the attenuation effect of the period (number of sexual partners, as in 3.3.1) in the regression model. Thus, the exposure variable is computed as the following:

$$\boldsymbol{x}(t) = \begin{cases} 0 \; if \; t < t_{mpox_{start}} or \; t > t_{mpox_{end}} \\ \dfrac{(t - t_{mpox_{start}}) + 1}{6 \; months} \; if \; t_{mpox_{start}} \leq t < t_{mpox_{end}} \end{cases}$$

where t is the visit date, $t_{mpox_{start}}$ is May 19th, 2022, and $t_{mpox_{end}}$ is August 14th, 2022.

Covariates

I adjusted for the following covariates: age, HIV status, months since January 1st, 2022, relationship status history, and sexual partnership history. The first two variables were categorized

in the same manner as in 3.2.1. We used calendar months since January 1st, 2022 (continuous) to account for recovering sexual activity after the COVID-19-related restrictions were lifted, according to results from 3.2.1. The relationship status history (categorized as in 3.2.1) and sexual partnership history were from the latest visit before 2022. The sexual partnership history was categorized into two levels (≤7 and >7 sexual partners) to account for potential effect modification in sexual partners in the P6M. Other groupings were also explored as sensitivity analyses. From the model fit, I obtained the rate ratio (RR) of the sexual partner numbers during the mpox outbreak period.

Analyses

Using data from *Engage* participants who had at least one visit in 2022, I estimated the change in sexual partner numbers during the mpox outbreak by fitting a Bayesian negative binomial regression model. I used a mixed-effect model since each observation unit in this analysis was a visit, and a participant can have multiple visits which could be correlated. To maximize power, the three cities were analyzed together.

3.2.6 Impact of past interventions (objective 2)

Rationale

To evaluate the impact of past interventions, I reproduced the mpox epidemics using mathematical modeling and computed the averted fraction (AF). Again, I chose a dynamic over static model. This allowed for a time-varying force of infection dependent on sexual behaviours adaptation, the number of infectious and isolated GBM, and the number immunized at a given time, thereby more accurately describing mpox transmission dynamics. A network model was not considered since data for individual-level disease status, sexual partnership duration and concurrency were not available.

Model Assumptions

I developed a *Susceptible-Vaccinated-Exposed-Infectious-Isolated-Removed* (SVEIJR) model of mpox transmission. My model considers mixing by 5 age groups, 10 sexual activity groups, and HIV status. I added mixing by age and HIV status compared to the model in 3.2.4, since surveillance data revealed that mpox cases concentrated among GBM aged between 30 and 39 years old and PLHIV [9,83]. Furthermore, to reduce the number of compartments and ensure

computational efficiency, I relaxed the assumptions that the exposed and infectious durations followed an Erlang-2 distribution. Hence, the model only has one exposed and one infectious compartment, with their respective durations assumed to follow exponential distributions. Finally, I modeled the epidemic for 150 days after the first reported case in each city, which covered most of the outbreak [6–8]. Based on the results of the analyses in 3.2.5**,** I assumed that GBM could reduce their sexual partner numbers in response to the mpox outbreak from May 19th to August 14th, 2022. All vaccines were assumed to be administered to GBM, as they were only offered to high-risk populations in Canada [20]. Given the *Comité sur l'immunisation du Québec*'s decision, all vaccinations during the model period were assumed to be first doses. Other model assumptions were the same as described in 3.2.4.

Model Structure

The model was adapted from the preceding objective (Figure 3.2) to include contact tracing/isolation, and vaccination. A time-varying fraction of susceptible GBM can be vaccinated against mpox with one-dose *Imvamune*® under the PrEP vaccination campaigns in the three provinces. Earlier studies have indicated modeling vaccine effectiveness as a leaky-type for *Imvamune*® was appropriate [39,145]. This means that all vaccinated individuals would acquire partial immunity, as opposed to the "*all-or-nothing*" type, which offers full immunity among a fraction of the vaccinated [146]. The model also includes an isolated compartment as once a GBM was exposed, they may be identified and notified through contact tracing and enter a 2-week isolation period.

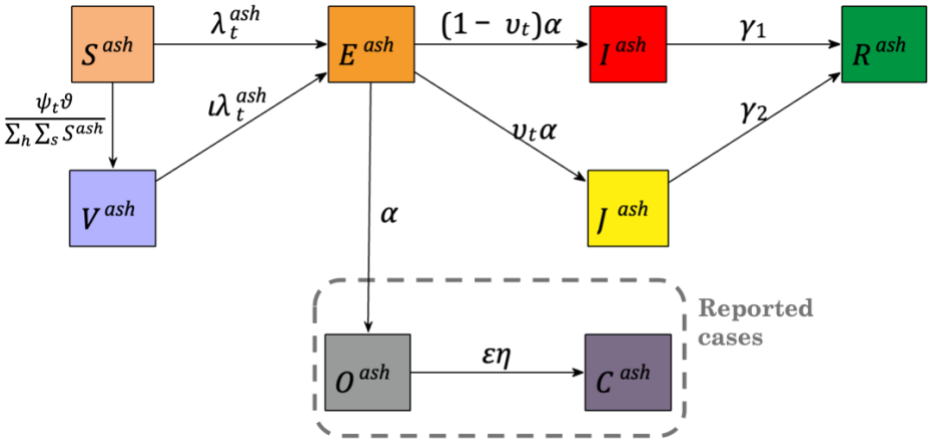

Figure 2. Diagram of the compartmental flows of the deterministic model of mpox virus transmission among gay, bisexual, and other men who have sex with men. *a*, *s*, *h*: superscripts for age groups, sexual activity groups, and HIV status, respectively. The name of the compartments refers to susceptible (S), exposed (E), infectious (I), removed (R), vaccinated (V), and isolated (J). Removed refers to the state where GBM are no longer infectious, stopped having sex, or developed natural immunity to mpox. Two other compartments are used to track symptom onset (O) and the case confirmation process (C). The main parameters are the following: ψ_t: first-dose vaccination doses at time t; $\boldsymbol{\vartheta}$: proportion of vaccinations received by age groups; $\boldsymbol{\iota}$: 1-vaccine effectiveness (assuming leaky type); $\boldsymbol{\lambda_t^{ash}}$: force of infection specific to group *a*, *s*, *h* at time t; $\boldsymbol{\alpha}$: rate of infectivity onset among exposed ≈ (latent period)$^{-1}$; υ_t: proportion traced and isolated among exposed at time t; $\boldsymbol{\gamma_1}$: rate of removal among infectious individuals who are not traced and isolated = (effective infectious period)$^{-1}$; $\boldsymbol{\gamma_2}$: rate of removal among infectious individuals who are traced and isolated = (self-isolation period)$^{-1}$; $\boldsymbol{\varepsilon}$: the reporting fraction (proportion of cases that are reported, calibrated parameter); $\boldsymbol{\eta}$: reporting delay.

Model parametrization

I parametrized the model using two major sources of data: *Engage* sexual partner numbers and the time series of administered vaccination doses in 3.1.3 [7,8,109]. From the *Engage* data, I derived the fitted distributions of sexual partner numbers (P6M) for each age-HIV status group using the approach described in 3.2.1. The numbers of sexual partners were obtained from the *Engage* data restricted to time in 2022 and before the mpox outbreak to best reflect GBM's sexual activity at the onset of the mpox outbreak.

I conducted a meta-analysis of the vaccine effectiveness of one-dose *Imvamune*®. I performed a search for English articles across PubMed and MedRxiv up to August 1st, 2023. I

included all studies that were published after the onset of the 2022-2023 mpox outbreak and originally reported the effectiveness of one-dose *Imvamune*® in human populations using various research designs, such as case control and cohort studies. I excluded non-human studies, modeling studies, and reviews. Other parameters were informed by previous literature.

Model calibration

I calibrated the SVEIJR model to the approximated city-specific daily reported mpox cases described in 3.1.2. We assumed a negative binomial likelihood for the observed daily mpox cases. The model calibration was performed for the cities together, using the same sampling importance resampling (SIR) procedure described in 3.2.4.

I calibrated five parameters: 1) the number of imported cases at the beginning of the epidemic, 2) the probability of transmission per effective contact, 3) the mixing parameter (i.e., scaler of the odds mixing matrix by sexual activity groups), 4) the duration of the infectious period among those not contact traced/isolated, 5) the RR of contact rate before the scale-up of vaccination in each city [7,109,111].

To obtain more stable parameter estimates, I assumed the probability of transmission per effective contact, the duration of the infectious period, and the RR of contact rate were constant across the three cities. The number of imported cases and the mixing parameter can vary across the cities.

Model scenarios

Once calibrated to the observed data, I used the model to evaluate the impacts of 1) the change in sexual partner numbers, 2) contact tracing/isolation, and 3) first-dose vaccination on mpox.

Specifically, for each posterior parameter set, I calculated the cumulative number of incident mpox cases (starting from the first imported cases to 150 days after) under the intervention scenario and a counterfactual scenario. The intervention scenario was implemented with keeping only the intervention of interest at the observed level and the other two interventions null. For the change in sexual partner numbers, the intervention scenario is implemented by running the model with the calibrated RR. The counterfactual scenario kept all three interventions null, while all else remained the same as the intervention scenarios. Using the cumulative number of infections under

the two scenarios, I estimated the impact of each intervention by the AF. Specifically, the AF was computed as the following.

$$AF = \frac{Cumulative\ Incidence_{counterfactual} - Cumulative\ Incidence_{intervention}}{Cumulative\ Incidence_{counterfactual}},$$

where cumulative incidence is the cumulative daily incidence of mpox over the first 150 days since the first reported mpox cases in each city.

3.3 Statistical software

All analyses were performed with R 4.3.2 [147]. The regression model for objective 1 and post-stratification were performed using package Stan (2.26.1) and *RStan* (2.32.3) [148,149]. The regression model for objective 2 was fitted using the package *rstanarm* (2.26.1) [150]. Finally, the compartmental model for objective 2 was coded using a C++ back-end, integrated in R with the package *Rcpp* (1.0.11) [151]. The compartment model was solved with a Euler algorithm with a time step of 6 hours.

3.4 Ethics

Ethics approval for *Engage* was obtained through following institutions: the Research Institute of the McGill University Health Centre and the Research Ethics Office of the Faculty of Medicine and Health Sciences, McGill University (A06-M32-23B), Toronto Metropolitan University (REB #2016-113), the University of Toronto (protocol #00033527), St. Michael's Hospital (REB #17-043), the University of Windsor (REB #33443), the University of British Columbia (H16-01226), Providence Health Care (H16-01226), the University of Victoria (H16-01226), and Simon Fraser University (H16-01226). Secondary analyses conducted as part of this thesis was approved by the Research Ethics Office of the Faculty of Medicine and Health Sciences at McGill University (A06-M32-23B). Data for mpox case time-series and vaccine doses were extracted from publicly available reports, for which no ethics approval was required.

Chapter 4

Study Results (Manuscript 1)

The first manuscript addresses objective 1 of my thesis and describes the distributions of sexual partner numbers across time periods, and mpox's transmission potential in Montréal, Toronto, and Vancouver. This manuscript was published in *The Journal of Infectious Diseases*.

> **Xiu F***, Flores Anato JL* (contributed equally), Cox J, Grace D, Hart T, Skakoon-Sparling S, Dvorakova M, Knight J, Wang L, Gatalo O, Campbell E, Zhang T, Sbihi H, Irvine M, Mishra S, Maheu-Giroux M. Characteristics of the sexual networks of gay, bisexual, and other men who have sex with men in Montréal, Toronto, and Vancouver: implications for the transmission and control of mpox in Canada. *The Journal of Infectious Diseases* 2024 Feb 7. https://doi.org/10.1093/infdis/jiae033.

I am a co-first author on this paper with Jorge Luis Flores Anato. He provided his written permission for me to include this manuscript into my MSc thesis. Here is the written agreement he provided via email below:

> "I, Jorge Luis Flores Anato, as co-first author, grant you permission to include in your thesis our manuscript '*Characteristics of the sexual networks of gay, bisexual, and other men who have sex with men in Montréal, Toronto, and Vancouver: implications for the transmission and control of mpox in Canada*' published in the *The Journal of Infectious Diseases* (2024)."

Characteristics of the sexual networks of gay, bisexual, and other men who have sex with men in Montréal, Toronto, and Vancouver: implications for the transmission and control of mpox in Canada

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Abstract

Background: The 2022-2023 global mpox outbreak disproportionately affected gay, bisexual, and other men who have sex with men (GBM). In Canada, almost all cases occurred among GBM and >70% of them were from the country's three largest cities: Montréal, Toronto, and Vancouver. We examined how the distributions of sexual partners 1) varied by city and over time (2017-2023) and 2) were associated with mpox transmission.

Methods: The *Engage Cohort Study* (2017-2023) recruited GBM via respondent-driven sampling in Montréal, Toronto, and Vancouver (n=2,449). We compared reported numbers of sexual partners in the past 6 months across cities and three time periods: pre-COVID-19 pandemic (2017-2019), pandemic (2020-2021), and post-restrictions (2021-2023). We modeled the distribution of sexual partners using Bayesian negative binomial regressions and post-stratification, adjusting for sampling design and attrition. We estimated mpox's basic reproduction number ($\mathcal{R}_0$) using a risk-stratified compartmental model.

Results: The pre-COVID-19 pandemic distributions of sexual partner numbers were similar across cities: participants' mean number of partners over the last 6 months was 10.4 (95%CrI: 9.4-11.5) in Montréal, 13.1 (11.3-15.1) in Toronto, and 10.7 (9.5-12.1) in Vancouver. Partner numbers decreased during the pandemic in all cities. Post-restrictions, sexual activity increased but remained below pre-pandemic levels. Based on reported cases and post-restrictions distributions of sexual partners, the estimated $\mathcal{R}_0$ for mpox varied from 2.4-2.7 between cities. The estimated mpox per-partnership transmission probability was 84% (uncertainty ranging from 51-98%). Cumulative incidences (0.7-0.9%) were similar across cities.

Conclusion: GBM sexual activity after restrictions were lifted remained below pre-pandemic levels. Comparable sexual partner distributions may explain similarities in mpox $\mathcal{R}_0$ and cumulative incidence across cities. With potential for further recovery in sexual activity, mpox vaccination and surveillance strategies should be maintained.

Key words: basic reproduction number; heavy-tailed network; mathematical model; men who have sex with men; mpox; sexual networks.

Background

A global outbreak of mpox unfolded from May-October 2022, predominantly affecting gay, bisexual, and other men who have sex with men (GBM). The outbreak was unprecedented in its spread through sexual networks, number of cases generated, and geographical distribution, with most of the nearly 90,000 confirmed cases worldwide (May 2022-June 2023) occurring among GBM in regions with no previous history of reported transmission [1–3]. These unusual transmission patterns of mpox virus were recognized by the World Health Organization (WHO) as a public health emergency of international concern (lasting from July 2022 to May 2023) [4].

In Canada, 98% of reported cases self-identified as men, nearly all of whom reported sex with other men [5]. At least 70% of all reported cases were concentrated in the country's three largest cities: Montréal, Toronto, and Vancouver [6–9]. Mpox cases were identified in hospitals and sexual health clinics, with swift responses from community, clinical, and public health partners [7–9]. After the initial exponential growth in May–June 2022, the number of cases declined rapidly. Since mid-November 2022, sporadic new cases have been reported to the *Public Health Agency of Canada* [5], and questions remain regarding the future risk of mpox reintroductions [10].

An important factor shaping transmission during the 2022-2023 mpox outbreak was the structure of GBM sexual networks [11,12]. Studies from Europe and North America attributed local outbreaks to densely clustered sexual networks among GBM with a high number of sexual partners [13–16]. Additionally, earlier case investigations revealed close linkages to international travel and sex-on-premises venues [2,13,17]. The concept of "core group" in sexually transmitted infections posits that a small number of individuals with a high number of sexual partners disproportionally contribute to transmission [18]. It recognizes that heterogeneity in sexual partners is crucial to transmission dynamics. In other words, the average number of sexual partners from a chosen member of the sexual network (i.e., degree) is not as informative as the distribution of sexual partner numbers (i.e., *degree distribution*) of that network. Mathematical modeling suggested that the basic reproduction number ($\mathcal{R}_0$) of mpox — the expected number of secondary cases arising from an initial infection in an entirely susceptible population— may be significantly greater than 1, as reported among GBM in the United Kingdom [15]. Estimates of $\mathcal{R}_0$ from other modeling studies based on European and Canadian populations ranged from 1.5 to 4.3 [19].

Although these findings have provided insights into the transmission dynamics of mpox, there remains uncertainty regarding how GBM sexual networks in major Canadian cities shaped transmission. The outbreak occurred in the aftermath of the COVID-19 pandemic, which may have affected usual sexual networks of GBM. For instance, the lifting of travel restrictions and other public health measures may have increased the number and types of sexual partnerships formed and facilitated international dissemination of the virus [13,17,20,21].

Given these uncertainties, we leveraged data from the *Engage Cohort Study* and mpox surveillance data to improve our understanding of the relationship between sexual networks and mpox transmission during 2022-2023 in Montréal, Toronto, and Vancouver. Specifically, we estimated the distribution of sexual partner numbers among GBM in each city and investigated how these distributions changed over time to assess the influence of COVID-19 pandemic on sexual behaviours. We also assessed the transmission potential of mpox in each city by estimating the $\mathcal{R}_0$ and the cumulative mpox incidence in each city.

Methods

Study setting and population

The *Engage Cohort Study* (*Engage*; 2017-present) is a prospective, population-based cohort study of GBM in Montréal, Toronto, and Vancouver. Eligible participants were self-identified cis or trans men living in one of the three cities, aged ≥16 years, who reported sex with another man in the past 6 months (P6M), understood English or French, and provided written consent. From February 2017 to August 2019, participants were recruited using respondent-driven sampling (RDS), a method used to sample hard-to-reach populations and estimate representative population characteristics [22]. Initial participants (i.e., "seeds") were purposively selected to represent diverse characteristics of the GBM community, and all participants were invited to recruit up to six peers in their social networks. Participants were followed up every 6 months after the baseline visit (12 months in the first 2 years for Montréal and Toronto). At each visit, participants completed an online questionnaire and underwent laboratory testing for sexually transmitted and blood borne infections. Details of the cohort, including use of RDS sampling and follow-up visits, have been detailed in previous research [23–26].

To investigate changes in sexual behaviours related to the COVID-19 pandemic, we used data from baseline visits and two follow-up visits:

- The *pre-pandemic period* was defined as the participants' baseline visit (February 2017–August 2019).
- The *pandemic period* was the earliest follow-up visit that occurred between June 2020–November 2021, covering successive waves of COVID-19 when physical distancing measures were common. The start of this period was chosen because *Engage* study visits only resumed three months after the COVID-19 pandemic was declared by the WHO (March 11th, 2020) [27].
- The *post-restrictions period* was defined as the latest follow-up visit that occurred between December 2021–February 2023. To ensure consistency of the time periods across cities, we defined the start of this period based on the easing of entry requirements for non-essential travel into Canada (September 3, 2021) [28]. The start of the period was shifted forward by three months to account for the 6-month recall period used in the *Engage* questionnaire. Additionally, we used travel restrictions given the history of international travel reported from initial mpox case investigations. The end of this period was the latest available data cut from the *Engage Cohort Study* (February 2023).

Variables

Our primary outcome was the self-reported number of sexual partners in the P6M, measured through the question "*During the PAST 6 MONTHS, with how many guys have you had any kind of sex (anal, oral, mutual masturbation, rimming, frontal/vaginal, etc.)?*". Informed by epidemiological data on mpox cases [2,13], the following bio-behavioural variables were considered potential correlates of the number of sexual partners in the P6M in the analyses (details in ***Table S1***):

- Age (16-29, 30-39, 40-49, 50-59, ≥60 years);
- Relationship status and sexual arrangement (no relationship, exclusive relationship, open relationship, unclear);
- HIV status (determined using 4th generation testing with a confirmatory assay; or self-reported for the 4% of baseline participants with unavailable testing data);
- Visit to bathhouses and/or sex clubs at least once in the P6M (binary);

- Attendance of group sex events at least once in the P6M (binary);
- Use of dating apps to find partners at least once in the P6M (binary); and
- Participation in transactional sex at least once in the P6M (i.e., receive money and/or goods in exchange for sex; binary).

Missing values for the last four variables were handled using the missing indicator method for all analyses [29].

Distribution of sexual partner numbers, rationale for weighting, and computation of weights

To estimate the distribution of sexual partner numbers in each city, we modeled the observed distributions in a Bayesian framework. Briefly, we first fitted a negative binomial regression model to the number of sexual partners in the P6M, using the correlates mentioned above as covariates in the model. We then incorporated sampling and attrition weights via post-stratification, by using the fitted posterior sample of the number of sexual partners in the P6M for each participant. Lastly, we computed the fitted population distribution of sexual partner numbers based on the post-stratified samples.

We chose a regression-based approach over direct distribution fitting to examine individual correlates and easily incorporate survey sampling and attrition weights. Regression models were fitted using Hamiltonian Monte Carlo in *Stan*, with 6,000 iterations (2 chains, 3,000 burn-in iterations, no thinning, ensuring that the effective sample size for each parameter was ≥1,000), using weakly informative priors and assessing convergence via Markov chain traceplots and the potential scale reduction factor ($\hat{R}$). We then used the posterior distribution of each participant's outcome to estimate the population distribution of sexual partner numbers, incorporating RDS-II weights and inverse probability of censoring weights (IPCW) via post-stratification. For the pre-COVID-19 pandemic time period, only RDS-II weights were used. To adjust for attrition in the pandemic and post-restrictions time periods, we used the product of RDS-II weights and IPCW (henceforth RDS-IPC weights).

Given that *Engage* is an RDS sample, we used RDS-II weights to ensure the estimated distributions of sexual partner numbers were representative of the target population (sexually active GBM in each city). With an RDS design, participants with larger social networks have a higher chance of being recruited; RDS-II weights adjust for this oversampling by assigning a weight that is inversely proportional to the self-reported network size [22]. To adjust for attrition

at follow-up visits, we used IPCWs to reduce potential biases stemming from correlation between the outcome (number of sexual partners in the P6M) and being lost to follow-up [30].

Finally, to compare the distribution of sexual partner numbers between a pair of cities or time periods, we computed the proportion of the iterations (posterior distribution samples) that had greater cumulative density for ≥25 and ≥100 partners. These thresholds were based on a previous modeling study from the Netherlands, which projected that GBM with a mean of 25 partners in the P6M are expected to constitute about 20% of mpox cases, and those with a mean of about 100 partners ≥60% of cases [31].

Mpox's basic reproduction number ($\mathcal{R}_0$)

The basic reproduction number $\mathcal{R}_0$ is a measure of an infectious agent's transmission potential [32,33]. To estimate $\mathcal{R}_0$ for mpox, we first calibrated a risk-stratified compartmental transmission model to surveillance data of reported mpox cases and then used the calibrated parameters to compute $\mathcal{R}_0$ using the next-generation matrix (NGM) approach [34,35].

Specifically, we used the sexual partner distributions of GBM from the post-restrictions period to partition the population into 20 sexual activity groups that effectively capture the small number of GBM with high numbers of sexual partners [15]. Then, we developed, parameterized, and calibrated a deterministic *Susceptible-Exposed-Infectious-Recovered* (SEIR) model of mpox transmission among GBM where both the exposed and infectious period follow an Erlang-2 distribution. The model was calibrated in a Bayesian framework using Sampling Importance Resampling to the daily number of reported mpox cases [5], accounting for reporting delays (average of 2 days), during the early phase of the outbreaks in the three provinces (i.e., before the scale-up of vaccination) since the overwhelming majority of cases at that time were from these cities [6–9]. We assumed that sexual behaviours were constant over that period. We calibrated five model parameters: 1) the transmission probability per effective contact (defined as a sexual partnership), 2) the duration of the effective infectious period, 3) the degree of assortativity by risk groups (i.e., mixing parameter), 4) the fraction of all incident mpox cases being reported to the surveillance databases, and 5) the number of imported cases at the start of the epidemic. GBM population sizes for each city were informed by previous estimates [36–39]. Model details are in the *Supplementary Methods* and parameters are presented in ***Table S2***.

Using the model-derived city-specific estimates for the transmission probability and mixing parameter, we estimated $\mathcal{R}_0$ for mpox in each city using the models' NGM. Briefly, the NGM describes the transmission events generated by one group towards another, and the $\mathcal{R}_0$ can be computed as the largest non-zero eigenvalue of this matrix. We also calculated the effective reproduction number $\mathcal{R}_e$ accounting for immunity in the top 0.2%, 0.4%, 0.6%, 0.8%, 1%, 2%, and 3%, 4%, and 5% of sexual activity groups. We repeated these procedures using the pre-pandemic distributions, to evaluate potential increases in mpox transmission if sexual activity recovered to pre-COVID-19 levels.

$\mathcal{R}_0$ and cumulative incidence proportion based on reported mpox cases

In order to compare our $\mathcal{R}_0$ estimates to those reported elsewhere, we also estimated $\mathcal{R}_0$ from the growth rate of reported mpox cases, using the same data source described above [5]. We used the formula $\mathcal{R}_0 = (1 + \Lambda D)(1 + \Lambda D')$, where the latent period D' was 5.1 days and the infectious duration D was the city-specific value calibrated in the SEIR model, for comparability with our NGM estimates [11,40–43]. The epidemic growth rate Λ was estimated from the slope of the log cumulative cases over time, using the period of initial exponential growth (first 50 days after the first case in each province) [35].

We finally estimated the cumulative incidence proportion of mpox cases among GBM during the 2022–2023 outbreak in each city using GBM population size estimates from previous studies [36–39].

Sensitivity analyses

We performed four sensitivity analyses. First, to verify the robustness of results regarding the distribution of sexual partner numbers to our weighting approach, we repeated the analyses restricting the analytical sample to participants who had visits at all three timepoints. Second, as age is an important determinant of sexual activity and differences in the age distribution of the participants across the three cities have been reported [44], we performed regression-based standardization to the one observed in Montréal. Third, given uncertainty regarding mpox transmission probabilities through different types of sex acts [2,45], we repeated the analyses focusing on the number of anal sex partners as the outcome. Lastly, we fitted zero-inflated

regression models to test whether participants reporting zero partners during follow-up significantly influenced our model fit.

All analyses were conducted using *R* (version 4.2.2), *Stan* (version 2.26.1), *RStan* version 2.21.7) [46–48]. Additional details on methods can be found in the *Supplementary Methods*. The code used for analyses is available from GitHub (https://github.com/pop-health-mod/mpox-engage-sex-networks).

Ethics

Ethics approval was obtained from the Research Institute of the McGill University Health Centre and the Research Ethics Office of the Faculty of Medicine and Health Sciences, McGill University (A06-M32-23B), Toronto Metropolitan University (REB #2016-113), the University of Toronto (protocol #00033527), St. Michael's Hospital (REB #17-043), the University of Windsor (REB #33443), the University of British Columbia (H16-01226), Providence Health Care (H16-01226), the University of Victoria (H16-01226), and Simon Fraser University (H16-01226).

Results

Study population

There were 2,449 GBM recruited to *Engage*, with 1,179 participants in Montréal, 517 in Toronto, and 753 in Vancouver. The effective sample size (accounting for RDS weights) was about half in each city: 516 (Montréal), 324 (Toronto), and 350 (Vancouver). Retention over the study period was slightly higher in Montréal, where 70% and 67% of participants had at least one visit during the pandemic and post-restrictions period, respectively, compared to 58% and 56% for Toronto, and 60% and 52% for Vancouver (***Table 1***, ***Table S3***).

Accounting for RDS-II weights, participants in Montréal were older on average than in Toronto and Vancouver: 37% aged ≥40 years, versus 25% and 29%, respectively. In all three cities, approximately half of participants reported not being in a relationship at baseline. There were fewer participants living with HIV in Montréal (14%; 95% Confidence Interval [CI]: 12%–16%), compared to 22% (95%CI: 19%–26%) in Toronto and 20% (95%CI: 18%–23%) in Vancouver. More participants reported attending bathhouses and group sex in Toronto (39% for bathhouses; 95%CI: 35%–43%; 23% for group sex; 95%CI: 19%–26%) than in Montréal (31% for bathhouses; 95%CI: 29%–34%; 16% for group sex; 95%CI: 14%–18%) and Vancouver (29% for bathhouses;

95%CI: 26%–32%; 21% for group sex; 95%CI: 18%–24%). Lastly, the RDS-II-weighted mean number of sexual partners in the P6M was 8.7 (95%CI: 7.4–9.9) in Toronto, compared to 8.1 (95%CI: 6.9–9.4) in Montréal and 8.0 (95%CI: 6.8–9.2) in Vancouver (***Table 1***).

Table 1. Unadjusted and RDS-II adjusted baseline estimates of the number of sexual partners in the past six months and its correlates among the Engage Cohort Study participants in Montréal, Toronto, and Vancouver, 2017–2019

	Montréal				Toronto				Vancouver				Overall			
			RDS-II weighted				RDS-II weighted				RDS-II weighted				RDS-II weighted	
	n	**(%)**	**% (95% CI)**		**n**	**(%)**	**% (95% CI)**		**n**	**(%)**	**% (95% CI)**		**n**	**(%)**	**% (95% CI)**	
	1179				517				753				2,449			
ESS	516				324				350				1,190			
Age group																
18-29	384	(33%)	36%	(34–39%)	222	(43%)	51%	(46–55%)	293	(39%)	45%	(42–49%)	899	(37%)	42%	(40–44%)
30-39	340	(29%)	27%	(24–29%)	183	(35%)	24%	(20–28%)	235	(31%)	26%	(23–29%)	758	(31%)	26%	(24–28%)
40-49	166	(14%)	15%	(13–17%)	57	(11%)	8%	(6–10%)	86	(11%)	10%	(8–12%)	309	(13%)	12%	(10–13%)
50-59	181	(15%)	12%	(10–14%)	39	(8%)	11%	(8–14%)	91	(12%)	11%	(9–13%)	311	(13%)	12%	(10–13%)
60+	108	(9%)	10%	(8–12%)	16	(3%)	6%	(4–8%)	48	(6%)	8%	(6–10%)	172	(7%)	9%	(8–10%)
Relationship status and sexual agreement																
Single	671	(57%)	56%	(53–59%)	279	(54%)	47%	(43–52%)	413	(55%)	57%	(54–61%)	1,363	(56%)	55%	(53–57%)
Open	330	(28%)	24%	(22–27%)	173	(33%)	25%	(21–29%)	221	(29%)	21%	(18–24%)	724	(30%)	23%	(22–25%)
Exclusive	97	(8%)	10%	(9–12%)	48	(9%)	21%	(17–24%)	83	(11%)	15%	(13–18%)	228	(9%)	14%	(13–15%)
Unclear	81	(7%)	9%	(8–11%)	17	(3%)	7%	(4–9%)	36	(5%)	7%	(5–8%)	134	(5%)	8%	(7–9%)
HIV status*																
Seropositive	215	(18%)	14%	(12–16%)	101	(20%)	22%	(19–26%)	132	(18%)	20%	(18–23%)	448	(18%)	18%	(16–19%)

Seronegative / unknown	964	(82%)	86%	(84–88%)	416	(80%)	78%	(74–81%)	621	(82%)	80%	(77–82%)	2,001	(82%)	82%	(81–84%)
Bathhouse/sex club attendance in the P6M[†]																
Yes	452	(38%)	31%	(29–34%)	273	(53%)	39%	(35–43%)	283	(38%)	29%	(26–32%)	1,008	(41%)	32%	(30–34%)
No	716	(61%)	67%	(65–70%)	237	(46%)	56	(52–61%)	464	(62%)	70%	(67–73%)	1,417	(58%)	66%	(64–68%)
Missing[‡]	11	(1%)	1%	(1–2%)	7	(1%)	5%	(3–7%)	6	(1%)	1%	(0–2%)	24	(1%)	2%	(1–2%)
Group sex event attendance in the P6M[†]																
Yes	273	(23%)	16%	(14–18%)	192	(37%)	23%	(19–26%)	208	(28%)	21%	(18–24%)	673	(27%)	19%	(17–20%)
No	900	(76%)	83%	(81–85%)	316	(61%)	72%	(68–75%)	540	(72%)	79%	(76–81%)	1,756	(72%)	79%	(78–81%)
Missing[‡]	6	(1%)	1%	(0–2%)	9	(2%)	6%	(4–8%)	5	(1%)	1%	(0–1%)	20	(1%)	2%	(1–2%)
Dating app use to find partners in the P6M[†]																
Yes	766	(65%)	56%	(53–59%)	403	(78%)	60%	(56–64%)	556	(74%)	65%	(61–68%)	1,725	(70%)	59%	(57–61%)
No	413	(35%)	44%	(41–47%)	114	(22%)	40%	(36–44%)	197	(26%)	35%	(32–39%)	724	(30%)	41%	(39–43%)
Transactional sex in the P6M[†]																
Yes	88	(7%)	6%	(5–7%)	54	(10%)	6%	(4–7%)	42	(6%)	6%	(4–8%)	184	(8%)	6%	(5–7%)
No	1,070	(91%)	91%	(89–93%)	454	(88%)	93%	(91–95%)	703	(93%)	93%	(91–94%)	2,227	(91%)	92%	(91–93%)
Missing[‡]	21	(2%)	3%	(2–4%)	9	(2%)	1%	(0–2%)	8	(1%)	1%	(1–2%)	38	(2%)	2%	(2–3%)

Number of sexual partners in the P6M (mean)																
	(SD				(SD				(SD				(SD			
12.4	22.1)	8.1	(6.9–9.4)	19	1.6)	8.7	(7.4–9.9)	12.2	19)	8	(6.8–9.2)	13.7	23.8)	8.2	(7.4–9.0)	
Number of anal sexual partners in the P6M (mean)																
	(SD				(SD				(SD				(SD			
7.4	15.3)	4.9	(3.9–5.8)	12.2	24.3)	5.9	(4.7–7.1)	8.3	15.4)	5.2	(4.3–6)	8.7	17.7)	5.2	(4.6–5.8)	

CI, confidence interval; *ESS*, effective sample size; *P6M*, past 6 months; *RDS*, respondent driven sampling; *SD*, standard deviation.

RDS-II weights are inversely proportional to participants' social network size.

* HIV status was determined based on 4th generation testing with a confirmatory assay. If the laboratory test result was unknown, self-reported status was used.

† At least once in the P6M.

‡ Missing includes "prefer not to answer."

Correlates of the networks' number of sexual partners

In all three cities, a higher number of sexual partners in the post-restrictions period was strongly associated with attendance of group sex events, with a rate ratio (RR) of 3.44 (95% Credible Interval [CrI]: 2.66–4.47) in Montréal, 3.62 (95%CrI: 2.59–5.13) in Toronto, and 3.09 (95%CrI: 2.24–4.34) in Vancouver. Other strong correlates were participation in transactional sex, usage of dating apps, and visit to bathhouses and/or sex clubs (***Table S4***).

Differences in the distribution of sexual partner numbers by city and time period

Overall, the fitted distribution of sexual partner numbers was similar across the three cities: the mean number of partners was 10.4 (95%CrI: 9.4-11.5) in Montréal, 13.1 (95%CrI: 11.3-15.1) in Toronto and 10.7 (95%CrI: 9.5-12.1) in Vancouver. However, pre-pandemic, sexual networks in Toronto had the heaviest-tailed distribution, with 1.4% (95%CrI: 1.0-1.9%) of GBM reporting ≥100 partners in the P6M, compared with 0.6% (95%CrI: 0.4-0.8%) in Montréal and 0.3% (95%CrI: 0.2-0.5%) in Vancouver. All posterior distribution samples showed that Toronto had a larger cumulative density of ≥100 numbers of sexual partners than Montréal and Vancouver. This result held during the post-restrictions period: 0.6% (95%CrI: 0.3-0.9%) of GBM in Toronto reported ≥100 partners, 0.3% (95%CrI: 0.2-0.5%) in Montréal, and 0.5% (95%CrI: 0.2-0.9%) in Vancouver. Post-restrictions, Toronto had a larger cumulative density of ≥100 numbers compared to Montréal and Vancouver (95% and 69% of the posterior distribution samples, respectively; ***Figure 1; Figure S1***).

Compared to the pre-pandemic period, all three cities witnessed a marked reduction in the number of sexual partner numbers during the COVID-19 pandemic. In all three cities across all samples from the posterior distributions, the cumulative density of ≥25 sexual partners in the P6M were consistently larger for the pre-pandemic versus pandemic period. Sexual activities appeared to have rebounded after lifting travel restrictions: in Montréal and Toronto, 100% of posterior distribution samples (93% in Vancouver) showed a larger proportion of participants reporting ≥25 sexual partners in the P6M as compared to the pandemic period. However, sexual activities have not fully recovered to pre-pandemic levels: in all three cities, 100% of the posterior distribution samples had a greater proportion of GBM with ≥25 sexual partners in the pre-pandemic than the post-restrictions period (***Figure 1***).

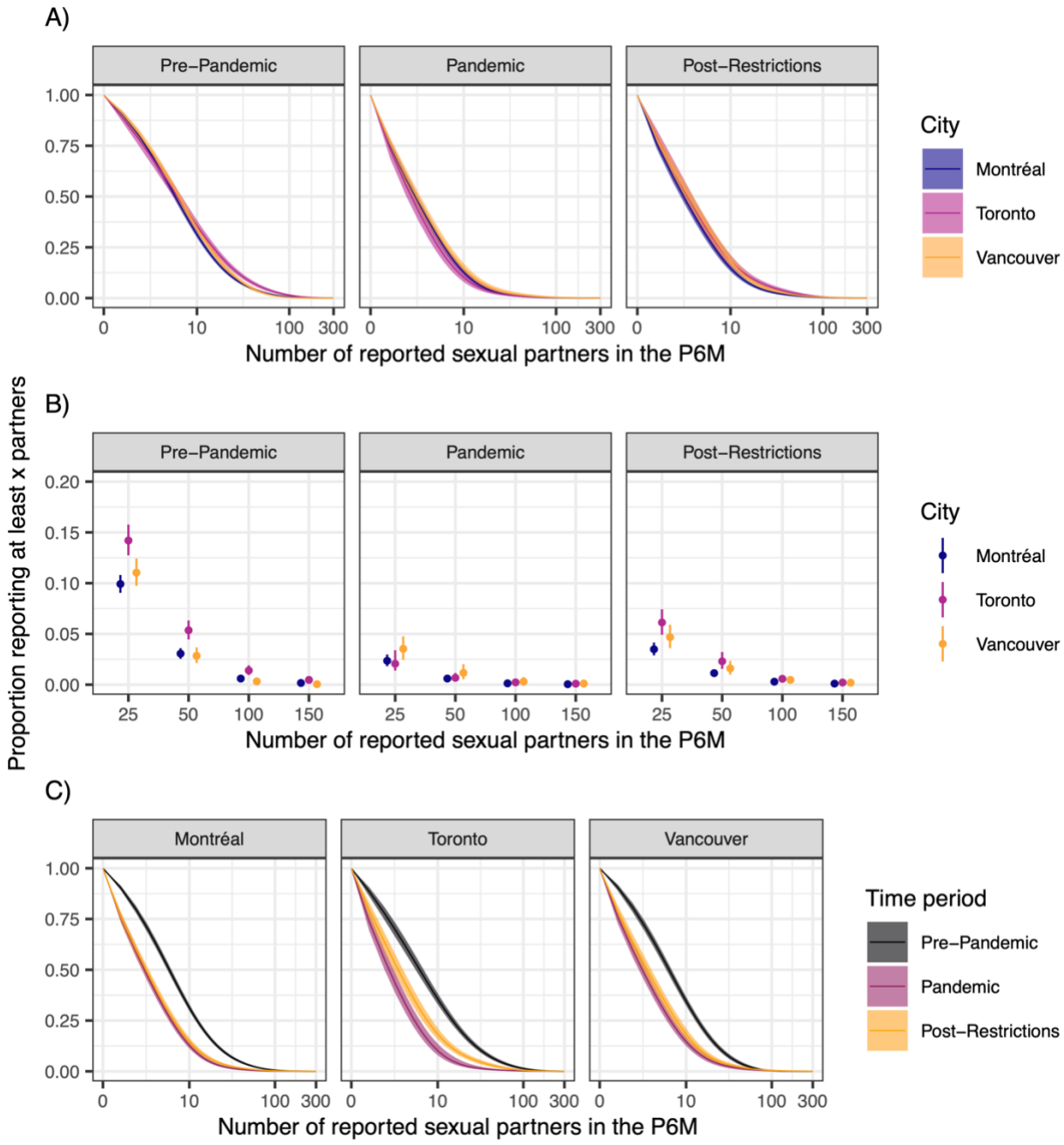

Figure 1. Cumulative distribution of sexual partner numbers in the past 6 months across Montréal, Toronto, and Vancouver at each time period, weighted by respondent driven sampling (RDS-II) and inverse probability of censoring weights, with 95% credible intervals. A) Full distribution (one time period per panel), B) Selected values (one time period per panel), C) Full distribution (one city per panel). P6M: past 6 months.

Model fit, and $\mathcal{R}_0$ from the next-generation matrix and reported case counts

The city-specific SEIR models replicated the daily number of reported cases from surveillance data (***Figure 2***). The calibrated parameter point estimates across cities were 0.80-0.87 for the transmission probability per effective contact, 3.6-4.2 days for the total duration of the effective infectious period, 0.67-0.78 for the degree of assortativity (mixing parameter), 0.78-0.85 for the reporting fraction, and 2-5 for the number of imported cases (***Table S2***).

Using the calibrated parameters from the SEIR model and the NGM method, we estimated $\mathcal{R}_0$ of 2.7 (95%CrI: 2.4–3.7), 2.4 (95%CrI: 2.1–3.2), 2.4 (95%CrI: 2.0–3.1) in Montréal, Toronto and Vancouver, respectively (***Figure 3A***). These are substantially higher than the $\mathcal{R}_0$ estimated from case counts of 2.0 (Montréal) and 1.9 (Toronto, Vancouver) as these can be biased by early saturation of high sexual activity groups (***Table S5***). We also estimated a cumulative incidence proportion of mpox-diagnosed GBM ranging from 0.7–0.9% in all cities (***Table S6***, ***Figure S2***).

According to the NGM estimates, the mpox $\mathcal{R}_e$ estimates were highly sensitive to the contact rates in the highest activity groups. The $\mathcal{R}_e$ would have been 1.5-1.6 if there was immunity in the 0.2% of the population with the highest contact rates, and $\mathcal{R}_e$ would have gone below 1 (start of epidemic decline) with immunity in the 0.8% highest activity groups. If the distributions of sexual partner numbers had been at pre-pandemic levels in 2022-2023, the $\mathcal{R}_e$ would have declined more slowly, especially in Montréal and Toronto, and $\mathcal{R}_e<1$ would have only been achieved with >1% immunity (>0.6% in Vancouver; ***Figure 3B***).

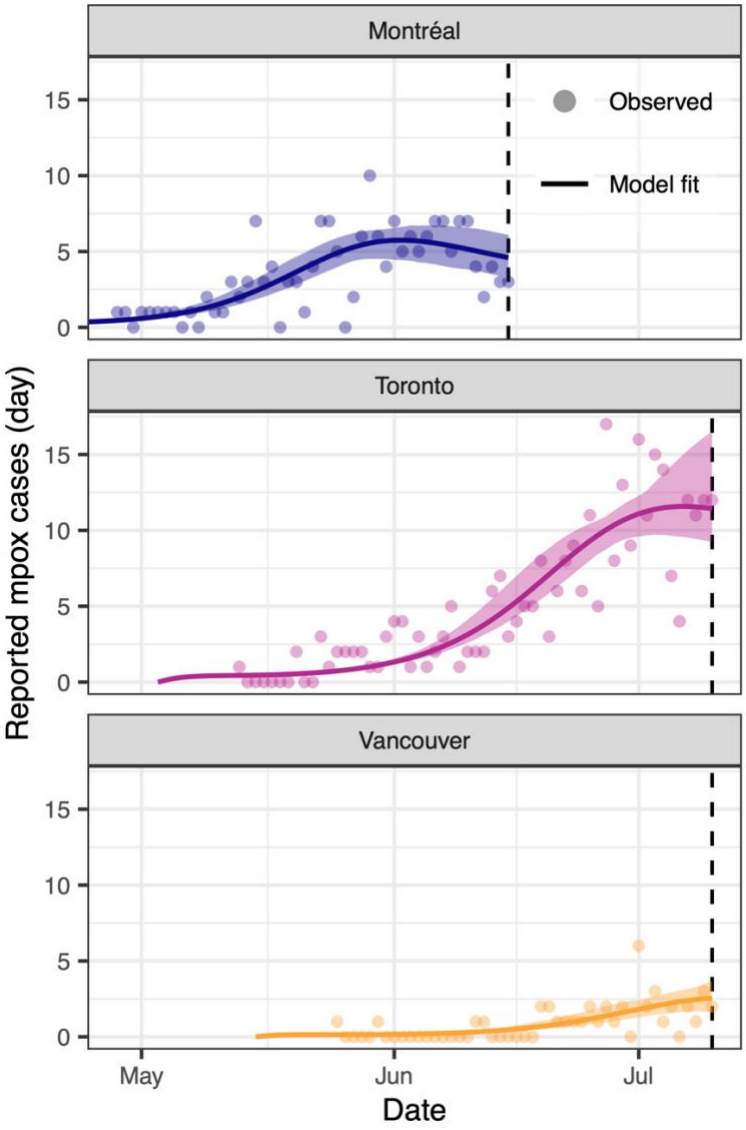

Figure 2. SEIR model fit. SEIR model fit to observed mpox incidence data for each city. Data up to mpox vaccination scale-up (dotted vertical lines): June 14th, 2022 for Montréal, July 10th, 2022 for Toronto and Vancouver. Shaded area shows the 95% credible intervals.

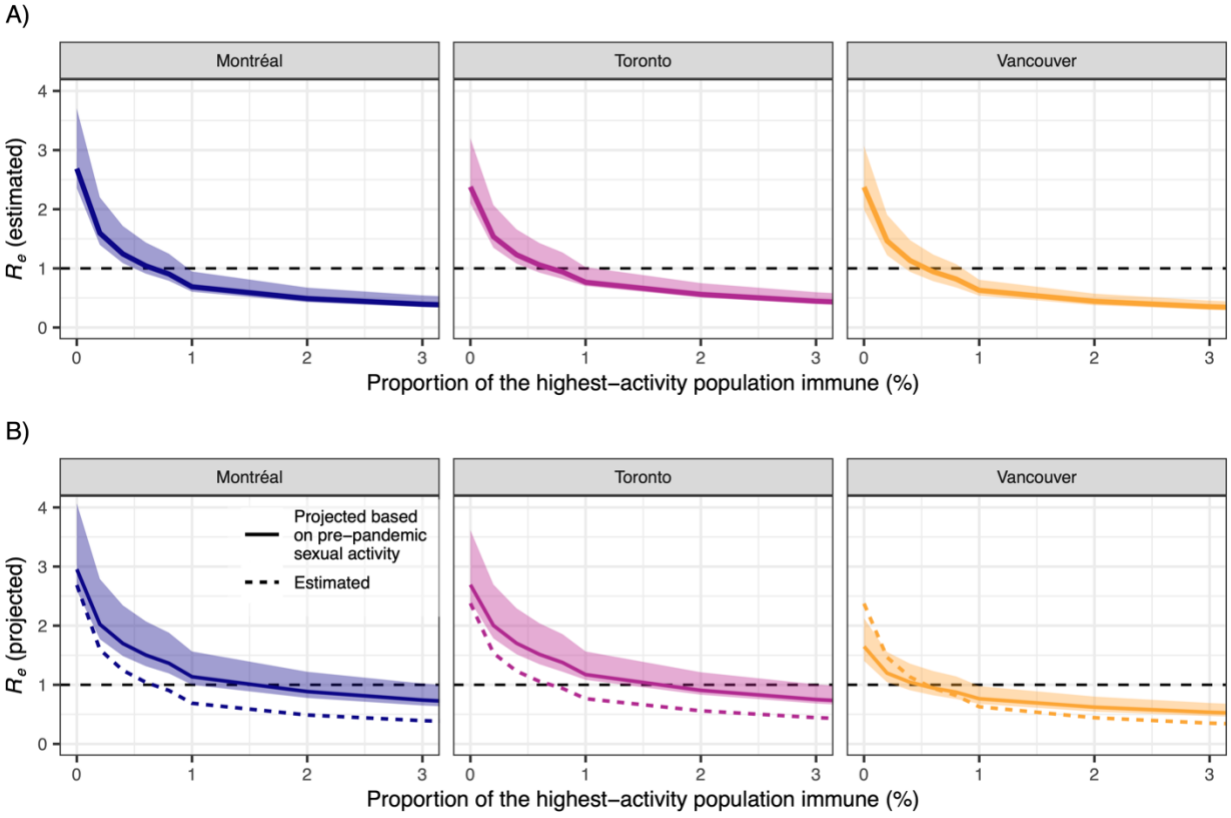

Figure 3. Basic ($\mathscr{R}_0$) and effective ($\mathscr{R}_e$) reproduction number of mpox. $\mathscr{R}_e = \mathscr{R}_0$ when the proportion immune is 0. A) $\mathscr{R}_e$ estimates from the next-generation matrix, assuming that the top x percent of the population is immune and using the SEIR-calibrated infectious duration, probability of transmission per effective contact, mixing parameter, and reporting fraction. B) Projected $\mathscr{R}_e$ to the pre-pandemic period, assuming pre-pandemic sexual activity and following the same procedure as for A. Shaded area shows the 95% credible intervals. NGM: next-generation matrix.

Sensitivity analyses

When restricting the sample to participants with follow-up at each time period only, the distributions of sexual partner numbers were broadly similar for all cities and periods (***Figure S3***). Similarly, standardizing the age distribution in Vancouver to that observed in Montréal did not substantially change the results. However, in Toronto, the tail of the distribution of sexual partner numbers was slightly lighter after standardization, especially for the pre-pandemic and post-restrictions time periods (***Figure S4***). When using anal sexual partner as outcome, the comparisons across cities and time periods did not qualitatively change, but the distributions had smaller means

and lighter tails (***Figure S5***). Lastly, using a zero-inflated model did not change results (***Figure S6***).

Overall, these sensitivity analyses suggest that the results are relatively robust to our weighting methods, assumptions, and to differences in covariate distributions across the cities.

Discussion

In a large population-based cohort of GBM in Canada's three largest cities, there was a marked decrease in the distribution of sexual partner numbers during the COVID-19 pandemic compared to the pre-pandemic period (2017-2019). Despite a small increase after travel restrictions were lifted (late 2021-early 2023), GBM sexual activity was well below pre-pandemic levels at the time of the 2022-2023 mpox outbreak. Despite the reductions in sexual partnerships, the $\mathcal{R}_0$ of mpox was 2.4–2.7 in all three cities during the 2022–2023 mpox outbreak. This high $\mathcal{R}_0$ was driven largely by contact rates of the small proportion of the GBM population with high number of sexual partners and would be substantially lower if members of these groups were not susceptible to infections through natural immunity or vaccination. These findings support prioritization of mpox vaccination to those at highest risk. Additionally, they suggest that the $\mathcal{R}_0$ for mpox may increase if the population's sexual behaviours further recover to pre-pandemic levels. Continued public health surveillance and preventative activities —community outreach, vaccination— to mitigate the local impacts of mpox re-introductions into Canada is advised.

We found that GBM had substantially fewer sexual partners in all three cities during the COVID-19 pandemic, and sexual activity remained lower than pre-pandemic levels even after restrictions were lifted. These findings are in line with previous research from Canada [49,50] and Europe [20,51,52] which suggest that GBM sexual behaviours were influenced by public health measures and messaging related to the COVID-19 pandemic. The implications of our findings are that as sexual behaviours are expected to return towards pre-pandemic levels, future mpox transmission remains possible. This is especially true if there is "turnover" among sexual activity groups. Infection risks are also further amplified with case importation risks in an interconnected world and limited availability of mpox vaccines and therapeutics in countries in Africa where mpox has been endemic for decades [53].

We found that attendance of group sex events, participation in transactional sex, usage of dating apps, and visits to bathhouse and/or sex clubs were associated with higher numbers of sexual partners in urban Canadian GBM. Notably, group sex events, use of dating apps, and visits to bathhouse and/or sex clubs were also associated with earlier mpox cases during the 2022-2023 outbreak [2,13]. In the context of ongoing low coverage of second dose mpox vaccination across the three cities, and across other cities in Canada, these venues therefore provide a potentially interesting focus for prioritized and tailored vaccine strategies to increase coverage. For example, pop-up vaccine clinics could be set at bathhouses and sex clubs in partnership with community organizations [54–56]. Additionally, focused communication campaigns to promote mpox vaccination could be rolled out on GBM-dating apps [7,57].

Across Montréal, Toronto, and Vancouver, we estimated an $\mathcal{R}_0$ of 2.4-2.7 based on the estimated post-restrictions distribution of sexual partner numbers. This is comparable to the 2.4 observed in Italy and in a pooled analysis of data from European countries [58,59]. However, the R_e declined substantially (down to 1.5-1.6) with even just 0.2% immunity in the highest activity groups. The absolute size of this group corresponds to roughly 100 GBM in Montréal, 150 in Toronto, and 50 in Vancouver. As it takes relatively few cases in these groups to reduce transmission potential, the $\mathcal{R}_0$ estimated from the growth rates of the epidemic are lower ($\mathcal{R}_0$ of 1.9-2.0). Moreover, despite the high $\mathcal{R}_0$, we estimated a cumulative incidence proportion of only 0.7-0.9% of GBM by October 2022, implying that the highest activity groups were quickly depleted. Similarly, Murayama et al. [16] found that epidemic growth reached its peak at cumulative incidence proportions of 0.2–0.5% in various North American and European countries. The high mpox $\mathcal{R}_0$ estimates, contrasted with such low cumulative incidence proportions, further highlight the important role of heterogeneous sexual activity and mixing in the 2022-2023 mpox outbreaks. These underscore that $\mathcal{R}_0$ estimates from case data only should be cautiously interpreted in outbreaks where high levels of heterogeneity in contact rates are suspected, as $\mathcal{R}_e<1$ can be more readily achieved and maintained if individuals at higher risk are preferentially protected by vaccination and/or prior infection [60].

The results should be interpreted considering four main limitations. First, our post-restrictions period overlaps with the time when spread of the SARS-CoV-2 Omicron variant took place. Thus, the estimated distribution of sexual partner numbers may have been affected by

measures introduced in response to the Omicron SARS-CoV-2 wave. However, these restrictions were relatively short-lived, and our definition enabled consistent and comparable time periods across cities [61]. Second, although we used IPCW to address attrition bias, this bias may not have been fully adjusted if the loss to follow-up model was misspecified (i.e., not all variables associated with attrition were included). Third, we quantified sexual networks using self-reported sexual partner numbers in the P6M, which could be subject to social desirability and recall bias. However, these biases were unlikely to be substantially differential across the cities. Lastly, our quantification of mpox transmission potential depends on the level of mixing among sexual activity groups and number of imported cases seeded. Since both these parameters were calibrated in our SEIR model, as they are difficult to measure empirically, their uncertainty was propagated to our results. Regarding mixing, the $\mathcal{R}_0$ could be higher if mixing was more "like-with-like" (assortative) by sexual activity, or lower if it was proportional.

Our approach to estimating the distribution of sexual partner numbers has several strengths. First, we implemented both RDS-II weights and IPCW to obtain estimates representative of sexually active GBM in the three largest Canadian cities. Furthermore, inter-city comparisons enabled us to account for potential differences in GBM communities in each city and explore their relative impact on the transmission dynamics of mpox. Finally, *Engage*'s longitudinal population-based data collection allowed us to quantify behaviour changes among GBM from pre-COVID-19 pandemic up to February 2023.

Conclusion

In Montréal, Toronto, and Vancouver, GBM had fewer sexual partners during the COVID-19 pandemic. Even after travel restrictions were lifted in late 2021, sexual activities among urban Canadian GBM had not fully recovered to pre-pandemic levels. The overall distribution of sexual partner numbers was similar across cities, potentially explaining the similar observed cumulative fraction of mpox cases diagnosed among GBM in the three cities. With sexual activity still below pre-pandemic levels, public health authorities should maintain vigilance. Improving first- and second- dose vaccination coverage among individuals at risk with high numbers of sexual partners should be prioritized.

Declarations

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Author contribution

JLFA, FX, and MM-G contributed to the conception and design. JC, DG, TAH, MD, and SM were involved in the design, data collection, and data management of the *Engage Cohort Study*. Analyses were performed by JLFA and FX, with support from MM-G. MM-G developed the SEIR model with assistance from JLFA and FX. JK, LW, OG, HS, MI, and SM provided input on preliminary methods discussions. The manuscript was drafted by FX and JLFA. All authors contributed to the interpretation of results and reviewed the manuscript for important intellectual content. Overall supervision for this project was provided by MM-G. All authors approved the final manuscript.

Conflict of interest

JC reports investigator-sponsored research grants from Gilead Sciences Canada and ViiV Healthcare, all outside of the submitted work. MM-G reports an investigator-sponsored research grant from Gilead Sciences Inc., and contractual arrangements from the World Health Organization and the Joint United Nations Programme on HIV/AIDS (UNAIDS), all outside of the submitted work. All other authors report no conflict of interest.

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Software and source code

Analysis code is available on a *GitHub* repository (https://github.com/pop-health-mod/mpox-engage-sex-networks).

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Supplementary Methods

Supplementary Table 1. Definitions of analysis variables.

Notation	Definition	Question from the Engage Cohort Study
y	Number of all-type sexual partners in the past 6 month (P6M) Number of anal sexual partners in the P6M (for ***Sensitivity Analysis***)	5.5 During the PAST 6 MONTHS, with how many guys have you had any kind of sex (anal, oral, mutual masturbation, rimming, frontal/vaginal, etc.)? _____ guys 5.12 During the past 6 months, how many guys have you had anal sex with (as top or bottom)? _____ guys
n	Number of Participants	See ***Supplementary Table 3*** for the sample size in each city for all time periods.
network size	Participant network size (for RDS-II estimation)	How many men who have sex with men aged 16 years or older, including trans men, do you know who live or work in the [Metro Vancouver/Greater Toronto/Metro Montreal depending on site] area (whether they identify as gay or otherwise)? This includes gay/bi guys you see or speak to regularly; e.g., close friends, boyfriends, spouses, regular sex partners, roommates, relatives, people you regularly hang out with, etc.
Age	Age at time of the visit	1.3 What is your age (i.e., how old are you)?
Relationship_Status	Relationship status at time of the visit	2.18 Do you currently have a relationship with a main partner? No | Yes 2.23 What discussions have you and your main partner had with each other in terms of only having sex with each other? We haven't explicitly discussed only having sex with each other or not | We have discussed only having sex with each other, but have not agreed to anything | We have discussed only having sex with each other and agreed to only have sex with each other | We agreed to have other sex partners, but only ones we share (we only play together) | We agreed to have other sex partners, some of whom we share and others whom we see separately (we play together and separately) | We agreed to have other sex partners whom we only see separately (we only play separately) | We agreed to another arrangement. Please describe: __ | No main relationship partner
HIV_Status	HIV serostatus	Derived by *Engage Cohort Study* from participant laboratory-tested and self-report HIV serostatus
Bathhouse	Visit to bathhouses and/or sex clubs during the P6M	5.46 During the past 6 months did you go to a bathhouse or sex club? No | Yes | Don't know / don't remember | Prefer not to answer

Group_Sex	Attendance in group sex events during the P6M	5.47 During the past 6 months did you attend any group sex events? By group sex we mean sex where 4 or more people get together and have some kind of sex with some or all of the other people there. This could include at a private organized sex party, at a bathhouse, in darkrooms, or other venues. No | Yes | Don't know / don't remember
Dating_App	Dating app usage during the P6M	4.3 In the PAST 6 MONTHS have you used a smartphone app or internet website to connect with other guys? Never | Less than once per month | About once per month | More than once per month | Prefer not to answer Note: this variable was only reported at the baseline (Pre-Pandemic)
Transactional_Sex	Participation in transactional sex (received money or goods in exchange for sex) in the P6M	5.45 In the past 6 months, have you... (Remember that for the following question, by "sex" we mean oral sex, anal sex, frontal/vaginal sex, masturbation, rimming, fisting, sex toys, or watersports.) i. RECEIVED money in exchange for sex? h. RECEIVED drugs in exchange for sex? m. RECEIVED other goods or services (e.g.,room, meal, gifts) in exchange for sex? Yes | No | Don't know / Don't remember | Prefer not to answer
Education	Highest educational level attained	2.25 What is the highest level of education you have completed? No formal education | Elementary | Some high school but did not graduate | High school diploma or a high school equivalency certificate | Trade or vocational or technical institute diploma/certificate | Some post-secondary education but no certificate or diploma | University or college diploma or certificate less than a bachelor's degree | Bachelor's degree | Graduate (PhD or Masters) or professional degree (doctor, lawyer, etc.) | Other (Please Specify): _____
Income	Reported annual employment income	2.29 What was your total annual income last year from all paid work and all other sources before taxes and other deductions: $0 or No Income | $1 - $9,999 | $10,000 - $19,999 | $20,000 - $29,999 | $30,000 - $39,999 | $40,000 - $49,999 | $50,000 - $59,999 | $60,000 - $69,999 | $70,000 - $79,999 | $80,000 - $89,999 | $90,000 - $99,999 | $100,000 or more
Ethnic_Min	Being part of a minority ethnic or racial group	2.12 What <u>single</u> ethnic group or family background do you **MOST** identify with? Aboriginal or Indigenous (for example Canadian First Nations, Métis, Inuit, American Indian, or North, Central, or South American

	Indigenous Peoples) | English Canadian | French Canadian | French | British (for example English, Scottish, Welsh) | Other Eastern & Western European (Irish, Italian, Greek, German, Spanish, Dutch, Belgian, Flemish, Ukrainian, Polish, Russian) | East Asian (for example Chinese, Taiwanese, Japanese, Korean) | South Asian (for example Indian, Punjabi, Pakistani, Sri Lankan, Bangladeshi) | South East Asian (for example Vietnamese, Cambodian, Filipino, Malaysian, Thai, Indonesian, Laotian) | West Asian (For example Iranian, Persian, Afghan, Assyrian) | Arab or North African (for example Egyptian, Saudi Arabian, Iraqi, Kuwaiti, Libyan, Moroccan) | Latin American (for example Mexican, Guatemalan, Costa Rican, Brazilian, Chilean, Argentinian) | African (for example East, West, Sub-Saharan African) | Black (for example African-Canadian or other Black ancestries) | Caribbean | Pacific (for example Hawaiian, Guamanian/Chamorro, Samoan, or from other Pacific Islands) | Mixed race/ethnicity | I use another term to describe my ethnicity or family background.

Distribution of sexual partner numbers (Bayesian regression and post-stratification)

Our main approach to estimate the distribution of sexual partner numbers can be summarized in three steps. First, we fit a negative binomial regression model to the reported number of sexual partners in the past 6 months (P6M). This approach was chosen as initial analyses showed that the regression-based approach provided a better fit than directly fitting a distribution (i.e., left-truncated Weibull, right-truncated Pareto, Gamma) to the data, based on comparing the models' deviance information criteria. The model covariates include the following variables: age group, relationship status and sexual arrangement, HIV serostatus, visit to bathhouses and/or sex clubs, attendance to group sex events, use of dating apps, and participation in transactional sex (***Supplementary Table 1***). An interaction between age group and HIV serostatus was included to reflect heterogeneity in the effect of HIV serostatus by age groups on the number of sexual partners. For each city-time period *j*, we fit this regression model, and then obtained the fitted posterior distribution of the mean number of sexual partners for each participant i, i.e., $\mathbb{E}\left[\hat{y}_{ij}|X_{ij}\right]^{(m)}$.

The regression models, with negative binomial likelihood (NB), can be written as

$$y_{ij} \sim NB(\lambda_{ij}, \phi_j)$$
$$\log(\lambda_{ij}) = \alpha_j + \beta_j X_{ij}$$

where:

i : index for participants, $i \in \{1,2,\dots,n_j\}$;

j : index for combination of city and time period, $j \in$ {*Montréal-Pre-Pandemic, Toronto-Pre-Pandemic, Vancouver-Pre-Pandemic, Montréal-Pandemic, Toronto-Pandemic, Vancouver-Pandemic, Montréal-Post-Restrictions, Toronto-Post-Restrictions, Vancouver-Post-Restrictions*};

y_{ij} : observed number of all-type sexual partners in the P6M for participant *i* in city-time-period *j*;

λ_{ij} : mean model-predicted number of partners for participant *i* in city-time-period *j*;

ϕ_j : overdispersion parameter for city-time-period *j*;

α_j : model intercept for city-time period *j*;

X_{ij} : a matrix containing the values of predictors for participants for city and time period *j*,

i.e., *Age*, *HIV_Status*, *Age x HIV_Status*, *Relationship_Status*, *Bathhouse*, *Group_Sex*, *Dating_App*, *Transactional_Sex*;

β_j : vector of regression coefficients for city-time period j, for set of covariates X_j;

m : index of samples from the posterior, $m \in \{1,2,\dots,6000\}$.

We used a $Normal(0,10)$ distribution for the regression intercept and all predictor coefficients. For the over-dispersion parameter ϕ, we used a $halfCauchy(0,5)$ distribution.

Second, in each city-time period j, for each participant i, we used the participant's posterior predictive mean $\left[\hat{y}_{ij}|X_{ij},\phi_j\right]^{(m)}$ to compute the probability of observing k partners for that participant, where $k \in \{0,1,2,\dots,300\}$ (and where 300 is the largest number of reported partners in the P6M at baseline). We performed this procedure separately for all m samples of the posterior.

Third, we performed post-stratification to incorporate respondent-driven sampling (RDS)-II weights and inverse probability of censoring weights (IPCWs), to adjust for the RDS sampling design and loss to follow-up, respectively. These weights were used to estimate a more representative distribution of sexual partner numbers in the P6M, the RDS-IPC-weighted distribution (computation of RDS-II weights, IPCWs, and the RDS-IPC weights is explained in the next section). The distribution of sexual partner numbers can be thought of as the proportion of men who report k partners in the P6M, i.e., $P(y_j = k)$ for $k \in \{0,1,2,\dots,300\}$. For each city-time period, the RDS-IPC adjusted distribution of partner numbers can thus be estimated using the equation

$$P\left(y_j = k\right)^{(m)} = \sum_{i=1}^{n_j} \frac{P\left(y_j = k|\left[\hat{y}_{ij}|X_{ij},\phi_j\right]^{(m)}\right) w_{ij}}{\sum_{i=1}^{n_j} w_{ij}}$$

where individual probabilities $P(y_{ij} = k)$ are computed from each participant's posterior predictive mean from the second step, and w_{ij} is the RDS-IPC weight for participant i at city and time period j. We used the mean of the posterior distribution as the point estimate and computed 95% credible intervals (CrI) from the 2.5th and 97.5th percentiles.

We verified that the data satisfies the assumptions for fitting a negative binomial regression. Briefly, we verified that the independence, linearity, and overdispersion assumption of the negative binomial regression model were satisfied. Further, the percentage of the population

reporting 0 partners was around 13% in each city during the pandemic and post-restrictions timepoints, and therefore, we also fit a zero-inflated model as a sensitivity analysis.

RDS-II weights and inverse probability of censoring weights

We computed RDS-II weights for each city separately, and the inverse probability of censoring weights (IPCW) for the two follow-up time periods (separately for each city). The RDS-II weights were computed using the RDS-II estimator and the self-reported network size, capped at 150 (a correction was applied if a participant reported knowing fewer gay men than they had recruited). For a participant i in city c, the RDS-II weight was:

$$\widetilde{w}_{RDS}^{ic} = \frac{\sum_{i=1}^{n_c} network\ size_i}{n_c} \frac{1}{network\ size_i}$$

and the normalized RDS-II weight was:

$$w_{RDS}^{ic} = \widetilde{w}_{RDS}^{ic} \frac{n_c}{\sum_{i=1}^{n_c} \widetilde{w}_{RDS}^{ic}}$$

where $c \in$ { *Montréal, Toronto, Vancouver* } and $n_c = n_j$ for the pre-pandemic period for each city.

For IPCW, we computed the propensity score for being loss to follow-up (LTFU), $P(LTFU = 1)$, referred to as $LTFU_{ij}$. For the pandemic and post-restrictions periods, a participant was considered LTFU if they did not have a visit during the defined period. We identified potential predictors of LTFU by computing RDS-weighted standardized mean differences (SMD) to assess the imbalance in the predictors (measured at pre-pandemic) between LTFU and retained participants. All identified LTFU predictors (i.e., with imbalance as measured by SMD) were used in the propensity score model in matrix Z_{ij} (variable definitions in ***Supplementary Table 1***):

$$logit\left(LTFU_{ij}\right) = \alpha'_j + \beta'_j Z_{ij}$$

where

α'_j : model intercept for city-time period j;

Z_{ij} : a matrix containing the values of predictors for participants i for city and time period j, i.e., *Age, Relationship_Status, HIV_Status, Bathhouse, Group_Sex, Dating_App, Transactional_Sex, Education, Income, Ethnic_Min, Nb_Partn_Ov5*, where

Nb_Partn_Ov5=$I(y_{ij} > 5)$;

β'_j : vector of regression coefficients for city-time period j, for set of covariates Z_j.

The propensity score ps for participant i being LTFU at time period j is therefore $ps_{ij} = P(LTFU = 1|Z_{ij})$, and pr_j is the weighted proportion of participants LTFU in city-time period j. The derived stabilized RDS-IPC weight for participant i is

$$w_{ij} = \begin{cases} w_{RDS}^{ic} & \text{for the pre} - \text{pandemic time period,} \\ w_{RDS}^{ic}\left(\frac{1}{1-ps_{ij}}\right)(1-pr_j) & \text{if } LTFU_{ij} = 0, \text{and} \\ w_{RDS}^{ic}\left(\frac{1}{ps_{ij}}\right)(pr_j) & \text{otherwise.} \end{cases}$$

$$pr_j = \frac{\sum_{i=1}^{n_c} w_{RDS}^{ic} I(LTFU_{ij} = 1)}{\sum_{i=1}^{n_c} w_{RDS}^{ic}}$$

where for each city-time period j the index c refers to its corresponding city.

Finally, we ensured that the RDS-IPC weights sum to the RDS-adjusted number of participants, i.e., $\sum_{i=1}^{n_j} w_{ij} = \sum_{i=1}^{n_j} w_{RDS}^{ic}$ and that the SMD after the adjustment is small.

$\mathcal{R}_0$ using a risk-stratified deterministic SEIR model and the next-generation matrix

First, we partitioned the GBM population into 20 groups according to the following percentiles: 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 92%, 94%, 95%, 96%, 97%, 98%, 99%, 99.2%, 99.4%, 99.6% and 99.8% percentiles. These groupings were chosen to capture the tail of the distribution while ensuring that the smallest group size in that upper tail was reasonable (e.g., in Vancouver, 0.2% of the GBM population would correspond to approximately 50 individuals). The contact rates for these groups were based on the fitted distributions of sexual partner numbers in the P6M estimated above (***Supplementary Table 7***). Our approach enabled us to capture heterogeneity in contact rates in the most sexually active groups. We then developed, parameterized, and calibrated a deterministic *Susceptible-Exposed-Infectious-Removed* (SEIR) model of sexual mpox transmission among a closed population of GBM [1]. We assumed that the average time spent in the latent and infectious stages followed an Erlang-2 distribution (i.e., partitioned the E and I states into two compartments with transition rates twice α or γ, respectively) and used an 8-hour timestep. As we calibrated the model to surveillance data, we

accounted for an average 2-day reporting delay between onset of infectiousness and case confirmation (i.e., getting tested positive). Further, we do not explicitly distinguish asymptomatic and symptomatic cases but assume that only a fraction (calibrated) of all infections would be reported in the surveillance data. Model parameters are presented in ***Supplementary Table 2***, and ***Supplementary Figure 7*** shows the model structure. The model equations are:

$$\begin{cases} \frac{dS^s(t)}{dt} = -\lambda_t^s S^s(t) \\ \frac{dE_1^s(t)}{dt} = \lambda_t^s S^s(t) - 2\alpha E_1^s(t) \\ \frac{dE_2^s(t)}{dt} = 2\alpha E_1^s(t) - 2\alpha E_2^s(t) \\ \frac{dI_1^s(t)}{dt} = 2\alpha E_2^s(t) - 2\gamma I_1^s(t) \\ \frac{dI_2^s(t)}{dt} = 2\gamma I_1^s(t) - 2\gamma I_2^s(t) \\ \frac{dR^s(t)}{dt} = 2\gamma I_2^s(t) \end{cases}$$

In addition, we tracked reported cases using the two equations below, where the compartment *O* tracks the onset of cases into the infectious period and compartment *C* is the cumulative number of reported cases,

$$\begin{cases} \frac{dO^s(t)}{dt} = 2\alpha E_2^s(t) - \eta O^s(t) \\ \frac{dC^s(t)}{dt} = \varepsilon\left(\eta O^s(t)\right) \end{cases}$$

where

s : sexual activity group $s \in \{1,2,\dots,20\}$;

β : transmission risk per effective contact (calibrated parameter);

λ_t^s : force of infection for the i-th sexual activity group at time *t*,

$$\lambda_t^s = \beta c^s \sum_{s'=1}^{20} \left(g^{ss'} \frac{I_1^{s'}(t) + I_2^{s'}(t)}{N^{s'}} \right);$$

$g^{ss'}$: probability that an individual in group s chooses a partner from the s'-th sexual activity group (defined below; calibrated parameter);

c^s : average contact rate per day of the s-th sexual activity group (from the fitted distribution);

α : rate of transition from exposed to infectious (fixed at 1/5.1 days);

γ : rate of transition between infectious to removed/isolated/recovered (calibrated parameter);

η : rate at which cases are reported (1/2 days)

ε : the reporting fraction (proportion of cases that are reported; calibrated parameter), assumed to be constant over the modeled period.

For $g^{ss'}$ —probability of partnership formation from group s with a partner from the s'-th sexual activity group— we incorporated a degree of assortativity ω as follows:

$$g^{ss'} = (1-\omega)\frac{c^{s'}N^{s'}}{\sum_{s''=1}^{20} c^{s''}N^{s''}} + \delta^{ss'}\omega$$

where $\delta^{ss'}$ represents entries from a fully assortative ("like-with-like") mixing matrix $\delta^{ss'} = \begin{cases} 1 & \text{for } s = s' \\ 0 & \text{otherwise.} \end{cases}$

We seeded the epidemic by importing cases in the 5% highest activity groups, with the number of imported cases as a calibrated parameter (bounded between 2–6 in Montréal, 3–6 in Toronto, 1–3 in Vancouver) [2]. As cases occurred 3-4 weeks earlier in Montréal, we assumed that the delay from first importation to case reporting beginning was 21 days in Montréal and 10 days in Toronto and Vancouver.

The model parameters were calibrated to daily incidence of confirmed mpox cases in the provinces where the cities are located [3] using a Poisson likelihood. We only modeled the first weeks of the outbreaks, before the scale-up of vaccination activities (June 14th for Montréal and July 10th, 2022 for Toronto and Vancouver) [4–6]. Using provincial reports should not bias results since, at that time, the overwhelming majority of cases were reported from the three cities: this early data is representative of the city-level transmission [7–9].

Calibration was performed using sampling importance resampling where the proposal distribution was estimated from the Laplace approximation. Posterior modes of the parameters were obtained using nonlinear optimization via the Broyden-Fletcher-Goldfarb-Shanno algorithm and initial samples (n=15,000) were drawn from a multivariate *t*-distribution with 2 degrees of freedom. Then, the full posteriors distributions were approximated by sampling 1,000 parameters sets from this proposal distribution. This calibration method was chosen for its computational efficiency. ***Supplementary Table 2*** presents summary statistics of the posterior mean and 95% CrIs of model parameters.

Five parameters were calibrated for each city independently. Prior distributions for the infectious duration were derived from a review of the literature, and we used weakly informative priors for the transmission, assortativity parameter, reporting fraction parameter, and number of imported cases (***Supplementary Table 2***). The likelihood of the model and priors are the following:

$$C_d^{obs} \sim Poisson\left(C_d^{mod}\right)$$

$$\beta \sim logit^{-1}\left(N(logit(0.5), 2)\right)$$

$$\gamma \sim e^{N\left(\ln\left(\frac{1}{3}\right), 0.5\right)}$$

$$\omega \sim logit^{-1}\left(N(logit(0.5), 1)\right)$$

$$\varepsilon \sim logit^{-1}\left(N(logit(0.8), 1)\right)$$

$$\tau \sim logit^{-1}\left(N(logit(0.5), 0.5)\right) * (b_u - b_l) + b_l$$

where C_d^{obs} is the daily (d) observed number of mpox reported cases; C_d^{mod} is the model-predicted daily number of reported mpox cases; β is the probability of transmission per effective sexual contact; γ^{-1} is the effective duration of infectiousness; ω is the assortativity parameter; ε is the fraction of all mpox infections that will be reported to the surveillance databases, and τ is the number of imported cases. For this last parameter, for Montréal $b_l = 2$ and $b_u = 6$, for Toronto $b_l = 3$ and $b_u = 6$ and for Vancouver $b_l = 1$ and $b_u = 3$, where b_l and b_u are the lower and upper bounds for the number of imported cases. As case counts are for the entire GBM population in each city, $C_d^{mod} = \sum_{s=1}^{20} \frac{dC^s(t)}{dt}|_{t=d}$, where $C^s(t)$ is the cumulative number of reported cases in sexual activity group s up to time t.

Once the model was calibrated to the surveillance data, we constructed a next-generation matrix (NGM) to estimate the population $\mathcal{R}_0$ and effective reproduction number $\mathcal{R}_e$ accounting for immunity in the highest sexual activity groups. We followed a simplified construction of the NGM which is equivalent to that proposed by Diekmann et al [1,10], where each $\rho_{ss'}$ entry of the NGM corresponds to the definition of $\mathcal{R}_0$ and can be defined as

$$\rho_{ss'} = \beta c^s g^{ss'} \gamma^{-1}$$

For each city, the $\mathcal{R}_0$ can be calculated as the largest non-zero eigenvalue of this matrix. To compute the $\mathcal{R}_e$ accounting for immunity, we set to zero the contact rate c^s in the groups corresponding to the top 0.2%, 0.4%, 0.6%, 0.8%, 1%, 2%, 3%, 4%, and 5% of sexual activity groups—equivalent to assuming that susceptibles were depleted sequentially, starting from the highest-activity group. To project what the transmission potential of mpox would have been under pre-pandemic sexual activity levels, we repeated these procedures for each city using the pre-pandemic distribution of sexual partner numbers.

$\mathcal{R}_0$ from reported case numbers and endpoint of exponential growth period

To enable comparisons with other studies, we also estimated the $\mathcal{R}_0$ from the cumulative incidence of confirmed mpox cases in the three provinces where Montréal, Toronto, and Vancouver are located (respectively, Québec, Ontario, and British Columbia), using the formula $\mathcal{R}_0 = (1 + \Lambda D)(1 + \Lambda D')$ where D is the duration of infectiousness, D' is the latent period (time from infection until start of infectiousness) and Λ is the epidemic growth rate. Since saturation of the high sexually activity groups could occur quite rapidly, these estimates of $\mathcal{R}_0$ are expected to be biased downward. For comparability with our own NGM $\mathcal{R}_0$ estimates, we used the calibrated values from the SEIR model for the duration of infectiousness (3.8 days). Based on the available evidence and assuming a pre-symptomatic period of 2 days (i.e., the latent period is the incubation period minus 2), we used the same latent period as the SEIR model, i.e., $D' = 5.1$ (***Supplementary Table 2***) [11–15].

To estimate Λ, we used the period in the outbreak during which mpox cases were growing exponentially. We ascertained the end of the exponential growth period by visual inspection of the curve of cumulative cases and by determining the initial period during which the effective reproductive number ($\mathcal{R}_e$) was relatively stable. We estimated the $\mathcal{R}_e$ from the reported cases using

the *EpiEstim* package [16], using a serial interval with mean of 9.0 and standard deviation of 8.9 days [11,12,14], a 14-day smoothing window and focusing on the first 200 days of the outbreak in each city, when the majority of mpox cases were diagnosed (Québec: April 28th, 2022 to November 14th, 2022; Ontario: May 13th, 2022 to November 29th, 2022; British Columbia: May 25th, 2022 to December 11th, 2022). Based on the curve of log-cumulative cases and the $\mathcal{R}_e$, we estimated Λ using the 50 days after the first mpox case was reported in a province (***Supplementary Figure 2, 8***). As a sensitivity analysis to this assumption, we also computed the $\mathcal{R}_0$ based on the first 40 and first 60 days.

Supplementary Results

Supplementary Tables

Supplementary Table 2. Natural history parameters for mpox and structure parameters for the SEIR model.

Parameter	Unit	Symbol	Prior	City	Value	Range* or 95% CrI	Sources
Natural history parameters							
Incubation period[†]	days				7.1	(5.6–9.0)	[11–14]
Latent period	days	D' or α^{-1}			5.1	(3.6–7.0)	Incubation period minus 2 days [15]
Infectious duration[‡]	days	D or γ^{-1}	95% of the prior density between 1.1 and 8.0 days	Montréal Toronto Vancouver	4.18 3.56 3.58	(3.33–6.43) (3.09–4.81) (2.66–6.30)	Calibrated
Risk of transmission per effective contact[‡]		β	95% of the prior density between 2% and 98%	Montréal Toronto Vancouver	0.87 0.86 0.80	(0.72–0.98) (0.69–0.95) (0.51–0.95)	Calibrated
Serial interval (mean)[†]	days				9.0	(8.5–9.5)	[11,12,14]
Serial interval (standard deviation)[†]	days				8.9	(5.0–10.9)	[11,12,14]
Model structure parameters							
Mixing parameter[‡]		ω	95% of the prior density between 0.12 and 0.88	Montréal Toronto Vancouver	0.78 0.67 0.72	(0.67–0.89) (0.48–0.76) (0.40–0.92)	Calibrated
Reporting delay	days	η^{-1}			2		Fixed
Reporting fraction[‡]		ε	95% of the prior density between 36% and 97%	Montréal Toronto Vancouver	0.82 0.85 0.78	(0.49–0.96) (0.58–0.97) (0.48–0.96)	Calibrated
Number of imported cases[‡]		τ	95% of the prior density between 3.1–4.9 (Montréal) 3.8–5.2 (Toronto) 1.5–2.5 (Vancouver)	Montréal Toronto Vancouver	4.1 4.7 2.0	(3.2–5.0) (3.9–5.2) (1.6–2.4)	Calibrated

CrI, credible interval.

* Range shows the range of estimates from the literature.

† Values estimated by averaging estimates reported by individual studies, weighted by study sample size.
‡ Values shown are city-specific parameter estimate and 95% CrI's.

Supplementary Table 3. Retention of *Engage Cohort Study* participants at each time period.

	n (%)		
	Montréal	**Toronto**	**Vancouver**
Pre-Pandemic	1,179 (100%)	517 (100%)	753 (100%)
Pandemic	831 (70%)	302 (58%)	449 (60%)
Post-Restrictions	786 (67%)	288 (56%)	393 (52%)

Supplementary Table 4. Association between number of sexual partners in the past 6 months and covariates among *Engage Cohort Study* participants in Montréal, Toronto, and Vancouver during the post-restrictions time period (December 2021–February 2023).

	Montréal		Toronto		Vancouver	
	RR (95% CrI)	**SE**	**RR (95% CrI)**	**SE**	**RR (95% CrI)**	**SE**
exp(intercept)	3.96 (3.09, 5.11)	0.0022	3.94 (2.74, 5.76)	0.0033	4.22 (2.98, 6.02)	0.0032
Age group						
16-29	REF	—	REF	—	REF	—
30-39	1.16 (0.88, 1.55)	0.0026	1.01 (0.67, 1.51)	0.0034	1.25 (0.88, 1.78)	0.0032
40-49	0.87 (0.62, 1.22)	0.0028	0.8 (0.5, 1.33)	0.004	1.18 (0.77, 1.8)	0.0035
50-59	0.7 (0.48, 1.03)	0.0029	1.18 (0.54, 2.75)	0.0059	1.09 (0.68, 1.78)	0.0039
≥60	0.88 (0.62, 1.25)	0.0029	0.43 (0.21, 0.92)	0.0056	0.84 (0.5, 1.45)	0.0038
Relationship status and sexual agreement						
Single	REF	—	REF	—	REF	
Exclusive	0.44 (0.32, 0.59)	0.0017	0.48 (0.3, 0.78)	0.0032	0.23 (0.16, 0.35)	0.0023
Open	1.12 (0.93, 1.37)	0.0011	1.06 (0.78, 1.43)	0.0019	0.98 (0.77, 1.28)	0.0016
Unclear	0.68 (0.49, 0.97)	0.0019	0.44 (0.2, 1.02)	0.005	0.84 (0.46, 1.67)	0.0036
HIV seropositive*	1.51 (0.6, 4.32)	0.01	2.45 (0.9, 7.83)	0.011	1.62 (0.23, 23.3)	0.028
HIV x Age group interaction						
HIV x 30-39	1.03 (0.32, 3.04)	0.011	0.38 (0.11, 1.15)	0.012	0.64 (0.04, 5.38)	0.029
HIV x 40-49	0.59 (0.18, 1.86)	0.011	0.66 (0.18, 2.13)	0.012	0.25 (0.02, 1.98)	0.03
HIV x 50-59	0.65 (0.21, 1.84)	0.011	0.21 (0.05, 0.92)	0.013	0.48 (0.03, 3.81)	0.029
HIV x ≥60	0.34 (0.11, 0.97)	0.011	0.51 (0.12, 2.03)	0.014	0.83 (0.05, 6.68)	0.029
Bathhouse/sex club attendance in the P6M†	1.74 (1.39, 2.17)	0.0013	1.8 (1.31, 2.44)	0.002	1.85 (1.37, 2.51)	0.0018
Group sex event attendance in the P6M†	3.44 (2.66, 4.47)	0.0016	3.62 (2.59, 5.13)	0.0022	3.09 (2.24, 4.34)	0.002
Transactional sex in the P6M†	3.46 (2.15, 5.76)	0.0029	2.93 (1.74, 5.13)	0.0032	3.57 (1.81, 7.67)	0.0044
1 / overdispersion parameter	2.42 (2.19, 2.68)	0.00063	3.12 (2.53, 3.95)	0.0014	2.89 (2.44, 3.51)	0.001

Table presents the mean and 95% credible interval from 6,000 posterior samples from a Bayesian negative binomial regression model.

CrI, credible interval; *SE*, standard error; *RR*, rate ratio.

Dating app use was only evaluated at the baseline survey (pre-pandemic time period).

* HIV status was determined based on 4th generation testing with a confirmatory assay. If the laboratory test result was unknown, self-reported status was used.

† At least once in the P6M.

Supplementary Table 5. Basic reproduction number ($\mathcal{R}_0$) estimates from the growth rate assuming different lengths of exponential growth.

	$\mathcal{R}_0$		
Assumed duration of the exponential growth period	**Québec (Montréal)**	**Ontario (Toronto)**	**British Columbia (Vancouver)**
40 days after first case	2.17	2.08	1.92
50 days after first case*	1.95	1.94	1.87
60 days after first case	1.79	1.83	1.77

* Primary results.

Supplementary Table 6. Estimated cumulative incidence proportion of confirmed mpox cases among sexually active gay, bisexual, and other men who have sex with men during the 2022–2023 mpox outbreak.

	Montréal	**Toronto**	**Vancouver**
Population size (all men ≥15 years old)*	1,735,065	2,529,370	1,102,200
Population size (sexually active GBM)*	54,000	78,000	26,100
Number of reported cases†	463	688	176
Cumulative incidence proportion	0.9%	0.9%	0.7%

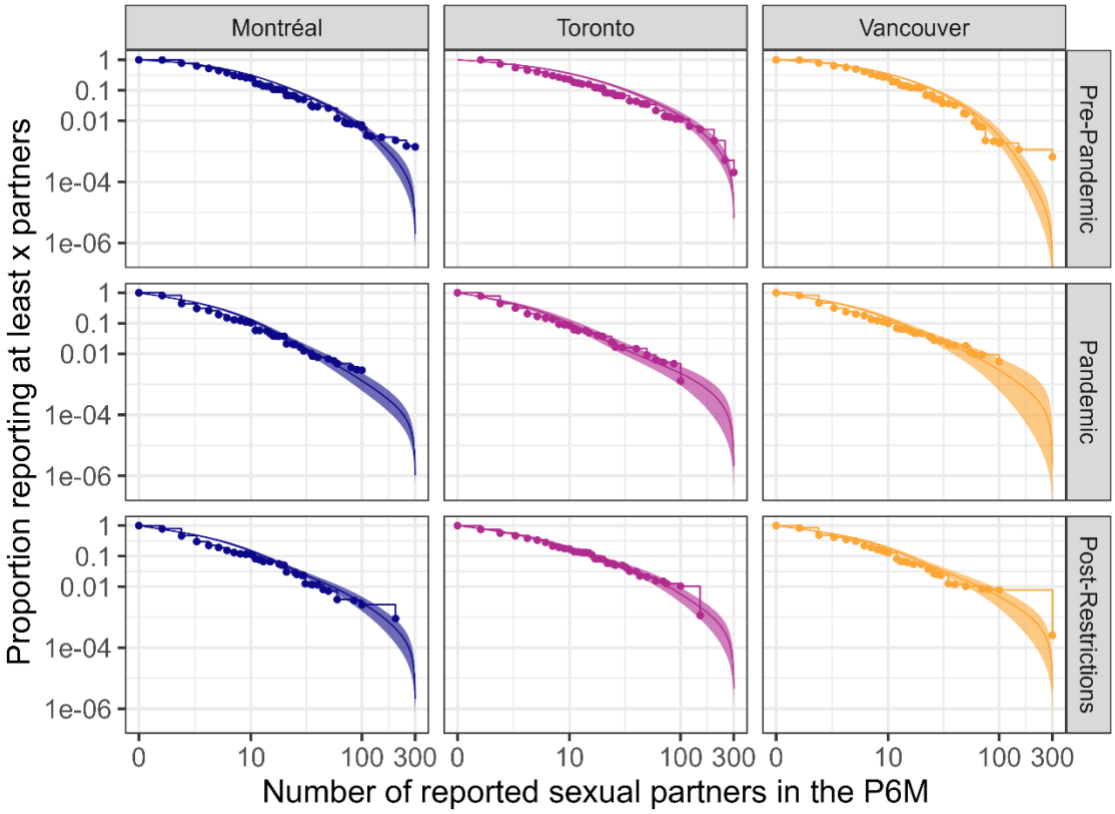
* Population size estimates were taken from the 2021 Canadian Population Census, for the corresponding census metropolitan area of Montréal and Toronto. The population size of sexually active GBM in these two cities was estimated as 3.1% of all men ≥15 years old in the metropolitan area of Montréal and Toronto. For Vancouver, we used a previously estimated population.
† The number of confirmed mpox cases (as of October 7th, 2022) were reported from the *Public Health Agency of Canada*.
GBM, gay, bisexual, and other men who have sex with men.

Supplementary Table 7. RDS-inverse probability of censoring weighted contact rates estimated among *Engage* participants and used to parametrize the SEIR model.

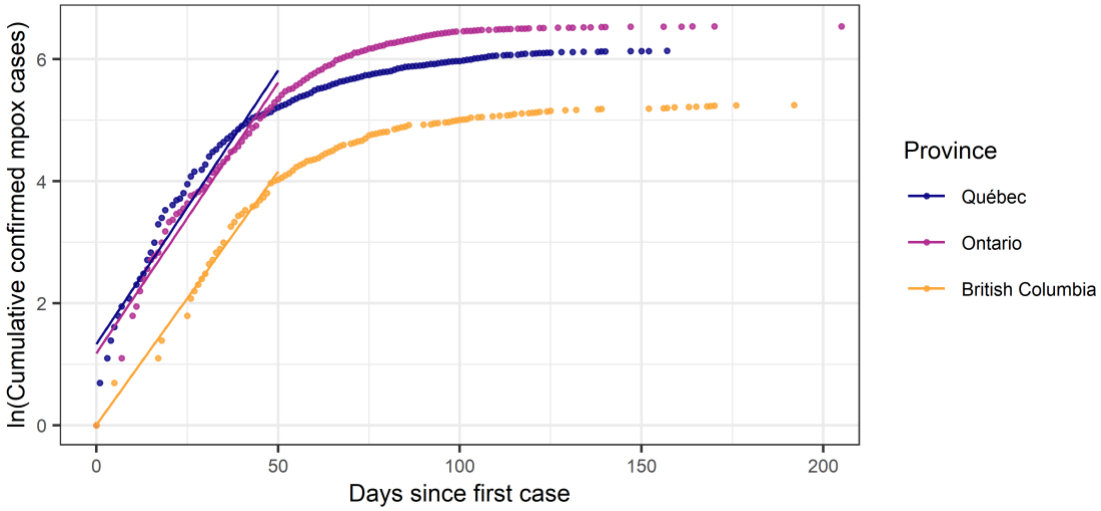
	Contact rate (number of partners) over 6 months					
	Montréal		Toronto		Vancouver	
Proportion of the population	Post-restrictions	Pre-pandemic	Post-restrictions	Pre-pandemic	Post-restrictions	Pre-pandemic
20.0%	0.0	0.5	0.0	0.4	0.0	0.6
10.0%	0.6	2.0	0.9	1.8	0.9	2.2
10.0%	1.0	3.2	1.4	3.1	1.4	3.4
10.0%	2.0	4.5	2.2	4.6	2.3	4.8
10.0%	2.8	6.2	3.3	6.8	3.4	6.8
10.0%	4.2	8.5	4.8	9.8	4.9	9.4
10.0%	6.1	12.0	7.1	14.6	7.2	13.3
10.0%	9.6	18.6	11.7	24.0	11.4	20.3
2.0%	13.5	26.2	17.7	35.0	16.0	27.8
2.0%	15.9	30.9	22.1	41.7	18.9	32.2
1.0%	18.5	35.7	26.8	48.8	22.0	36.5
1.0%	20.9	40.2	31.4	55.2	25.2	40.3
1.0%	24.6	46.2	37.8	63.8	29.8	45.3
1.0%	30.4	55.0	47.3	76.3	37.4	52.4
1.0%	42.5	70.1	63.9	97.5	52.6	63.7
0.2%	56.9	85.7	81.4	119.1	70.3	74.9
0.2%	65.4	94.4	91.5	130.7	80.9	80.8
0.2%	78.1	106.5	106.3	146.7	96.8	89.0
0.2%	100.0	126.6	132.2	171.9	124.9	101.9
0.2%	167.1	183.5	203.0	229.0	200.7	139.0

The post-restrictions contact rates were used to parametrize the SEIR model and to compute $\mathcal{R}_0$ and $\mathcal{R}_e$ using the next-generation matrix. The pre-pandemic contact rates were used to project the $\mathcal{R}_e$ using the next-generation matrix. These contact rates were scaled down to daily to match the timescale of the model parameters by dividing by 180 days.

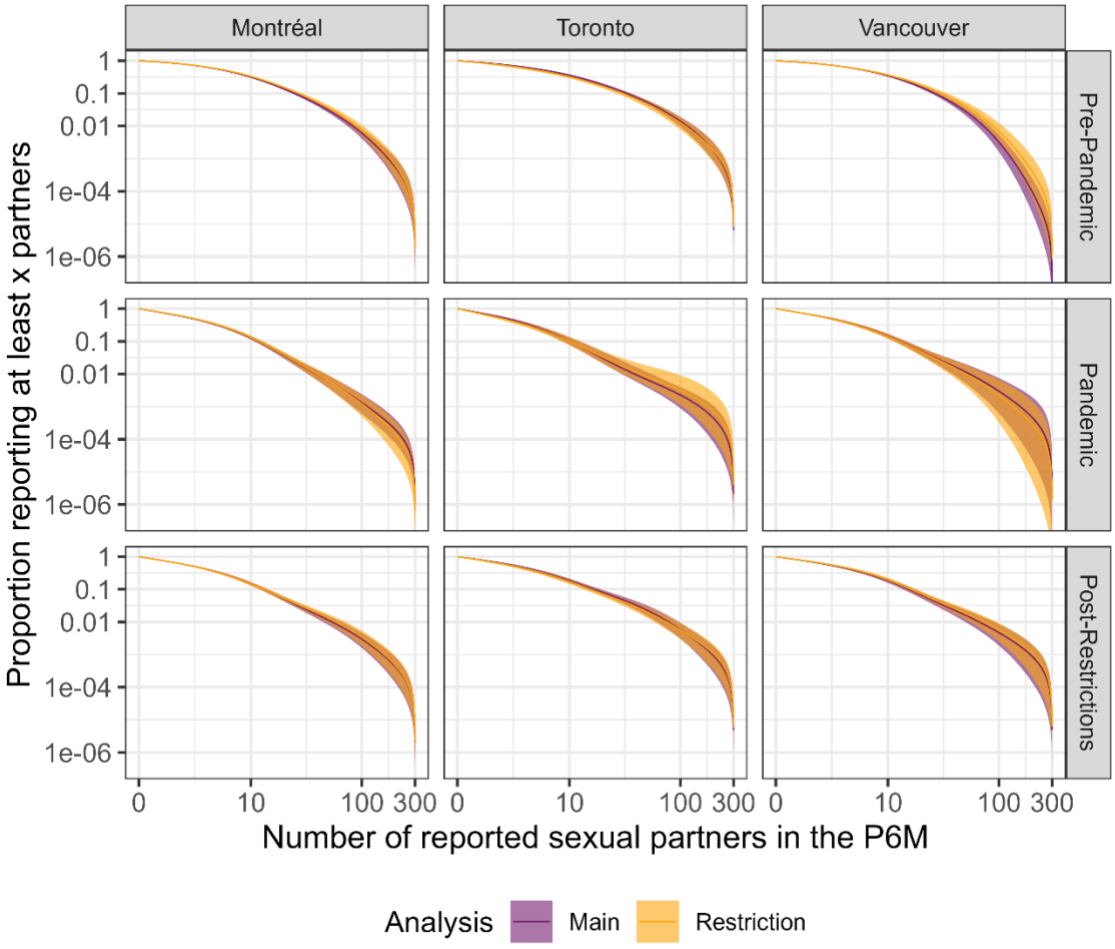
Supplementary Figures



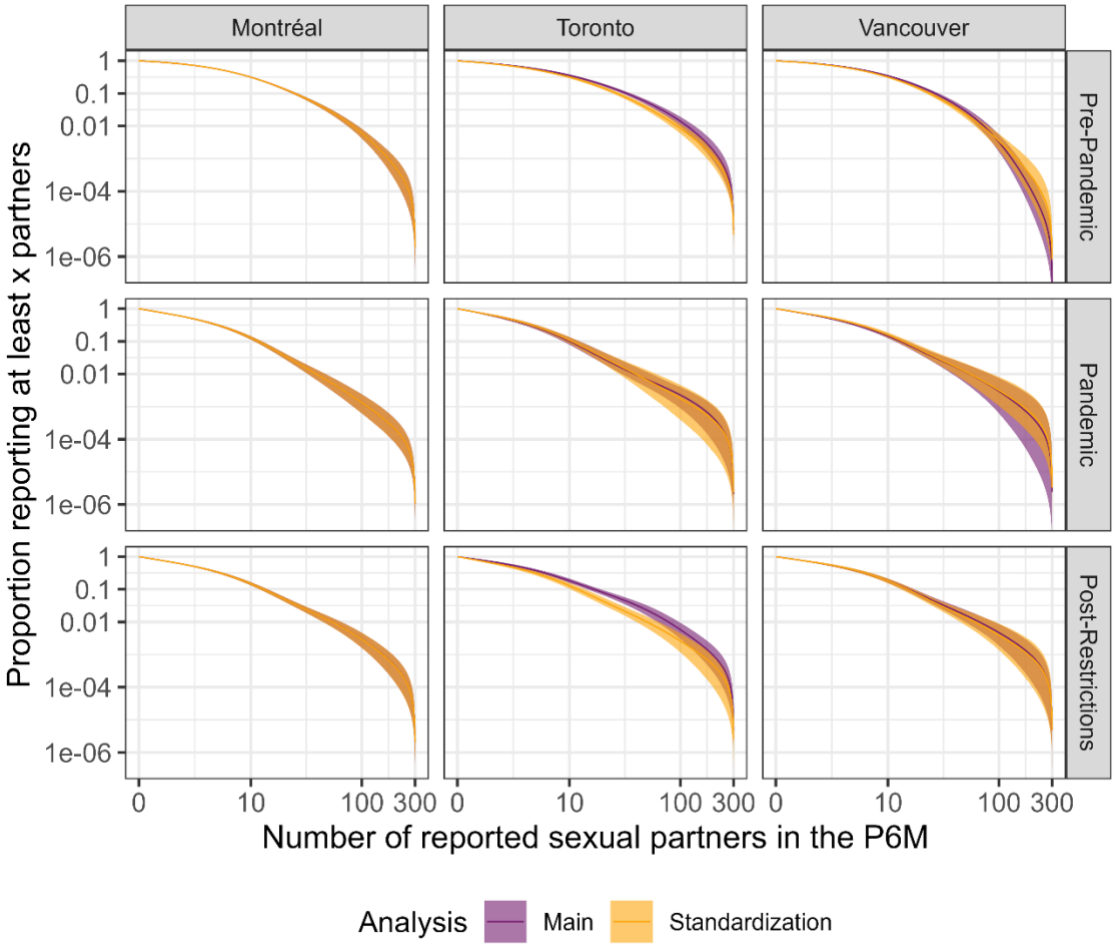
Supplementary Figure 1. Observed (RDS and inverse probability of censoring weighted) and fitted distributions of sexual partner numbers in the past 6 months for participants of the *Engage Cohort Study*. Lines with dots show the observed distributions, solid lines show the fitted distributions using negative binomial regression with post-stratification. Shaded area shows 95% credible intervals. RDS: respondent-driven sampling.



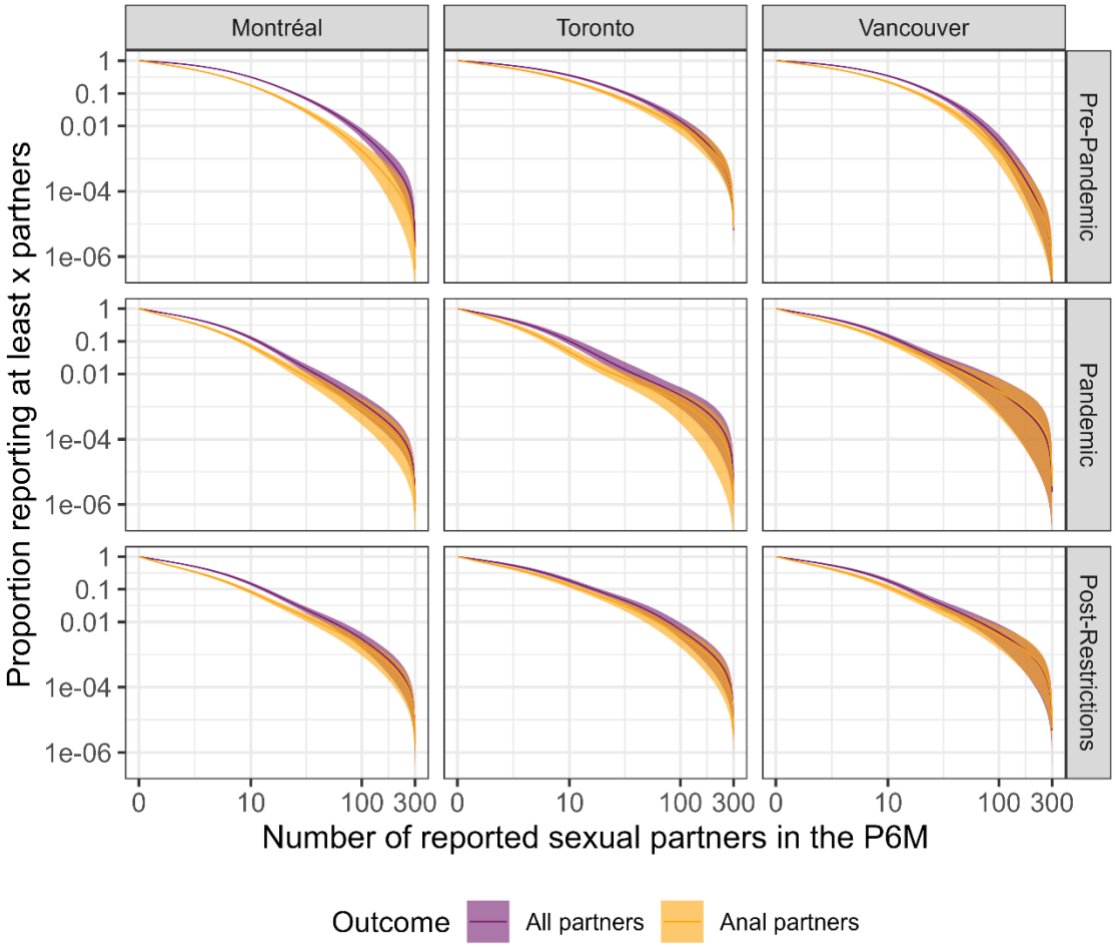
Supplementary Figure 2. Cumulative incidence of confirmed mpox cases in the provinces of Québec, Ontario, and British Columbia (natural log scale). The growth rate used for estimating $\mathcal{R}_0$ was computed as the slope of the log cumulative cases over time, using data from the first 50 days after the first mpox case was reported in each province (solid line shows the fitted regression).



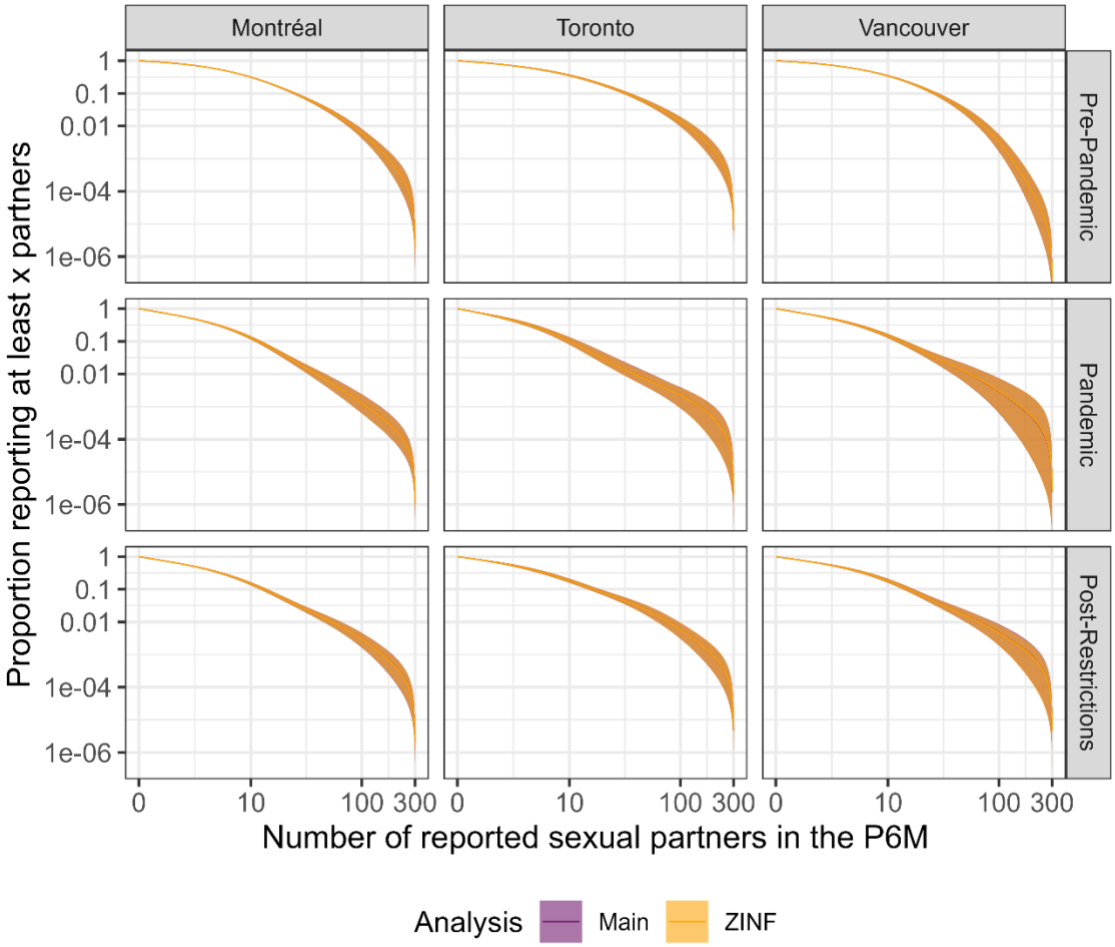
Supplementary Figure 3. Comparison of cumulative distribution of sexual partner numbers in the past 6 months between the main analysis (adjusted for RDS-IPC weights) and the restriction analysis (RDS-II weighted, using only participants with data for all time periods). RDS: respondent-driven sampling; IPC: inverse probability of censoring.



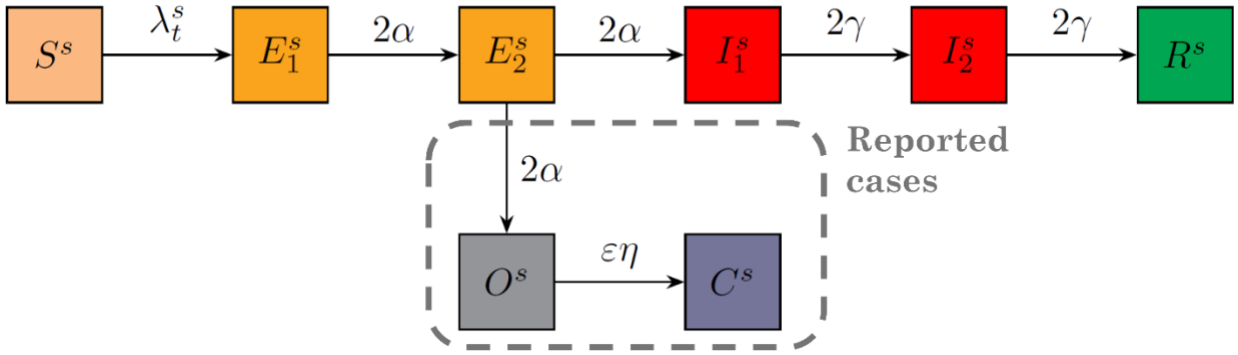
Supplementary Figure 4. Comparison of cumulative distribution of sexual partner numbers in the past 6 months between the main analysis (adjusted for RDS-IPC weights) and the standardization analysis (adjusted for RDS-IPC weights and standardized to the Montréal population). RDS: respondent-driven sampling; IPC: inverse probability of censoring.



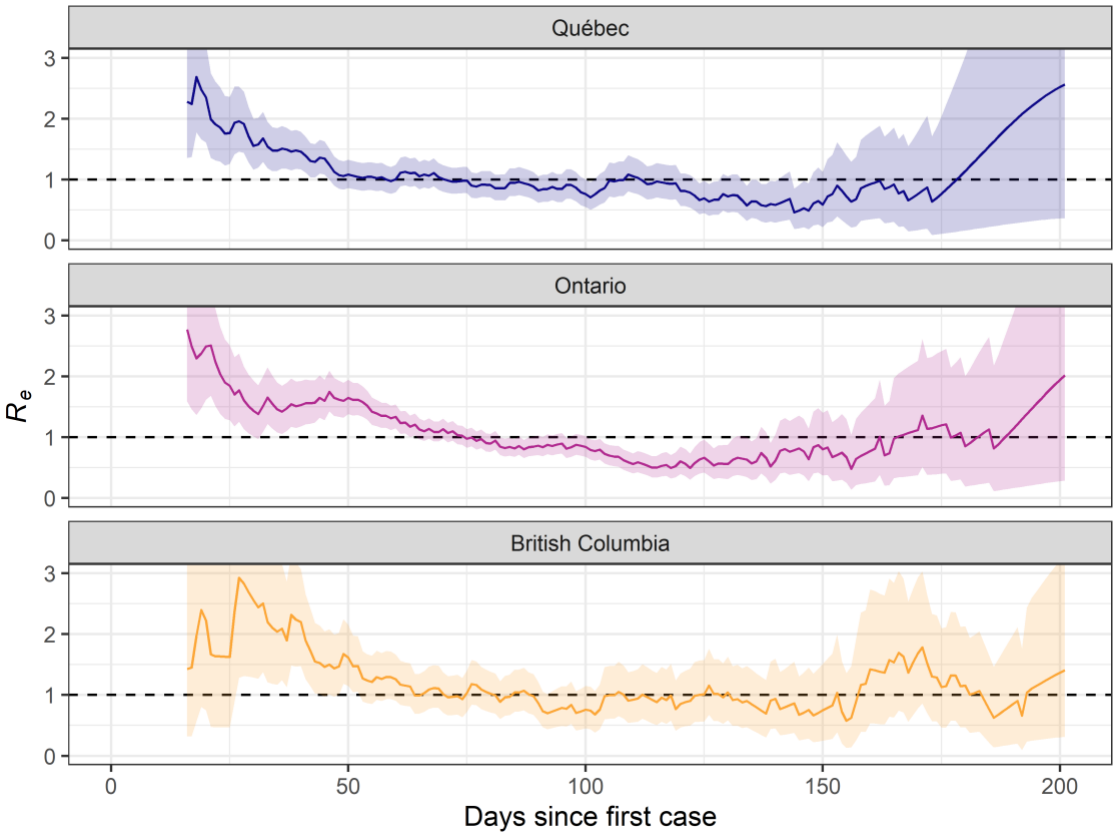
Supplementary Figure 5. Comparison of cumulative distribution of sexual partner numbers in the past 6 months between the main analysis (outcome: all sexual partners) and the sensitivity analysis using anal sexual partners as the outcome. Both analyses were adjusted for RDS-IPC weights. RDS: respondent-driven sampling; IPC: inverse probability of censoring.



Supplementary Figure 6. Comparison of cumulative distribution of sexual partner numbers in the past 6 months between the main analysis (negative binomial) and the zero-inflated negative-binomial sensitivity analysis. Both analyses were adjusted for RDS-IPC weights. RDS: respondent-driven sampling; IPC: inverse probability of censoring; ZINF: zero-inflated.



Supplementary Figure 7. Model structure of the deterministic SEIR model of mpox virus transmission among GBM. The duration of the latent and infectious periods is assumed to follow an Erlang-2 distribution. Gray box indicates compartments used to track the number of reported mpox cases, accounting for the delay between symptoms onset and case confirmation and for the reporting fraction. GBM: gay, bisexual, and other men who have sex with men.



Supplementary Figure 8. Effective reproduction number ($\mathcal{R}_e$) with 95% confidence interval in the province of Quebec, Ontario, and British Columbia. $\mathcal{R}_e$ was estimated based on confirmed mpox cases (data as of June 13th, 2023), using the first 200 days since the first case was reported in each province and a time window of 14 days.

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Chapter 5

Study Results (Manuscript 2)

The second manuscript addresses objective 2 of my thesis and describes the change in GBM's sexual behaviours during the mpox outbreak, and the impact of change in sexual behaviours, contact tracing/isolation, and first-dose vaccination in Montréal, Toronto, and Vancouver.

Xiu F, Doyle C, Flores Anato JL, Cox J, Grace D, Hart T, Zhang T, Skakoon-Sparling S, Dvorakova M, Shahin R, Sachdeva H, Knight J, Wang L, Lachowsky N, Sbihi H, Tan DHS, Irvine M, Mishra S, Maheu-Giroux M. Impact of interventions on mpox transmission during the 2022 outbreak in Canada: a mathematical modeling study of three different cities

Impact of interventions on mpox transmission during the 2022 outbreak in Canada: a mathematical modeling study of three different cities

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Abstract: 250 words
Main text: 3,226 words

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Key words: mpox; monkeypox; mathematical model; men who have sex with men; vaccination; contact tracing; behavioural change; Modified vaccinia Ankara; MVA-BN.

Abstract

Background: The 2022-2023 global mpox outbreak primarily affected gay, bisexual, and other men who have sex with men (GBM). It was met with swift community and public health responses. The impact of GBM's reductions in sexual partners, contact tracing/isolation, and vaccination on transmission in Canadian cities remain unknown.

Methods: We estimated changes in sexual behaviours during the outbreak using 2022 data from the *Engage Cohort Study* which recruited self-identified GBM in Montréal, Toronto, and Vancouver (n=1,445). The number of sexual partners in the past 6 months (P6M) was modelled using negative binomial regressions. A transmission-dynamic compartmental model was calibrated to surveillance data. We estimated the averted fraction of new mpox infections attributable to reductions in sexual partners, contact tracing/isolation, and first-dose vaccination, as compared with an unmitigated epidemic scenario in each of the three cities.

Results: The empirical results for sexual behaviours changes were imprecise: number of sexual partners decreased by 20% (RR=0.80; 95% credible intervals [95%CrI]: 0.47-1.36) among those reporting ≤7 partners (P6M) and by 33% (RR=0.67; 95%CrI: 0.31-1.43) among those with >7 partners (P6M). Compared to the unmitigated epidemics, the three interventions averted 46%-58% of cases. Reduction in sexual partner numbers and contact tracing/isolation prevented approximately 12% and 14% of cases, respectively. Vaccination had the largest effect, but varied by cities, with 21%-39% mpox infections prevented.

Conclusions: Reduction in sexual activity, contact tracing/isolation, and vaccination all contributed to accelerating epidemic control and averting infections. Vaccination had the largest impact, but the city-specific effect was affected by coverage.

Background

The 2022-2023 global mpox outbreak resulted in more than 90,000 infections across 110 historically non-endemic regions, including Canada; it also disproportionately impacted gay, bisexual, and other men who have sex with men (GBM) [1]. Unlike historically reported cases in Central and West Africa, the recent global outbreak was sustained due to human-to-human transmission, primarily via sexual contact [2]. From May 2022 to October 2023, 98% of 1,443 confirmed cases with available data in Canada, occurred among GBM [3], and >70% of the reported cases were concentrated in Montréal (Québec), Toronto (Ontario), and Vancouver (British Columbia), the country's three largest cities [4–6]. Mpox's cumulative incidences among GBM were around 1% in all three cities, despite differences in timing of outbreaks and interventions [7].

On May 19th, 2022, the first confirmed mpox case in Canada was reported in Montréal, the site of the first North American outbreak [8]. Cases in Toronto and Vancouver were respectively confirmed first on May 26th and June 6th of that year [8,9]. The outbreaks were met with swift responses from community organizations, sexual health professionals, laboratorians, and public health teams. The number of mpox cases peaked in all three cities from late-June to mid-July 2022 and declined thereafter, alongside the roll-out of public health interventions [3]. Various factors that govern the underlying transmission dynamics could have contributed to reductions in transmission, including saturation of groups at high risk of infection [10–13], changes in sexual behaviours following community outreach [14–16], contact tracing and isolation of traced contacts by local public health units [17,18], and use of vaccination [19,20].

Previous work showed that the effective reproduction number (i.e., $\mathscr{R}_t$: the average number of secondary infections from one infectious individual where some people are no longer susceptible) could drop below 1 if even a small proportion (<2%) of GBM with the highest levels of sexual activity acquired immunity [7,11]. In Canada, public health authorities partnered with community-based organizations to amplify messaging about mpox prevention by reducing sexual partner numbers, prevention, testing, and vaccination on digital platforms and at gathering places [21,22]. Online surveys among convenience samples of GBM in the United Kingdom and the United States found that nearly half of interviewed GBM reported reducing their sexual partner numbers and visits to sex-on-premises venues after the onset of the mpox outbreak [15,16]. It remains uncertain if, and to which extent, GBM living in Canada similarly adapted their sexual

behaviours in response to the mpox outbreaks, and what impact this had on the course of the epidemics.

Local health authorities conducted case and contact management to identify source infections and encouraged exposed symptomatic contacts to self-isolate [23]. In Montréal, 20% of contacts of confirmed cases were successfully traced/notified since late May 2022, resulting from the high number of anonymous sexual contacts [4,24]. Identified contacts were advised to self-monitor for symptoms and based on exposure risks, advised to receive post-exposure prophylaxis (PEP) using the Modified Vaccinia Ankara-Bavarian Nordic (MVA-BN) vaccine [4,23,24].

MVA-BN is a third-generation smallpox vaccine that offers cross-protection against the mpox virus [25,26]. In early June 2022, one-dose of vaccine for pre-exposure prophylaxis (PrEP) became available to individuals at high risk of exposure [5,24,27], including GBM who had sex with more than one partner and engaged in sexual contact in sex-on-premises venues [28]. As of mid-October 2022, approximately 24,000 first-doses in Montréal, and 35,000 in Toronto, of MVA-BN vaccines were administered [24,27]. In Vancouver, 18,000 first- and second-doses had been given over that same period [5].

Since mid-November 2022, case activity has been sporadic [3]. Understanding the impact of the main interventions in Montréal, Toronto, and Vancouver could generate new evidence, inform mpox prevention, and prioritize future public health actions. We aimed to evaluate the relative contribution of a) changes in sexual partner numbers, b) contact tracing/isolation, and c) first-dose vaccination on 2022 mpox outbreak dynamics among GBM in three different cities, while considering potential saturation of infections within high-risk groups. Specifically, we leveraged the *Engage Cohort Study*, a population-based study of GBM in the three cities, to empirically evaluate changes in sexual partner numbers during the period of high mpox transmission. We then developed a risk-stratified dynamic model of mpox transmission calibrated to mpox case surveillance data, to retrospectively assess the impact of various interventions on the final epidemic size, disentangling their unique contributions.

Methods

Data Source

The *Engage Cohort Study* (n=1,445) is a prospective cohort of GBM in Montréal, Toronto, and Vancouver. Detailed descriptions of *Engage* can be found elsewhere [29–32]. Briefly, eligible participants were self-identified cisgender or transgender men living in one of the three cities, aged

≥16 years, reported sex with another man in the past 6 months (P6M), understood English and/or French, and provided written informed consent [33]. Participants were recruited during 2017-2019 in each city using respondent-driven sampling (RDS) with subsequent study follow-up visits every 6-12 months [34]. At each visit, participants completed an online questionnaire including questions about sexual behaviours.

Changes in number of sexual partners during the mpox epidemics

To empirically estimate changes in self-reported number of all-type sexual partners, we first excluded visits prior to 2022, given disruptions in sexual behaviours during the COVID-19 pandemic in 2020 and 2021 [7,35,36]. We defined the period over which mpox-driven behaviour changes could have occurred from May 19th, 2022 (first reported mpox case in Canada) to August 14th, 2022 (vaccination coverage >30% in all three cities). The latter date was chosen to ensure a reasonable sample size and account for mpox vaccination scale-up. Using data from all *Engage* participants who had at least one visit in 2022, we fit a Bayesian negative binomial regression model to the number of sexual partners in the P6M, with a random intercept for each participant. We defined our exposure as the continuous fraction of the 6-month recall period that overlapped with the period of potential behaviour changes (i.e., adjusting for attenuation given the long recall period) . We also included the following covariates: age (16-29, 30-39, 40-49, 50-59, ≥60 years), relationship status history (single, exclusive, open, or unclear relationship at latest visit before 2022), HIV status (positive, negative/unknown), calendar month (continuous), and sexual partnership history (≤7 or >7 male sexual partners in the P6M at the latest visit before 2022). We then computed the relative change in sexual partner numbers (rate ratio, RR) during the mpox outbreak by sexual partnership history, to examine potential effect modification. Details on variable definitions and the regression model are available in the ***Supplementary Methods***.

To assess the sensitivity of our results, we repeated the analysis using alternative categorizations of sexual partnership history (≤3 or >3, and ≤5 or >5 male sexual partners in the P6M). We used a different end point of the behaviour change period (July 14th, 2022) to assess the sensitivity to an alternative exposure definition. We used a Bayesian logistic regression model to study two alternate outcomes: visit to bathhouses and/or sex clubs at least once in the P6M (binary) and attendance at group sex events at least once in the P6M (binary).

All empirical data analyses were performed with *R* (4.3.2) [37], using the *RStan* (2.32.3) [38] and *rstanarm* (2.26.1) [39] packages.

Dynamic model of mpox transmission

We developed a dynamic, deterministic compartmental model of mpox transmission and control among a closed population of GBM. Surveillance data suggest that 30-39-year-olds, high numbers of sexual partners, and living with HIV were associated with mpox diagnosis [3,40]. We stratified the model into 5 age groups (16-29, 30-39, 40-49, 50-59, ≥60 years), 10 sexual activity groups (representing 60%, 90%, 95%, 96%, 97%, 98%, 99%, 99.5%, and 99.8% percentiles in the distribution of P6M sexual partner numbers), and HIV status (positive, negative/unknown). All GBM are assumed susceptible at the start of the outbreak, and they can acquire mpox and transition into the exposed (but not yet infectious) compartment, depending on a time-varying force of infection (***Figure 1***). The latter considers the degree of assortativity in sexual mixing between GBM by age, sexual activity, and by HIV status. Based on a previous analysis [7], we allowed for underreporting and reporting delays [41,42]: 77%-86% of all infections were reported in the surveillance data.

In terms of interventions, community and public health messaging could have led to potential behaviour changes. GBM's contact rates were allowed to vary using a rate ratio that reflected potential reductions in sexual activity (as informed by a prior from the empirical analysis above). Exposed GBM can be traced and isolated by local public health authorities. Local public health authorities in Montréal suggested that on 20% of contacts of reported cases were traced [4,24]. We adjusted that 20% by the fraction of cases reported in each city and the fraction of contacts traced before being infectious. Given limited vaccine supply, first-dose vaccination coverage was maximized by delaying the administration of second doses [24]. We only modelled first-dose vaccination, as it constituted >90% of vaccines administered before mid-October 2022 in all three provinces [5,24,27]. We used the number of weekly doses administered from publicly available reports [5,24,27]. Vaccine effectiveness was modelled using a leaky-type vaccination compartment [43]. Values of model parameters are defined in ***Table S2***. Model structure is presented in ***Figure 1*** and details are in ***Supplementary Methods***.

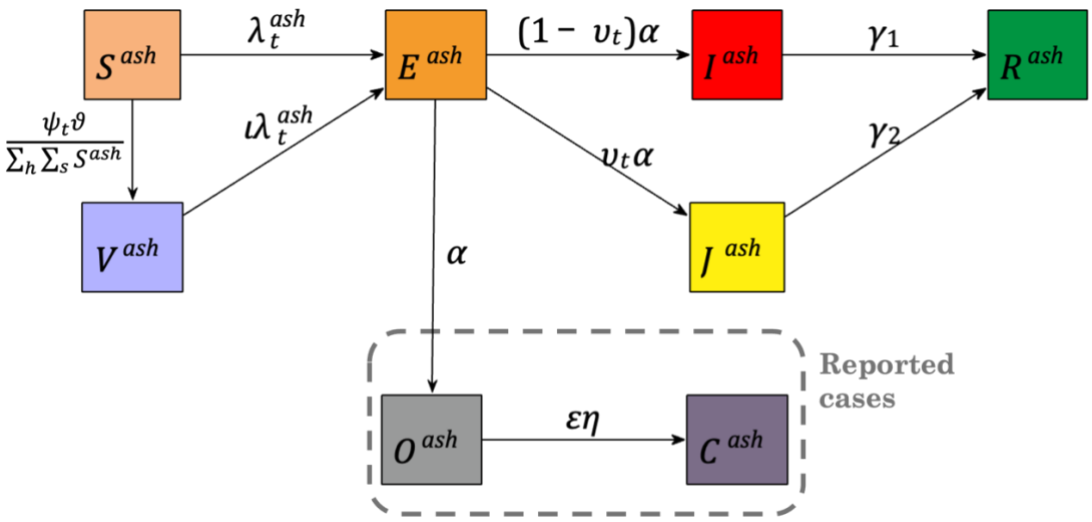

Figure 1. Diagram of the compartmental flows of the deterministic model of mpox virus transmission among gay, bisexual, and other men who have sex with men (GBM). *a*, *s*, *h*: superscripts for age groups, sexual activity groups, and HIV status, respectively. The name of the compartments refers to susceptible (S), exposed (E), infectious (I), removed (R), vaccinated (V), and isolated (J). Removed refers to the state where GBM are no longer infectious, stopped having sex, or developed natural immunity to mpox. Two other compartments are used to track symptoms onset (O) and the case confirmation process (C). The main parameters are the following: ψ_t: first-dose vaccination doses at time t; $\boldsymbol{\vartheta}$: proportion of vaccinations received by age groups; $\boldsymbol{\iota}$: 1-vaccine effectiveness (assuming leaky type); $\boldsymbol{\lambda_t^{ash}}$: force of infection specific to group *a*, *s*, *h* at time t; $\boldsymbol{\alpha}$: rate of infectivity onset among exposed ≈ (latent period)$^{-1}$; υ_t: proportion traced and isolated among exposed at time t; $\boldsymbol{\gamma_1}$: rate of removal among infectious individuals who are not traced and isolated = (effective infectious period)$^{-1}$; $\boldsymbol{\gamma_2}$: rate of removal among infectious individuals who are traced and isolated = (self-isolation period)$^{-1}$; $\boldsymbol{\varepsilon}$: the reporting fraction (proportion of cases that are reported, calibrated parameter); $\boldsymbol{\eta}$: reporting delay. Values of parameters are defined in *Table S2*.

Model calibration

We calibrated the model using mpox surveillance data, assuming all reported cases were among GBM [3–6,24,44]. The model was calibrated jointly for the 3 cities using a Bayesian sampling importance resampling and a negative binomial likelihood for daily numbers of total reported cases.

We cross-validated our results to the following outcomes (whenever available): the proportion of mpox cases who were among people living with HIV in Montréal, the age distribution of cases in Montréal and Toronto, and the age distribution of vaccines received in Montréal and Toronto.

Averted fraction of new infections (AF) from past interventions

Using the calibrated model, we evaluated the impacts of 1) changes in number of sexual partners, 2) contact tracing/isolation, 3) first-dose vaccination, 4) all three measures combined (i.e., the observed scenario), and 5) combinations of any two interventions on mpox transmission. We estimated the impact using the cumulative fraction of new infections averted (AF), calculated as the difference in the cumulative incidence between each of the interventions scenarios above divided by the counterfactual cumulative incidence corresponding to an unmitigated epidemic.

Sensitivity analysis for the fraction of averted infections

First, we assessed the model sensitivity to our prior for the changes in sexual partner numbers by fixing the RR to the point estimates found in the empirical analysis. Second, we reduced the proportion of contacts traced from 20% to 15% and 10% to reflect potential non-disclosure of sexual contacts. Third, we examined the sensitivity of our results to vaccine effectiveness by using the minimum and maximum of estimates from literature (35.8% and 86.0%, respectively) [45–51]. Finally, to directly compare the impact of vaccination in all three cities, we looked at a scenario where vaccination was started the same number of days after detection of the first local cases and reached the same daily coverage, using Vancouver as the reference since it had an earlier start of vaccination and achieved the highest vaccine coverage. For the first three analyses, we re-calibrated the model and re-calculated the averted fractions.

The model was coded in R, using a C++ back-end [52], and solved using an Euler algorithm with a 6-hour time step. Additional details on methods can be found in the ***Supplementary Methods***.

Results

Changes in numbers of sexual partners during the mpox epidemics

Out of 1,957 visits from participants that occurred during 2022, 424 visits partly overlapped with the potential behaviour change period (May 19th-August 14th, 2022). Although imprecise, the results from the regression model were indicative of a decrease in sexual partners. Specifically, we estimated a RR of 0.80 (95% Credible interval [CrI]: 0.47-1.36) and 0.67 (95%CrI: 0.31-1.43) among those with >7 (P6M) and ≤7 sexual partners at their last visit before 2022 (***Table 1***). Summary statistics of the study population from *Engage* and the effect estimates of covariates are presented in ***Table S6*** and ***Table S7***. Sensitivity analyses are shown in ***Table S8***. The results on changes in visits to sex-on-premises venues and attendance of group sex were inconclusive.

Table 1. Changes in the number of reported sexual partners in the past 6 months during the period of mpox-driven potential behaviour changes among participants in the *Engage Cohort Study,* by sexual partnership history.

Numbers of sexual partners at the latest visit before 2022	Number of visits		RR (95%CrI)
	During Mpox outbreak	*Rest of 2022*	
≤7 sexual partners	324	1211	0.80 (0.47, 1.36)
>7 sexual partners	100	322	0.67 (0.31, 1.43)

There were 424 visits for which the past 6 months recall period overlapped with the mpox epidemic. Among those, an average of 19% of the recall period was within the epidemic period. Models adjusted for months since January 1st, 2022 (1, 2, …, 12; continuous), age (16-29, 30-39, 40-49, 50-59, ≥60 years), relationship status history (single, exclusive relationship, open relationship, unclear), and HIV status (binary). *CrI* = credible interval; *RR* = rate ratio.

Model calibration

The city-specific models replicated the daily number of reported cases (***Figure 2***), with a slight overestimation of cases in Toronto during the Fall of 2022. Furthermore, the model-predicted age distribution and HIV status of cases generally matched well with the one reported

from local surveillance data (***Figure S2***). The model slightly overestimated cases in the 16-29 age groups and underestimated those in the 30-39 groups in Montréal and Toronto. The posterior parameter distributions for calibrated parameters are in ***Table S9***.

Fraction of cases averted by interventions

In the three cities, we found that the outbreaks would have reached a downturn without any interventions, but with nearly 50% more infections (***Figure 3***). Combined, we estimated that the three interventions averted 48% (35%-66%), 46% (34%-67%), and 58% (52%-69%) infections in Montréal, Toronto, and Vancouver, respectively. The calibrated RR for changes in number of sexual partners was 0.94 (95%CrI: 0.80-0.99) across sexual partnership history level defined by >7 partners and 0.94 (0.70-0.99) among those defined by ≤7 partners. The changes in number of sexual partners moderately decreased transmission: the estimated AF was 15% (3%-34%) in Montréal, 11% (2%-27%) in Toronto, and 10% (2%-22%) in Vancouver. Contact tracing averted 14% (12%-21%), 14% (12%-22%), and 14% (12%-16%) of infections in Montréal, Toronto, and Vancouver, respectively. We estimated that first-dose vaccine coverage among GBM reached 44% (Montréal), 45% (Toronto), and 58% (Vancouver) by mid-October 2022 (***Figure S3***). The impact of vaccination varied according to vaccine coverage and the timing of vaccine campaign initiation relative to the beginning of the outbreak. Vaccination averted 21% (16%-33%), 22% (16%-41%), and 39% (35%-48%) of infections in Montréal, Toronto, and Vancouver, respectively. The added effects of any combinations of two interventions were roughly equal to the sum of their individual effects (***Table S10)***.

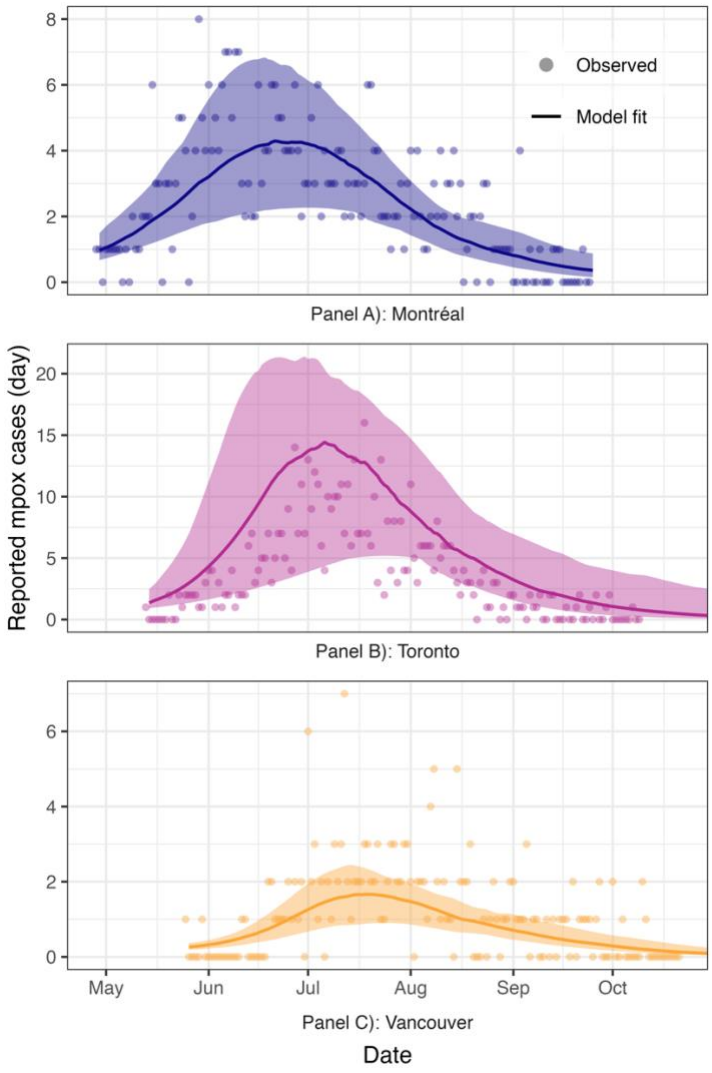

Figure 2. Model-calibrated epidemic curves and observed mpox case data in Montréal (A), Toronto (B), and Vancouver (C) during 2022. The case data (points) and model fits (curves) are presented up to 150 days after the first reported mpox cases in each city. The solid line is the median of the modelled cases, and the shaded area shows the 95% credible interval for the mean number of daily cases.

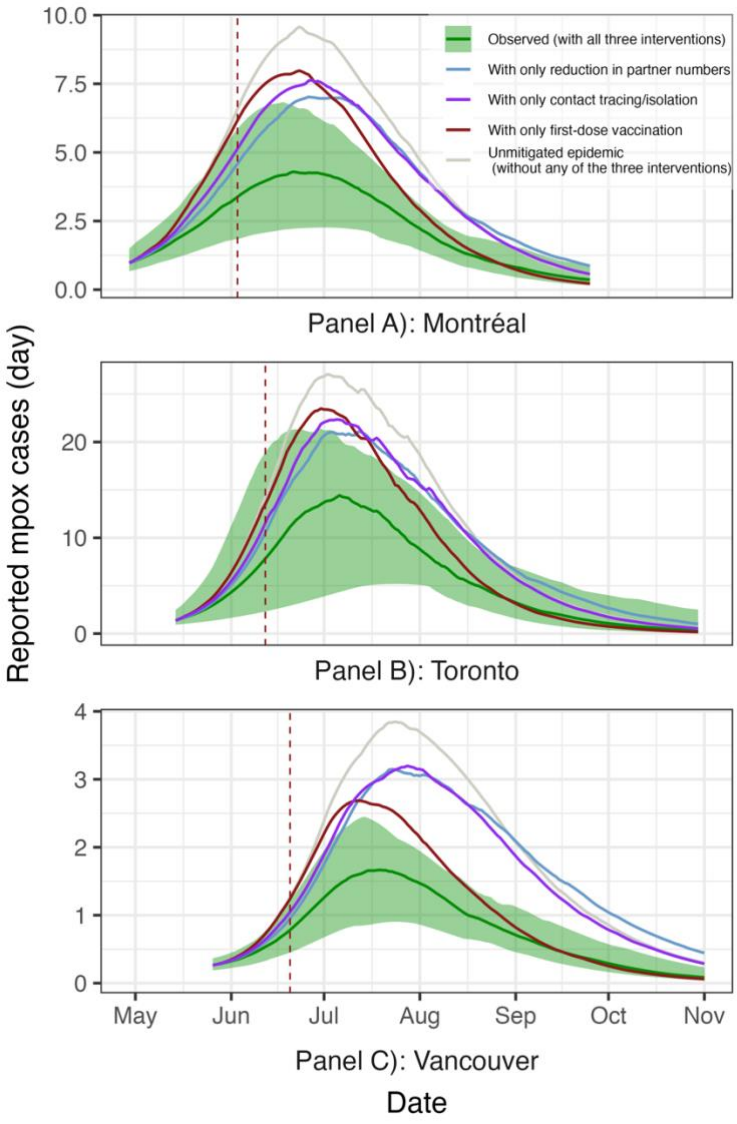

Figure 3. Model-predicted daily reported mpox cases in 2022 in Montréal, Toronto, and Vancouver under observed interventions levels and scenarios with selected interventions. The lines represent the median. The green lines and shaded area (95% credible intervals) correspond to the observed epidemic curves in the three cities. The grey lines are the modelled unmitigated epidemic. The blue lines are the epidemic curves with reduction in sexual partner numbers alone, the purple lines are with contact tracing/isolation alone, and the maroon lines are with first dose vaccination alone. Vertical dashed lines show the start of one-dose vaccination in each city: June 3rd, June 12th, and June 20th, 2022, in Montréal, Toronto, and Vancouver, respectively. The estimates for intervention scenarios were shown in ***Table S10***.

Sensitivity analyses for the fraction of cases averted by interventions

Fixing the values of the RR for the reduction in numbers of sexual partners to the point estimates from the empirical behaviour change analysis did not replicate the epidemic well. This suggests that such parameters are not compatible with the observed outbreak trajectories. The fraction of cases averted by contact tracing was reduced to 10%-11% and 7% when using a proportion of 15% and 10% of cases traced, respectively (***Table S10***). First-dose vaccination prevented 14%-29% of cases when using 35.8% vaccine effectiveness (1-dose). Conversely, assuming 86.0% vaccine effectiveness, the number of cases prevented increased to 38%-59%. Finally, standardizing the start of vaccination and vaccine coverage to Vancouver resulted in a similar fraction of cases averted by vaccination in the three cities (38%-41%).

Discussion

The 2022-2023 mpox outbreak was met with swift community and public health responses in Canada, inspired by GBM communities' decades-long fight against HIV. Using cohort data from a representative sample of urban GBM in Canada and a calibrated risk-stratified dynamic model of mpox transmission, we estimated that, altogether, behaviour changes, contact tracing/isolation, and vaccination averted 46%-58% of cases among GBM in Canada's three largest cities. Among these, vaccination had the largest impact on averted cases despite moderate coverage of first doses (44%-58%) among GBM. Vaccines alone averted an estimated 21%-39% of new infections, depending on the city. Our findings support implementing vaccination quickly and at-scale if localized epidemics resurge and continuing immunization among GBM with multiple sexual partners. This measure is relevant given current low coverage of the second doses, higher vaccine effectiveness conferred by two-doses [46], current absence of vaccination clinics in the cities, and localized epidemic resurgence in Toronto in early 2024 [44].

Our analysis, based on a large, population-based cohort, suggests that GBM may have changed sexual behaviours to have fewer sexual partners during the mpox outbreak. However, the estimate was highly uncertain, particularly given the drop in sexual partner numbers that had already occurred due to previous COVID-19 lockdowns [36], precluding a definite conclusion from the empirical analysis. Nevertheless, our calibrated dynamic models suggest that small declines in partner numbers are compatible with the observed epidemics. These averted 10%-15% of cases across the three cities.

Assuming that 20% of contacts were traced (as reported from Montréal), contact tracing and isolation of exposed cases averted 14% of infections in the three cities. This impact was sensitive to the proportion of traced sexual contacts. Lack of contact information reported by cases, largely due to anonymous partnering, limited the proportion of contacts traced and isolated.

As of mid-October 2022, we estimated that the large-scale vaccination of first-dose of MVA-BN vaccine attained coverage of 44%, 45%, and 58% among GBM in Montréal, Toronto, and Vancouver, respectively [5,24,27]. Assuming 51.5% vaccine effectiveness, first-dose vaccination averted 39% of infection in Vancouver (95%CrI: 35%-48%), 22% in Toronto (95%CrI: 16%-41%) and 21% in Montréal (95%CrI: 16%-33%). High vaccine coverage in Vancouver may explain the higher impact in that city (***Table S10***).

Despite these notable impacts, the mpox outbreaks could have waned without any of the three interventions. This is consistent with the saturation of "core groups", resulting in the accumulation of infection-derived immunity against mpox and, ultimately, the epidemic downturn. However, it is likely that, the community and public health responses greatly accelerated the decline in incidence, as has been found in other settings [10,12].

Our results should be interpreted considering several limitations. First, we had limited information on contact tracing/isolation and it is difficult to effectively model this intervention using compartmental models. We used an approximation to estimate the proportion of publicly traced cases that would be isolated before onset of infectiousness. However, case self-notification of partners was not captured by public health contact tracing data, which means we could have underestimated the impact of contact tracing/isolation. Second, we assumed that, at the beginning of the outbreak, all GBM had no immunity against mpox. However, some GBM born before smallpox vaccination stopped in Canada in 1972 and those that immigrated from certain countries could have previously received smallpox vaccines [53,54]. This should not change our results much because people aged >50 years old represented only <14% all cases in Canada [3]. Finally, we allocated vaccinations proportionally within each age group, whereas individuals at perceived higher-risk of mpox acquisition could have preferentially sought vaccines.

The strengths of this study include the use of data from a large population-based cohort to inform model parameterization and statistical analyses. This approach allowed us to empirically explore the impact of behaviour changes. Second, we accounted for balanced mixing by age groups, sexual activity groups, and HIV status in the mpox transmission model, all strongly associated

with mpox diagnoses in surveillance data [3,55]. Finally, we calibrated the model in a Bayesian framework, ensuring that parameter uncertainty is reflected in our model estimates, and cross-validated our model predictions.

Conclusion

GBM in Montréal, Toronto, and Vancouver may have decreased sexual partnering during the transmission period of the 2022 mpox outbreak, which alongside contact tracing/isolation, contributed to averting mpox infections. Early vaccination was key to reducing the number of mpox infections. While mpox outbreaks in Canada could have eventually subsided without intervention, 50% more cases could have been infected, leading to unnecessary harms and potentially serious health consequences.

Declarations

Ethics

The Research Institute of the McGill University Health Centre and the Research Ethics Office of the Faculty of Medicine and Health Sciences, McGill University (A06-M32-23B), Toronto Metropolitan University (REB #2016-113), the University of Toronto (protocol #00033527), St. Michael's Hospital (REB #17-043), the University of Windsor (REB #33443), the University of British Columbia (H16-01226), Providence Health Care (H16-01226), the University of Victoria (H16-01226), and Simon Fraser University (H16-01226) provided ethics approvals for the *Engage Cohort Study*. The Research Ethics Office of the Faculty of Medicine and Health Sciences at McGill University approved the secondary analyses of the data in this study.

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Author contribution

FX, CD, SM, MI, and MM-G contributed to the conception and design. JC, DG, TAH, MD, NJL, SSS, and SM were involved in the design, data collection, and data management of the *Engage Cohort Study*. Analyses were performed by FX, with support from CD, JLFA, and MM-G. LW, JK, MI, and SM provided input on preliminary methods discussions. JK and LW developed and coded the preferential mixing matrices. The manuscript was drafted by FX. All authors reviewed the manuscript for important intellectual content. Overall supervision for this project was provided by MM-G. All authors approved the final manuscript.

Conflict of interest

JC reports research grants from Gilead Sciences Canada and ViiV Healthcare, all outside of the submitted work. MM-G reports contractual arrangements from the World Health Organization, the Joint United Nations Programme on HIV/AIDS (UNAIDS), and the Public Health Agency of Canada, all outside of the submitted work. TAH reports educational grants from being an Advisory Committee member for the Canadian Institutes of Health Research (CIHR)'s Institute of Infection and Immunity and funds for community engagement events from ViiV Healthcare and Gilead Sciences Canada, all outside of the submitted work. DHST's institution has received investigator-initiated grants from Abbvie and Gilead, and support for participation in clinical trials sponsored by Glaxo Smith Kline. All other authors report no conflict of interest.

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Software and source code

The model package and codes for analyses are available on a GitHub repository (https://github.com/pop-health-mod/mpox-intervention).

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Supplementary Methods

Changes in numbers of sexual partners during the mpox epidemics

We fitted a Bayesian negative binomial regression model (with a random intercept for each participant estimated using partial pooling) to estimate the relative change (rate ratio, RR) in sexual partner numbers in the past 6 months (P6M) during the period of mpox-driven behaviour changes (May 19th, 2022-August 14th, 2022; 87 days). We chose a negative binomial likelihood since it best described GBM's distribution of numbers of sexual partners in previous work [1]. Given the 6-month recall period for our outcome, we expect that the change in the log-number of sexual partners will be proportional to how much of the recall period overlaps with the mpox outbreak. To adjust for that effect attenuation, we defined the exposure variable as the fraction of the recall period that covers the period of mpox-driven behaviour changes, as follows:

$$\boldsymbol{x}(t) = \begin{cases} 0 \; if \; t < t_{mpox_{start}} \; or \; t > t_{mpox_{end}} \\ \dfrac{(t - t_{mpox_{start}}) + 1}{6 \; months} \;\; if \; t_{mpox_{start}} \leq t < t_{mpox_{end}} \end{cases}$$

where t is the visit date, $t_{mpox_{start}}$ is May 19th, 2022, and $t_{mpox_{end}}$ is August 14th, 2022.

Given the short window of the defined period, we conducted a pooled analysis across the three cities to improve precision. Additionally, each participant i has a unique random intercept to account for correlation between their multiple visits. Informed by the peer-reviewed literature [1–5], we included the following variables as covariates in the model: age group (16-29, 30-39, 40-49, 50-59, ≥60 years), relationship status history (single, exclusive relationship, open relationship, unclear), and sexual partnership history (≤7 or >7 sexual partners in the P6M at the latest visit before 2022), HIV status (binary), and calendar month since January 1st, 2022 (continuous) (***Table S1***). We included the last variable to account for potential secular trends in sexual activity among GBM in the aftermath of the COVID-19 pandemic [1]. A product term between the exposure and sexual partnership history (i.e., ≤7 or >7 male sexual partners in the P6M at the latest visit before 2022) was included to reflect potential heterogeneity in the effect of the mpox outbreak by sexual activity levels on the number of sexual partners.

The regression model was fitted using Hamiltonian Monte Carlo in *rstanarm*, with 4,000 iterations (2 chains, 2,000 burn-in iterations, no thinning, ensuring that the effective sample size for each parameter was ≥1,000 or larger). We used weakly informative priors and assessed

convergence via traceplots and the potential scale reduction factor ($\hat{R}$). The regression models, with negative binomial likelihood (NB), can be written as

$$y_{it} \sim NB(\lambda_{it}, \phi)$$
$$\log(\lambda_{it}) = \alpha_0 + \mu_i + \beta X_{it}$$

where

i: index for participants, $i \in \{1,2,\dots,1445\}$;

y_{it}: observed number of all-type sexual partners in the P6M for participant i at time t;

λ_{it}: mean model-predicted number of partners for participant i at time t;

ϕ: overdispersion parameter;

α_0 : fixed intercept;

μ_i : random intercept for participant i;

X_{it} : a vector containing the values of predictors for participant i at time t, i.e., *exposure variable, age, relationship status, HIV status, calendar month, sexual partnership history level, exposure × sexual partnership history level.*

β: vector of regression coefficients corresponding to the matrix of covariates X;

We used the following prior distributions for the regression parameters. Note the second argument refers to the standard deviation.

$$\alpha_0 \sim Normal(0, 10)$$
$$\beta_k \sim Normal(0, 10)$$

$\forall k \in$ {*exposure variable, age, relationship status, HIV status, calendar month, sexual partnership history level, exposure × sexual partnership history level*}

$$\phi \sim halfCauchy(0, 5)$$

The covariance matrix of the random intercepts can be decomposed into the correlation matrix and variances:

$$\begin{bmatrix} \sigma_{\mu_1}^2 & \cdots & \rho_{\mu_1,\mu_{1445}}\sigma_{\mu_1}\sigma_{\mu_{1445}} \\ \vdots & \ddots & \vdots \\ \rho_{\mu_1,\mu_{1445}}\sigma_{\mu_1}\sigma_{\mu_{1445}} & \cdots & \sigma_{\mu_{1445}}^2 \end{bmatrix}$$
$$= \begin{bmatrix} \sigma_{\mu_1} & \cdots & 0 \\ \vdots & \ddots & \vdots \\ 0 & \cdots & \sigma_{\mu_{1445}} \end{bmatrix} \begin{bmatrix} 1 & \cdots & \rho_{\mu_1,\mu_{1445}} \\ \vdots & \ddots & \vdots \\ \rho_{\mu_1,\mu_{1445}} & \cdots & 1 \end{bmatrix} \begin{bmatrix} \sigma_{\mu_1} & \cdots & 0 \\ \vdots & \ddots & \vdots \\ 0 & \cdots & \sigma_{\mu_{1445}} \end{bmatrix}$$

The priors for the correlation matrix and variances are:

$$\begin{bmatrix} 1 & \cdots & \rho_{\mu_1,\mu_{1445}} \\ \vdots & \ddots & \vdots \\ \rho_{\mu_1,\mu_{1445}} & \cdots & 1 \end{bmatrix} \sim LKJcorr(1)$$

$$\sigma_{\mu_i} \sim exponential(1)\ \forall i \in \{1,2,\ldots,1445\}$$

The $LKJcorr(1)$ is the Lewandowski-Kurowicka-Joe distribution with shape parameter equals to 1.

Structure for the dynamics model of mpox transmission and control

We modelled transmission in Montréal, Toronto, and Vancouver, using separate but jointly calibrated compartmental models, for 150 days after first confirmed cases in each respective city [6,7]. The modelled period covered the majority of cases in the outbreaks, after which only sporadic cases were observed in the three cities [8–10]. The model considers the degree of assortativity in sexual mixing between GBM by age, sexual activity, and by HIV status. Given the short timeframe of the mpox outbreaks, we did not model HIV dynamically and assumed a closed population (that is, individuals did not enter or exit the modelled population during the outbreak period). The model considers that all GBM were equally susceptible to mpox at the beginning of the outbreak. Given reports of asymptomatic cases and case underreporting [11], we assumed that only a 77%-86% of all infections was reported in the surveillance data based a previous modeling study [1]. Finally, we accounted for an average 2-day delay between symptom onset and case confirmation reported in the surveillance data [12].

Susceptible GBM can acquire mpox and transition into the exposed (but not yet infectious) compartment, depending on a time-varying force of infection (***Figure 1***). After an average of 5.1 days [13–17] (***Table S2***), exposed GBM become infectious but a time-varying proportion can isolate if traced by local public health authorities (due to limited data, we assumed isolation only came from case contacts traced by public health agencies). In the infectious stage, people will remain infectious until they recover (no longer infectious) or stop sexual activity due to mpox symptoms (i.e., the effective infectious period, to be calibrated).

Equations for the dynamics model of mpox transmission and control

The system of ordinary differential equations describing mpox's transmission dynamics is presented below. GBM in each city are partitioned into age groups *a*, sexual activity level *s*, and HIV status *h*. The natural history parameters are presented in ***Table S2***.

$$\frac{dS^{ash}(t)}{dt} = -\lambda_t^{ash} S^{ash}(t) - \psi_t \vartheta^a \frac{S^{ash}(t)}{\sum_h \sum_s S^{ash}(t)}$$

$$\frac{dV^{ash}(t)}{dt} = \psi_t \vartheta^a \frac{S^{ash}(t)}{\sum_h \sum_s S^{ash}(t)} - \iota \lambda_t^{ash} V^{ash}(t)$$

$$\frac{dE^{ash}(t)}{dt} = \lambda_t^{ash} S^{ash}(t) + \iota \lambda_t^{ash} V^{ash}(t) - \alpha E^{ash}(t)$$

$$\frac{dI^{ash}(t)}{dt} = (1 - \upsilon_t)\alpha E^{ash}(t) - \gamma_1 I^{ash}(t)$$

$$\frac{dJ^{ash}(t)}{dt} = \upsilon_t \alpha E^{ash}(t) - \gamma_2 J^{ash}(t)$$

$$\frac{dR^{ash}(t)}{dt} = \gamma_1 I^{ash}(t) + \gamma_2 J^{ash}(t)$$

where λ_t^{ash}: is the time-varying force of infection for individuals in group *a*, *s*, *h* at time *t*; ψ_t: first-dose vaccination doses at time t; ϑ^a: cumulative proportions of vaccines by age groups *a*; ι: 1-vaccine effectiveness (assuming leaky type); α: rate at which individuals who acquired the infection become infectious (latent period)$^{-1}$; υ_t: proportion traced and isolated among exposed at time *t*; γ_1: effective rate of recovery among infectious individuals who are not traced and isolated = (effective infectious period)$^{-1}$; γ_2: rate of recovery among infectious individuals who are traced and isolated = (self-isolation period)$^{-1}$.

Additionally, we track the number of people with onset of symptoms (O^{ash}) and the cumulative number of people with symptoms that will be confirmed as mpox cases (C^{ash}), accounting for asymptomatic infections and underreporting (ε) and confirmation delays (η).

$$\frac{dO^{ash}(t)}{dt} = \alpha E^{ash}(t) - \eta O^{ash}(t)$$

$$\frac{dC^{ash}(t)}{dt} = \varepsilon \eta O^{ash}(t)$$

Force of infection and mixing patterns

The force of infection (λ_t^{ash}) was defined as the time-varying (t) age (a), sexual activity (s), and HIV status-specific (h) per capita rate of mpox acquisition. It is a function of the time-varying sexual mixing matrix ($C_{ash,a's'h'}(t)$, reflecting an average number of sexual partnerships per-person per-day among group ash with group $a's'h'$), transmission probability per effective contact (defined as a sexual partnership, β), and prevalence of people infectious with mpox among

GBM available for sexual activities at time t (i.e., not isolating). The force of infection is the following, where N^{ash} is the size of the group ash.

$$\lambda_t^{ash} = \beta \sum_{a's'h'} C_{ash,a's'h'}(t) \frac{I^{a's'h'}(t)}{N^{a's'h'} - J^{a's'h'}(t)}$$

The time-varying mixing matrix $C_{ash,a's'h'}(t)$ was defined to reflect 5 factors: 1) changing numbers of non-isolating GBM and 2) changing contact rates during the mpox outbreak; and preferential mixing by 3) 5 age groups, 4) HIV status, and 5) 10 sexual activity groups.

Mixing: group sizes and contact rates

Numbers of non-isolating GBM in group ash at time t were defined as $K^{ash}(t) = N^{ash} - J^{ash}(t)$.

Contact rates were defined as the number of sexual partners per-person per-day, including the rate ratio of the change in sexual partner numbers during the mpox outbreak (before first-dose vaccines were massively available on June 14th, 2022):

$$c^{ash}(t) = \begin{cases} c^{ash}, & \text{if } t < t_{\text{mpox}_{\text{start}}} \text{ or } t \geq t_{\text{mpox}_{\text{end}}} \\ c^{ash} \cdot RR, & \text{if } t_{\text{mpox}_{\text{start}}} \leq t < t_{\text{mpox}_{\text{end}}} \end{cases}$$

Mixing: age and HIV status

Mixing preferences by age and HIV status were informed by previous modeling of GBM in Montréal [18] (**Tables S3** and **S4**), while mixing preferences by sexual activity were specified parametrically with a single calibrated parameter ω. All preferences were specified via odds ratios per [19], with iterative proportional fitting to maintain specified contact rates [20,21]. We defined a set of 15 (age) + 1 (HIV) odds ratios ψ, which were mapped to two symmetric matrices as follows:

$$\Psi_{aa'} = \begin{bmatrix} \psi_1 & \psi_2 & \psi_4 & \psi_7 & \psi_{11} \\ \psi_2 & \psi_3 & \psi_5 & \psi_8 & \psi_{12} \\ \psi_4 & \psi_5 & \psi_6 & \psi_9 & \psi_{13} \\ \psi_7 & \psi_8 & \psi_9 & \psi_{10} & \psi_{14} \\ \psi_{11} & \psi_{12} & \psi_{13} & \psi_{14} & \psi_{15} \end{bmatrix}, \qquad \Psi_{hh'} = \begin{bmatrix} \psi_0 & \cdot \\ \cdot & \psi_0 \end{bmatrix}$$

These matrices can be used to specify mixing by age and HIV status at the population-level (total number of contacts) via:

$$X_{ah} = \sum_s c^{ash} K^{ash}$$

$$X^R_{ah,a'h'} = \frac{X_{ah}X_{a'h'}}{\sum_{ah} X_{ah}}$$

$$X^{[0]}{}_{ah,a'h'} = X^R_{ah,a'h'} \exp(\Psi_{aa'} + \Psi_{hh'})$$

where X_{ah} reflects the total numbers of contacts "offered" by group ah (after summing over activity groups s), and $X^R_{ah,a'h'}$ reflects random (or "proportional") mixing. The above definition of $X^{[0]}{}_{ah,a'h'}$ changes the total numbers of contacts modelled for each group due to nonlinear effects of multiplication, but the original contact numbers can be recovered using iterative proportional fitting (denoted IPF(X)) [20,21]:

$$X^{[n+1]}_{ah,a'h'} = X^{[n]}_{ah,a'h'} \frac{X^R_k}{X^{[n]}_k}, \qquad k = \begin{cases} ah, & \text{if } n \text{ is even} \\ a'h', & \text{if } n \text{ is odd} \end{cases}$$

which typically converges to machine precision (10^{-12}) within 5-50 iterations.

From the resulting population-level mixing matrix $X_{ah,a'h'} = X^{[n\to\infty]}_{ah,a'h'}$, we can obtain probability-scale mixing matrices for age and HIV via:

$$p_{ah,a'h'} = \frac{X_{ah,a'h'}}{X_{ah}}, \qquad p_{aa'} = \frac{\sum_{hh'} X_{ah,a'h'}}{\sum_h X_{ah}}, \qquad p_{hh'} = \frac{\sum_{aa'} X_{ah,a'h'}}{\sum_a X_{ah}}$$

The matrices $p_{aa'}$ and $p_{hh'}$ should then match the data in **Tables S3** and **S4**, when using pre-mpox group sizes N^{ash} and contact rates c^{ash} to compute X. Thus, we estimated ψ by minimizing the mean absolute differences between $p_{aa'}$ and $p_{hh'}$ from the data (**Tables S3** and **S4**) and from the parametric model for mixing described above. The advantage of this odds-based approach is that mixing matrices can remain both "balanced" and reflective of empiric mixing preferences despite changes to effective group sizes $K^{ash}(t)$ and contact rates $c^{ash}(t)$ during the simulated epidemic.

Mixing: sexual activity

We used a similar approach as above to define the time-varying mixing matrix further stratified by sexual activity: $X_{ash,a's'h'}(t)$. First, we defined the total numbers of contacts "offered" by group ash to group $a'h'$ as:

$$X_{ash[a'h']}(t) = K^{ash}(t)\, c^{ash}(t)\, p_{ah,a'h'}(t)$$

which incorporates mixing preference by age and HIV status. Then we specify increased odds of mixing by sexual activity group (conditional on age and HIV status) via a matrix $\Psi_{ss'}$ applied to the random mixing matrix, and adjusted with IPF:

$$X^{R}_{ash,a's'h'}(t) = \frac{X_{ash[a'h']} X_{a's'h'[ah]}}{\sum_{ash} X_{ash[a'h']}}$$

$$X_{ash,a's'h'}(t) = \text{IPF}\left(X^{R}_{ash,a's'h'} \exp \Psi_{ss'}\right)$$

In this case, we had no data to inform the odds matrix $\Psi_{ss'}$. So, we assumed a gaussian "fuzzy diagonal" with fixed mean $\mu = 0$ and standard deviation $\sigma = 2$ (95% probability mass within ±5 activity groups), whose overall magnitude was scaled by the calibrated degree of assortativity parameter, $\omega \in (0, 100)$:

$$\Psi_{ss'} = \omega \cdot \text{norm}(|s - s'|, \mu, \sigma) \cdot \sigma$$

Finally, we converted the resulting population-level mixing matrix X to the per-person scale C for use in the force of infection equation via:

$$C_{ash,a's'h'}(t) = \frac{X_{ash,a's'h'}}{K^{ash}}$$

Model parameterization

Population sizes

Using previous estimates of the GBM population size in each city [1,22,23], we modeled 54,000, 78,000, and 26,100 sexually active GBM in Montréal, Toronto, and Vancouver, respectively. The prevalence of HIV among GBM was estimated from the *Engage* baseline visit, accounting for the RDS survey design by incorporating the RDS-II weights [24]. The age distribution was informed by the *Canadian 2021 Census of Population* [23]. To model only sexual active GBM, we adjusted the size of the population aged ≥60 years old in our model, as sexual activity tends to decline at older ages [25]. The *Institut de la statistique du Québec* estimated 35.6% of men ≥65 years old were sexually active in 2020-2021 [25], which is similar to estimates from a 2022 UK study of GBM [4]. We assumed this proportion applied to GBM and was similar across Montréal, Toronto, and Vancouver.

Sexual activity groups

To describe the contact rates among GBM, we obtained the distribution of sexual partner numbers during 2022 prior to the first reported mpox case in Canada (May 19th, 2022). Specifically, we leveraged our previous results from a Bayesian negative binomial regression model where we described the distributions of sexual partner numbers for participants in each combination of age group and HIV status [1]. We chose to use the fitted, as opposed to the empirical distribution, to account for *Engage*'s RDS study design and loss to follow-up. This was achieved by incorporating

RDS-II and inverse probability of censoring weights via post-stratification. Then, we partitioned each age-HIV status combination into 10 sexual activity groups based on 60%, 90%, 95%, 96%, 97%, 98%, 99%, 99.5%, and 99.8% percentiles, which effectively described the heterogeneity in GBM partner numbers and captured well the heavy-tailed distributions [26]. We converted the P6M contact rates to daily rates. This procedure was repeated for each of the three cities independently to obtain city-specific contact rates for each combination of age group, sexual activity group, and HIV status.

Modeled change in sexual partner numbers

We used the rate ratio from the analysis of sexual partner numbers to inform the prior for the RR parameter in the model. The RR parameter is calibrated to account for a potential reduction in the contact rate during the period of mpox-driven behaviour changes (May 19th-August 14th, 2022) and capped it at 1, as increases in sexual activity during mpox are qualitatively unlikely. Furthermore, we allowed the RR to vary based on whether the sexual activity group's contact rate was defined by ≤7 or >7 partners, as informed by the empirical analyses.

Contact tracing/isolation

We assumed that since the first reported case in each city, 20% of contacts were identified through contact tracing and were advised to self-isolated, based on data from *Direction régionale de santé publique de Montréal* [27]. We assumed that a similar proportion of cases would be traced in the two other cities [8,27]. Although some individuals exposed to mpox might self-isolate after being informed by their partners, and could therefore not be captured through contact tracing, it is unlikely given that most sexual contacts reported were casual and often anonymous. As such, we only conceptualized the tracing/isolation of cases when originated by public health authorities.

Compartmental models, such as ours, cannot accurately represent contact tracing/isolation activities. Hence, we adjusted the 20% of contact traced for several factors. First, we posited that traced and untraced contacts have the same probability of having acquired mpox. Second, we assumed that only contacts of reported cases can be traced. The city-specific reporting fractions were informed by the estimates from our previous study: 82% for Montréal, 86% for Toronto, and 77% for Vancouver [1]. Third, we conservatively assumed that sexual contacts were exposed 4 days before a contact was traced: 2 days to confirm a reported cases and 2 days to perform the contact tracing. Fourth, we accounted for the fraction of contacts that would still be in the latent

period 4 days after being infected. Based on previous studies [13–17], GBM stay on average 5.1 days in the exposed state and the underlying assumption of compartmental models is that the time spent in a compartment is exponentially distributed. The fraction of contacts traced before being infectious is therefore estimated as the cumulative proportion in the exposed compartment after 4 days (2 days for contact tracing and 2 days for reporting delay), as following:

$$Fraction\ of\ contacts\ traced\ before\ infectiousness = P\left(T_{exposed} \geq 4\right) = 46\%$$

where $T_{exposed} \sim Exp(\frac{1}{5.1})$.

Hence, the fraction of exposed cases that are traced and isolated is 7.5% in Montréal (20%×82%×46%), 7.9% in Toronto (20%×86%×46%), and 7.0% in Vancouver (20%×77%×46%).

Vaccinations

The *Direction régionale de santé publique de Montréal, Public Health Ontario*, and the *British Columbia Centre for Disease Control* published data on weekly numbers of first-dose vaccination administered [9,27,28]. We did not model second-dose vaccinations as the great majority of second-doses were administered during Fall 2022, at a time where the outbreaks had been controlled [9,27,28]. All first-dose vaccines were assumed to have been offered as pre-exposure prophylaxis in the model (i.e., prior to a potential exposure). This is a reasonable assumption given only a small proportion of all doses administered were PEP (<3% in Ontario) [28], and those offered PEP were also likely to be notified through contact tracing and isolated, which was accounted for by the isolated compartment. We utilized city-level vaccination doses for Montréal and Vancouver, and provincial administered doses for Toronto (assumed all allocated to the city). We assumed that all vaccines were administered to local GBM, as only sexually active GBM, sex workers, and workers on sex-on-premises venues were eligible for the PrEP vaccination in Canada [29]. Vaccination was attributed to each age group according to the proportion of vaccines received by each age group from immunization reports (***Table S5***) [8,28]. In Vancouver, the information was unavailable, and we therefore estimated this distribution by averaging the vaccine's age distribution from the other two cities. Among each age group, vaccines were allocated proportionally to combinations of sexual-activity-HIV status groups according to their respective size. Vaccine effectiveness of single-dose mpox vaccines were informed by our meta-analysis of 7 recent studies (***Figure S1***) [3,30–35].

Seeding of the epidemics

We seeded the mpox epidemics according to the predominant characteristics of people with confirmed mpox from early case investigations [36]. Specifically, we imported cases among the 5% highest activity groups and among the 16-29, 30-39, and 40-49 age groups. Cases were allocated proportionally to the relative size of the groups and distributed equally to the exposed and infectious compartments. The number of imported cases were calibrated to reflect the uncertainty in the parameter.

As the outbreak first took place in Montréal, followed shortly by Toronto, and last occurred in Vancouver [9,10,27], we assumed a duration of 21 days from case importation to first reported cases in Montréal and Toronto, and 10 days for Vancouver.

Model calibration

Confirmed mpox cases

I utilized data on mpox reported to public health agencies (i.e., "reported cases"), including daily confirmed and probable mpox cases. A confirmed mpox case is an individual with symptoms compatible with mpox and a positive nuclear acid amplification test (NAAT) for mpox virus DNA from an appropriately-procured specimen. A suspect case is a person with at least one systemic symptom of mpox (not caused by another disease) or cutaneous lesions. A probable case is a person with a positive NAAT for the genus *Orthopoxvirus*, a suspect case with significant exposure to a confirmed case, or a suspect case who was male and had sex with another man in the 21 days before symptom onset [27].

First, provincial daily cases for Québec, Ontario, and British Columbia were publicly available from the website of the *Public Health Agency of Canada* [36]. Only the total (confirmed and probable) cases counts were available for Québec.

I then used weekly-varying city fractions of provincial cases to estimate the confirmed cases in each city. For Montréal, the *Direction régionale de santé publique de Montréal* published the weekly-varying fractions of total provincial cases that were from the city [27]. For Toronto, the weekly-varying number of total city cases was available from a publication by the *Public Health Ontario* [37]. Using this data, we were able to estimate weekly-varying total city cases over confirmed provincial cases. Finally, the weekly fractions of confirmed provincial cases that were

from the city was available from a surveillance report by the *British Columbia Centre for Disease Control* [9].

To estimate the daily confirmed cases in Montréal, I leveraged the weekly fractions of total reported cases that were confirmed in the city [8] and multiplied this quantity with the daily provincial total cases and the weekly-varying fractions of total provincial cases that were from the city. For Toronto, the fraction of probable cases in Ontario that were confirmed was 98% as of June 2023 [37], and we estimated the confirmed city cases in a similar fashion as in Montréal. Finally, the daily confirmed cases in Vancouver were estimated using the product of the daily provincial cases and fractions of confirmed provincial cases that were confirmed in the city.

Calibration algorithm

We used a Bayesian framework to obtain posterior distributions of parameters and outcomes [49]. First, the model parameters were calibrated to daily (*d*) incidence of observed mpox cases ($C_d^{observed}$) in the cities using a negative binomial likelihood with mean equal to the daily incidence of modeled mpox cases ($C_d^{modeled}$) and overdispersion parameter equal to 0.1.

$$C_d^{observed} \sim NB\left(C_d^{modeled}, 0.1\right)$$

$$C_d^{modeled} = \sum_{s=1}^{20} \frac{dC^s(t)}{dt}\Big|_{t=d}$$

We then performed optimization, using the *Broyden-Fletcher-Goldfarb-Shanno* algorithm, to obtain the posterior modes (maximum a posteriori estimates) of the parameters. We utilized a sampling importance resampling (SIR) algorithm with 5,000 parameter sets from the proposal distribution estimated from the optimization routine (multivariate *t* distribution with 2 degrees of freedom).

The three city were calibrated together and five parameters were estimated: 1) the number of imported cases (τ), 2) transmission probability per effective contact (defined as a sexual partnership, β), 3) duration of the effective infectious period (defined as time from infectivity onset to sexual abstinence or recovery, ${\gamma_1}^{-1}$), 4) the degree of assortativity by risk groups (i.e., mixing parameter, ω), and 5) the RR of contact rate during periods of mpox-driven behaviour changes (*RR*). All parameters, except the number of imported cases and the degree of assortativity, were assumed constant across the cities.

The prior distributions for the duration of infectiousness and transmission probability per effective contact were derived from a previous modeling study [1]. Prior distributions for the number of imported cases were informed by the relative size of the mpox outbreak in each city [36]. The prior distribution for the RR was informed by the change in sexual partner numbers analysis: the prior of RR among the ≤7 sexual activity level ($RR_{\leq 7 \text{ partners}}$) was capped between the lower bound of the 95% CrI (0.47) and 1. Since GBM of >7 sexual activity level likely have a greater decrease in partner numbers during the mpox outbreak (i.e., a lower RR), we constraint $RR_{>7 \text{ partners}}$ to be lower than $RR_{\leq 7 \text{ partners}}$. This was achieved by adding an $RR_{\text{multiplier}} = \frac{RR_{>7 \text{ partners}}}{RR_{\leq 7 \text{ partners}}}$ smaller than 1. Finally, the prior for the assortativity parameter was capped under 100 and was determined by manual fitting to the observed epidemics. The priors are the following:

$$\gamma_1^{-1} \sim \left(3 + logit^{-1}\left(N\left(logit\left(\frac{5-3}{15-3}\right), 1\right)\right) \times (15-3)\right)$$

$$\beta \sim logit^{-1}\left(N(logit(0.87), 1)\right)$$

$$RR_{\leq 7 \text{ partners}} \sim 0.47 + logit^{-1}\left(N\left(logit\left(\frac{0.80-0.47}{1-0.47}\right), 1.5\right)\right) \times (1-0.47)$$

$$RR_{\text{multiplier}} \sim 0.70 + logit^{-1}\left(N\left(logit\left(\frac{0.67}{0.80}\right), 5\right)\right) \times (1-0.70)$$

$$\tau_{t_0}^{c} \sim \begin{cases} 2 + logit^{-1}\left(N(logit(0.5), 0.5)\right) \times (8-2); if\ c = Montréal \\ 3 + logit^{-1}\left(N(logit(0.5), 0.5)\right) \times (8-3); if\ c = Toronto \\ 1 + logit^{-1}\left(N(logit(0.5), 0.5)\right) \times (6-1); if\ c = Vancouver \end{cases}$$

$$\omega \sim logit^{-1}\left(N\left(logit\left(\frac{5}{100}\right), 1\right)\right) \times 100$$

Supplementary Results

Supplementary Tables

Table S1. Variables used to empirically estimate changes in numbers of sexual partners during the mpox outbreak using data from the Engage Cohort Study.

Notation	Definition	Domain	Question from the *Engage Cohort Study*
y	Number of all-type sexual partners in the past 6 months (P6M) reported at the 2022 visit	[0,1000]	5.5 During the PAST 6 MONTHS, with how many guys have you had any kind of sex (anal, oral, mutual masturbation, rimming, frontal/vaginal, etc.)? _____ guys
Age	Age at time of the 2022 visit	16-29, 30-39, 40-49, 50-59, ≥60 years	1.3 What is your age (i.e., how old are you)?
Relationship status history	Relationship status reported at the latest visit before 2022	single, exclusive relationship, open relationship, unclear	2.18 Do you currently have a relationship with a main partner? No | Yes 2.23 What discussions have you and your main partner had with each other in terms of only having sex with each other? We haven't explicitly discussed only having sex with each other or not | We have discussed only having sex with each other, but have not agreed to anything | We have discussed only having sex with each other and agreed to only have sex with each other | We agreed to have other sex partners, but only ones we share (we only play together) | We agreed to have other sex partners, some of whom we share and others whom we see separately (we play together and separately) | We agreed to have other sex partners whom we only see separately (we only play separately) | We agreed to another arrangement. Please describe: __ | No main relationship partner
HIV status	HIV status at time of the 2022 visit	Seropositive, seronegative	Derived by *Engage Cohort Study* from participant laboratory-tested and self-report HIV status (determined using 4th generation testing with a confirmatory assay; or self-reported if testing data

			unavailable)
Calendar month	Calendar month of visit during 2022	{1, 2, …, 12}; continuous	-
Sexual partnership history	Number of all-type sexual partners in the past 6 months reported at the latest visit before 2022	≤ 7, >7	5.5 During the PAST 6 MONTHS, with how many guys have you had any kind of sex (anal, oral, mutual masturbation, rimming, frontal/vaginal, etc.)? _____ guys

Table S2. Parameter values used for the mpox dynamic transmission model in Montréal, Toronto, and Vancouver (2022).

Parameters	Unit	Symbol	Value	95% CrI of prior density*	Sources
Outbreak parameters					
Number of imported cases‡	cases	τ	—	Montréal: (3.6, 6.3) Toronto: (4.4, 6.6) Vancouver: (2.4, 4.6)	Calibrated [36]
Reporting delay	day	η^{-1}	2	—	Assumed
Reporting fraction	%	ε	Montréal: 82% Toronto: 86% Vancouver: 77%	—	[1]
Natural history parameters					
Incubation period†	day		7.1	—	[14–17]
Latent period	day	α^{-1}	5.1	—	[13]
Effective infectious period among GBM not traced and isolating	day	${\gamma_1}^{-1}$	—	(4.7, 13.7)	Calibrated [1,17,38]
Self-isolation period	day	γ_2^{-1}	14	—	[39–41]
Risk of transmission per effective contact	%	β	—	(49%, 98%)	Calibrated [1,42]
Public health intervention parameters					
Percentage traced and isolated among the exposed	%	v_t	Montréal: 7.5% Toronto:7.9% Vancouver: 7.0%	—	[8,27]
First-dose vaccination doses	doses	ψ_t	Time-varying	—	[9,27,28]
Percentage vaccinations received by age groups	%	ϑ	***See Table S5***	—	[8,28]
Vaccine effectiveness of the first dose†	%	ι	51.5%	—	[3,30–35]
Sexual behaviour parameters					
GBM population size	persons		Montréal: 54,000 Toronto: 78,000 Vancouver: 26,100	—	[1,22,23]
Mixing parameter		ω	—	(0.75, 27.40)	Calibrated [1]
Reduction in partner change rate during mpox		RR	—	≤7 sexual partners (P6M): (0.51, 0.99) >7 sexual partners (P6M): (0.40, 0.97)	Calibrated

GBM, gay, bisexual, and other men who have sex with men; *CrI*, credible interval.
* For parameters to be calibrated, the 95% CrI from the prior density distribution (described in ***Supplementary Methods***) was shown.
† Values estimated from a meta-analysis of studies (***Figure S1***).

Table S3: Age mixing matrix ($p_{aa'}$). The mixing matrix represents the proportion of GBM in each age group who reported that the age of their last sexual partner fell within the corresponding age group in each city. The data was derived from the age mixing matrix from Milwid et al. (2022) [18] and the age distribution from the *Engage Cohort Study* (2017-2023).

Montréal		**Partner's age group**				
		16-29	*30-39*	*40-49*	*50-59*	*>60*
GBM's age group	*16-29*	0.716	0.181	0.079	0.018	0.005
	30-39	0.284	0.37	0.292	0.036	0.017
	40-49	0.161	0.369	0.361	0.088	0.022
	50-59	0.144	0.281	0.387	0.161	0.027
	>60	0.497	0.141	0.13	0.175	0.056
Toronto		**Partner's age group**				
		16-29	*30-39*	*40-49*	*50-59*	*>60*
GBM's age group	*16-29*	0.715	0.182	0.079	0.019	0.005
	30-39	0.288	0.369	0.291	0.036	0.017
	40-49	0.161	0.368	0.361	0.088	0.022
	50-59	0.144	0.281	0.388	0.161	0.027
	>60	0.492	0.144	0.133	0.174	0.057
Vancouver		**Partner's age group**				
		16-29	*30-39*	*40-49*	*50-59*	*>60*
GBM's age group	*16-29*	0.706	0.187	0.082	0.019	0.005
	30-39	0.287	0.369	0.291	0.036	0.017
	40-49	0.161	0.369	0.361	0.088	0.022
	50-59	0.144	0.281	0.388	0.16	0.027
	>60	0.497	0.141	0.131	0.174	0.056

Table S4: Mixing matrix by HIV status ($p_{hh'}$) for Montréal. The mixing matrix represents the proportion of partnerships among GBM of a given HIV status with partners living or not living with HIV. "HIV- / unknown" represents GBM who received a negative test result or do not know their HIV status. The matrix was taken from Milwid et al. (2022) [18].

		Partner's HIV status	
GBM's HIV status		*HIV- / unknown*	*HIV+*
	HIV- / unknown	0.924	0.076
	HIV+	0.660	0.340

Table S5: Proportion of mpox vaccines received by age groups in Montréal and Toronto. The data was from the *Direction régionale de santé publique de Montréal* and *Public Health Ontario* [8,28]. Proportions for 50-59 and 60+ age groups were not available, and vaccines were assumed to be distributed equally between the two groups.

Age	**Proportion of mpox vaccines**	
	Montréal	**Toronto**
16-29	21.5%	22.1%
30-39	26.5%	33.4%
40-49	20.0%	18.2%
50-59	16.0%	13.2%
60+	16.0%	13.2%

Table S6: Unadjusted and RDS-II adjusted characteristics of *Engage Cohort Study* visits in 2022. Unadjusted and RDS-II adjusted estimates of percent coverage of the period of mpox-driven behaviour changes, number of sexual partners in the past six months, and covariates.

	Visit during the rest of 2022				Visit during the period of mpox-driven behaviour changes				Overall			
	N/mean	**(%)**	**RDS-II weighted % (95% CI)**		***N/mean***	**(%)**	**RDS-II weighted % (95% CI)**		***N/mean***	**(%)**	**RDS-II weighted % (95% CI)**	
Number of participant visits	1533				424				1957			
Number of participants	1078				367				1445			
ESS of participants	721				174				547			
Percent coverage (%) of the period of mpox-driven behaviour changes (mean)												
	0.0%	(SD0%)	0%	(0–0%)	19.5%	(SD13.4%)	19.5%	(16.3–22.8%)	4.2%	(SD10.2%)	3.8%	(3.1–4.5%)
Months since 2022-01-01 (mean)												
	5.1	(SD3.5)	5.3	(4.7–6)	6.2	(SD0.9)	6.2	(5.3–7.1)	5.4	(SD3.2)	5.5	(4.9–6.1)
Age group												
16-29	217	(14%)	18%	(16–20%)	68	(16%)	24%	(19–28%)	285	(15%)	19%	(17–21%)
30-39	613	(40%)	40%	(37–42%)	196	(46%)	39%	(34–44%)	809	(41%)	40%	(37–42%)
40-49	273	(18%)	13%	(11–14%)	70	(17%)	16%	(12–20%)	343	(18%)	13%	(12–15%)
50-59	203	(13%)	11%	(9–13%)	45	(11%)	9%	(6–12%)	248	(13%)	10%	(9–12%)
60+	227	(15%)	18%	(16–20%)	45	(11%)	13%	(10–17%)	272	(14%)	17%	(16–19%)
Relationship status history												
Single	818	(53%)	54%	(51–57%)	222	(52%)	51%	(46–57%)	1040	(53%)	54%	(51–56%)
Open	426	(28%)	19%	(17–21%)	136	(32%)	29%	(24–34%)	562	(29%)	21%	(19–23%)
Exclusive	205	(13%)	20%	(18–22%)	44	(10%)	14%	(10–17%)	249	(13%)	19%	(17–21%)
Unclear	84	(5%)	6%	(5–8%)	22	(5%)	6%	(3–8%)	106	(5%)	6%	(5–7%)
HIV status*												
Seropositive	312	(20%)	18%	(16–20%)	52	(12%)	9%	(6–12%)	364	(19%)	16%	(14–18%)
Seronegative / unknown	1221	(80%)	82%	(80–84%)	372	(88%)	91%	(88–94%)	1593	(81%)	84%	(82–86%)
Sexual partner numbers at the latest visit before 2022												
≤ 7 sexual partners	1211	(79%)	88%	(86–89%)	324	(76%)	83%	(79–87%)	1535	(78%)	87%	(85–88%)
> 7 sexual partners	322	(21%)	12%	(11–14%)	100	(24%)	17%	(13–21%)	422	(22%)	13%	(12–15%)
Number of sexual partners in the past 6 months (mean)												
	7.1	(SD14.1)	4.6	(4–5.3)	7.4	(SD14.4)	5.3	(3.8–6.8)	7.1	(SD14.2)	4.8	(4.2–5.4)

N: number of visits (unless specified in the first column); *CI*, confidence interval; *ESS*, effective sample size (of participants) is the size of a simple random sample that would produce the same variance as the RDS-II design and was estimated using *survey* package in R; *RDS*, respondent driven sampling; *SD*, standard deviation. *HIV status was ascertained from 4th generation laboratory testing with a confirmatory assay. Self-reported status was used if the test result was unknown (number of visits=52). RDS-II weights are inversely proportional to participants' social network size.

Table S7. Association between number of sexual partners in the past 6 months and covariates among *Engage Cohort Study* participants during the period of mpox-driven potential behaviour changes (May 19th –August 14th, 2022).

	RR (95% CrI)
Period of mpox-driven behaviour changes	0.80 (0.47, 1.36)
Months since January 1st, 2022	1.01 (1, 1.03)
Age group	
16-29	Reference
30-39	0.91 (0.77, 1.09)
40-49	0.85 (0.69, 1.04)
50-59	0.62 (0.5, 0.78)
≥60	0.51 (0.41, 0.64)
Relationship status history	
Single	Reference
Open	1.44 (1.27, 1.64)
Exclusive	0.74 (0.61, 0.91)
Unclear	0.82 (0.62, 1.09)
HIV seropositive*	1.13 (0.97, 1.31)
Sexual partner numbers at the latest visit before 2022	
≤ 7 sexual partners	Reference
> 7 sexual partners	5.61 (4.9, 6.45)
Period of mpox-driven behaviour changes by sexual partners interaction	0.83 (0.32, 2.15)
1 / overdispersion parameter	3.7 (3.02, 4.47)

Table presents the mean and 95% credible interval of a negative binomial regression model with a random intercept for each participant estimated using partial pooling. The percent coverage of the period of mpox-driven behaviour changes and calendar month variables are centred.

CrI, credible interval; *RR*, rate ratio.

* HIV status was determined based on 4th generation testing with a confirmatory assay. If the laboratory test result was unknown, self-reported status was used.

Table S8. Effect of the mpox epidemic on the number of sexual partners and visits to sex-on-premises venues. Sensitivity analyses using various sexual activity level groupings, endpoints for the mpox outbreak period, or using visit to bathhouses and/or sex clubs at least once in the P6M or attendance of group sex events at least once in the P6M as the outcome.

Analysis	Partner numbers at the latest visit before 2022	*N*		RR (95% CrI)
		period of potential behavior change	*rest of 2022*	
Using the 2022-08-14 endpoint				
	≤ 3 sexual partners	251	930	0.91 (0.48, 1.67)
	> 3 sexual partners	173	603	0.75 (0.31, 1.83)
	≤ 5 sexual partners	299	1112	0.85 (0.49, 1.49)
	> 5 sexual partners	125	421	0.64 (0.29, 1.41)
(main analysis)	***≤ 7 sexual partners***	324	1211	0.80 (0.47, 1.36)
	> 7 sexual partners	100	322	0.67 (0.31, 1.43)
Using the 2022-07-14 endpoint				
	≤ 3 sexual partners	197	984	1.48 (0.55, 4.06)
	> 3 sexual partners	132	644	0.86 (0.20, 3.66)
	≤ 5 sexual partners	235	1176	0.99 (0.39, 2.54)
	> 5 sexual partners	94	452	0.92 (0.25, 3.41)
	≤ 7 sexual partners	249	1286	1.03 (0.42, 2.57)
	> 7 sexual partners	80	342	0.54 (0.15, 1.98)
Using visit to bathhouses and/or sex clubs as the outcome				
		424	1533	0.26 (0.03, 1.89)
Using attendance of group sex events as the outcome				
		424	1533	2.42 (0.25, 23.8)

Models adjusted for month of the visit (1, 2,…,12; continuous), age (16-29, 30-39, 40-49, 50-59, ≥60 years), relationship status history (single, exclusive relationship, open relationship, unclear), and HIV status (seropositive, seronegative). *N*, number of visits; *CrI*, credible interval; *RR*, rate ratio of the percent coverage of the period of period of mpox-driven behaviour changes to the number of sexual partners in the past 6 months.

Table S9. Calibrated parameters for the dynamic model of mpox transmission in Montréal, Toronto, and Vancouver.

Parameters	Unit	*Symbol*	Prior median (95% CrI)	Posterior median (95% CrI)
Effective infectious period among GBM not isolating	day	γ_1^{-1}	9.50 (4.71,13.72)	5.87 (4.83, 7.15)
Risk of transmission per effective contact	%	β	87 (49, 98)	86 (63, 95)
Change in sexual partner numbers		*RR*	≤7 sexual activity level: 0.81 (0.51, 0.99) >7 sexual activity level: 0.63 (0.30, 0.91)	≤7 sexual activity level: 0.94 (0.80, 0.99) >7 sexual activity level: 0.94 (0.70, 0.99)
Number of imported cases‡	cases	τ	Montréal: 5.00 (3.61, 6.34) Toronto: 5.50 (4.37, 6.61) Vancouver: 3.50 (2.37, 4.64)	Montréal: 4.98 (3.53, 6.17) Toronto: 5.44 (4.26, 6.34) Vancouver: 3.40 (2.43, 4.46)
Mixing parameter		ω	5.06 (0.75, 27.40)	Montréal: 6.17 (3.85, 8.35) Toronto: 6.92 (2.87, 14.58) Vancouver: 10.95 (7.40, 18.81)

CrI, credible interval.
‡ Values shown are city-specific parameter estimate and 95% CrI's.

Table S10. Median averted fraction (AF) of mpox cases due to interventions that led to change in numbers of sexual partners, contact tracing/isolation, and first-dose vaccination in Montréal, Toronto, and Vancouver (Canada). The estimates from the main scenario are presented, as well as several sensitivity analyses.

Analyses	City	Averted Fraction (95% CrI)						
		Change in sexual partner numbers	Contact tracing/isolation	Vaccination	All three combined	Change in sexual partner numbers and contact tracing/isolation	Change in sexual partner numbers and vaccination	Contact tracing/isolation and vaccination
Main (as reported in manuscript)	Montréal	15% (3%-34%)	14% (12%-21%)	21% (16%-33%)	48% (35%-66%)	29% (17%-48%)	36% (23%-55%)	33% (27%-49%)
	Toronto	11% (2%-27%)	14% (12%-22%)	22% (16%-41%)	46% (34%-67%)	25% (16%-40%)	36% (22%-56%)	33% (26%-57%)
	Vancouver	10% (2%-22%)	14% (12%-16%)	39% (35%-48%)	58% (52%-69%)	23% (16%-33%)	50% (43%-60%)	49% (44%-59%)
Informative prior for RR‡	Montréal	49% (44%-53%)	11% (10%-13%)	15% (13%-20%)	67% (59%-77%)	56% (51%-63%)	61% (54%-70%)	26% (22%-32%)
	Toronto	39% (31%-42%)	12% (11%-14%)	17% (15%-26%)	62% (59%-71%)	46% (42%-49%)	56% (53%-64%)	27% (25%-38%)
	Vancouver	29% (26%-32%)	12% (11%-13%)	34% (32%-38%)	70% (67%-73%)	38% (35%-42%)	65% (62%-67%)	42% (40%-46%)
10% of contract traced (instead of 20%)	Montréal	16% (3%-35%)	7% (6%-11%)	22% (16%-33%)	44% (30%-61%)	24% (10%-41%)	38% (24%-55%)	28% (22%-42%)
	Toronto	13% (2%-28%)	7% (6%-11%)	22% (16%-41%)	42% (29%-62%)	20% (10%-34%)	37% (23%-58%)	27% (21%-50%)
	Vancouver	11% (2%-23%)	7% (6%-9%)	40% (35%-50%)	56% (48%-66%)	18% (9%-29%)	51% (44%-62%)	45% (40%-55%)
15% of contact traced (instead of 20%)	Montréal	15% (3%-36%)	11% (9%-17%)	21% (16%-34%)	46% (33%-63%)	26% (14%-46%)	37% (24%-55%)	31% (24%-47%)
	Toronto	12% (2%-28%)	10% (9%-16%)	22% (16%-41%)	45% (31%-65%)	22% (13%-37%)	36% (23%-57%)	30% (24%-53%)
	Vancouver	10% (2%-23%)	10% (9%-12%)	40% (35%-48%)	57% (50%-67%)	20% (13%-31%)	50% (43%-62%)	47% (42%-56%)
Vaccine effectiveness of 35.8% (instead of 51.5%)	Montréal	14% (3%-31%)	14% (12%-20%)	14% (11%-22%)	41% (29%-57%)	28% (17%-46%)	28% (16%-47%)	27% (23%-40%)
	Toronto	11% (2%-26%)	14% (12%-21%)	14% (11%-28%)	39% (28%-56%)	24% (16%-39%)	27% (16%-44%)	26% (22%-46%)
	Vancouver	10% (2%-22%)	14% (13%-17%)	29% (25%-36%)	49% (42%-59%)	23% (16%-33%)	39% (31%-49%)	40% (35%-49%)
Vaccine effectiveness of 86.0% (instead of 51.5%)	Montréal	19% (4%-43%)	14% (11%-22%)	38% (28%-55%)	64% (50%-80%)	34% (18%-55%)	56% (41%-74%)	48% (37%-66%)
	Toronto	14% (3%-25%)	17% (12%-23%)	56% (30%-66%)	75% (52%-84%)	29% (19%-40%)	67% (43%-77%)	66% (39%-77%)
	Vancouver	11% (3%-21%)	12% (11%-15%)	59% (52%-71%)	74% (68%-83%)	23% (17%-31%)	69% (62%-79%)	66% (59%-77%)
Standardizing the start and coverage of vaccination	Montréal	15% (3%-34%)	14% (12%-21%)	41% (33%-57%)	63% (52%-78%)	29% (17%-48%)	55% (42%-70%)	51% (42%-68%)
	Toronto	11% (2%-27%)	14% (12%-22%)	38% (29%-60%)	58% (46%-79%)	25% (16%-40%)	50% (37%-70%)	47% (38%-72%)
	Vancouver	10% (2%-22%)	14% (12%-16%)	39% (35%-48%)	58% (52%-69%)	23% (16%-33%)	50% (43%-60%)	49% (44%-59%)

CrI: 95% Credible interval; VE: vaccine effectiveness.
‡: model does not fit observed epidemic trajectory.

Supplementary Figures

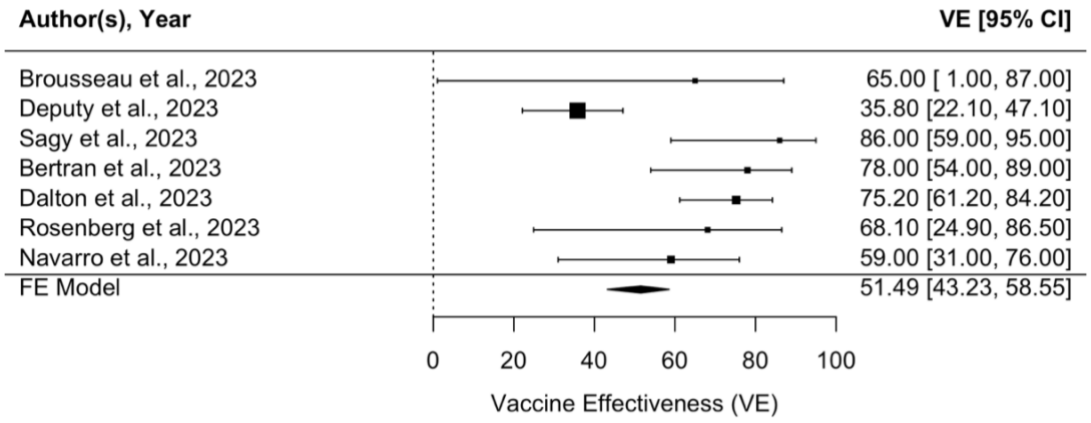

Figure S1. Effectiveness of a single dose of mpox vaccine (VE) across 7 studies. CI: confidence interval. Note that Sagy et al. estimated using hazard ratio, the rest of the studies used odds ratio. Squares are the mean and bars represent 95% confidence intervals.

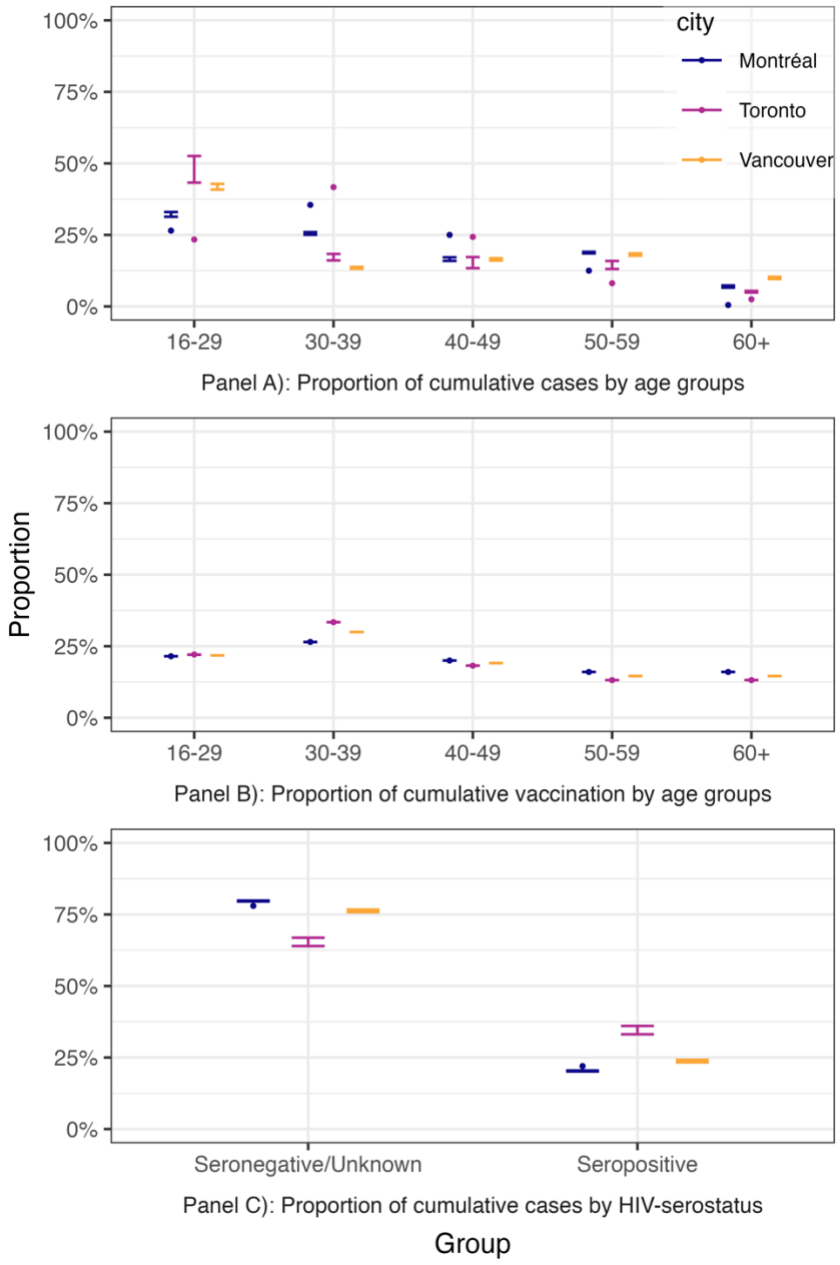

Figure S2. Cross-validation of model outcomes to available reported indicators. Modeled and observed proportion of cumulative cases A) age groups (not available from Vancouver), B) proportion of cumulative vaccinations by age groups (not available from Vancouver), and cumulative cases by HIV status (not available from Toronto and Vancouver) for each city. Bars represent the 95% credible intervals of model estimates, and points are the observed data. The lack of points for some cities and indicators indicate that the information is not available.

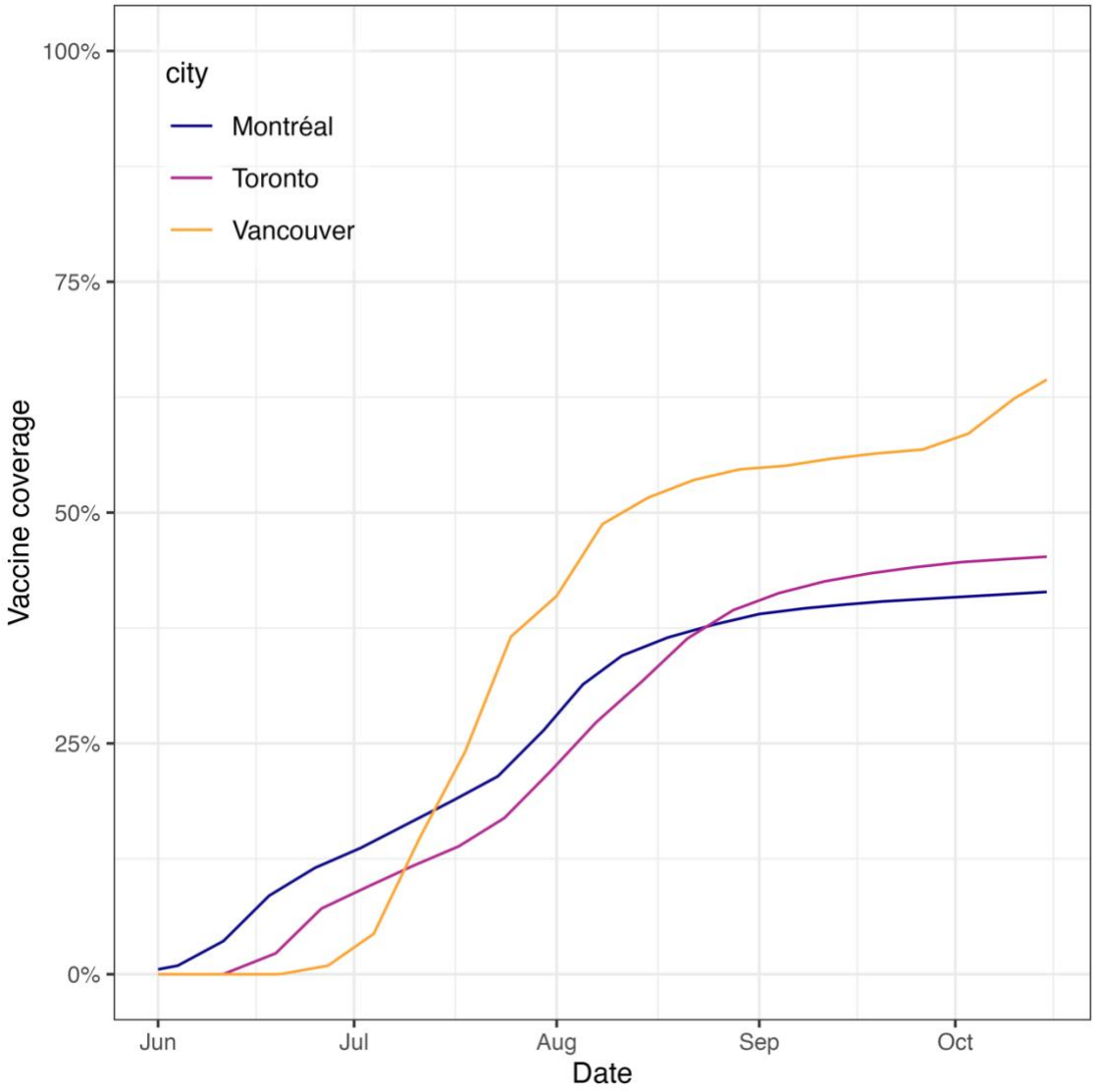

Figure S3. Estimated first-dose vaccine coverage of MVA-BN (Imvamune®) in Montréal, Toronto, and Vancouver from June 1st to October 15th, 2022. Lines represent the estimated vaccine coverage across time using population sizes of gay, bisexual, and other men who have sex with men (denominators) and weekly-varying number of first doses (numerators). The city-specific number of first doses in Toronto was approximated by the provincial number of first doses in Ontario. For Vancouver, only the total number of first- and second-doses is available but few second-doses were administered before October 2022 in that city.

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Chapter 6

Discussion

6.1 Main findings

In a globalizing world, some neglected tropical diseases such as mpox have shown the potential to disseminate internationally and cause outbreaks in previously non-endemic regions [152,153]. The 2022-2023 mpox epidemic rapidly became a global health challenge, occurring immediately in the wake of the COVID-19 pandemic (2020-2023), which overburdened and strained health systems [154]. The mpox outbreaks disproportionately affected often marginalized populations, including gay, bisexual, and other men who have sex with men (GBM) and people living with HIV (PLHIV), exacerbating stigma towards these groups [96]. The unprecedented nature, high case counts, and the initial lack of experience by public health authorities in dealing with mpox calls for more research on the prevention, immunology, and control of the disease [37].

This thesis improves our understanding of mpox transmission potential among GBM in Montréal, Toronto, and Vancouver –the main epicenters of the mpox epidemics in Canada. It describes GBM's heavy-tailed sexual network and the temporal changes in the degree distribution of those network as it relates to the COVID-19 pandemic. It also provides estimates of the basic reproduction number ($\mathscr{R}_0$) of mpox in Canada and the level of immunity required to achieve epidemic control (effective reproduction number $\mathscr{R}_e<1$). Finally, to the best of my knowledge, it constitutes the first study to offer insights into the impact of interventions on mpox transmission in Canada.

My first manuscript showed that GBM's sexual partner numbers largely decreased during the COVID-19 pandemic in all cities. Although there was a small rebound in sexual activity after travel restrictions were lifted, sexual partner numbers remained well below pre-pandemic levels at the onset of the mpox outbreak in the spring of 2022. This implies that the mpox transmission potential could have been higher if sexual activity had recovered to the pre-COVID-19 level by that time. Although mpox was largely contained within a few months in Canada and other non-endemic countries, endemic regions continue to report cases. Public health authorities should carry on monitoring the risk of mpox case importation and caution travelers to endemic countries of the ongoing transmission risk. The option to offer *Immavune* vaccine to at-risk travelers to endemic

regions could be considered. Furthermore, global health actors should collaborate to further develop mpox prevention and treatment strategies in endemic regions.

I estimated an $\mathscr{R}_0$ of 2.4-2.7 across the three cities during the 2022-23 mpox outbreak. This high $\mathscr{R}_0$ was largely driven by cases among the small portion of GBM in the highest sexual activity group (0.2% of GBM in each city). Despite this high $\mathscr{R}_0$, we estimate that the cumulative incidence of mpox was <1% among all GBM from May to October 2022, suggesting that susceptibility in the highest sexual activity group was rapidly depleted through acquisition of naturally-derived immunity [12]. The result highlights the need for effective communications and prioritization strategies to GBM with high numbers of sexual partners. Since it only takes a few immunized GBM in the highest sexual activity group to lower $\mathscr{R}_e$ below 1 (e.g., achieve epidemic control), reaching and vaccinating these individuals will be highly effective in preventing mpox. Overall, the first manuscript adds to our growing understanding of the spread of pathogens in densely clustered sexual networks with a high degree distribution, highlighting the important role played by the distribution's heavy tail in transmission dynamics of infectious agents.

My second manuscript provides evidence that mpox outbreaks in Canada would have eventually subsided –without interventions– due to saturation in the groups composed of GBM with a high number of sexual partners, in line with results from previous modeling studies [12,85,100,155]. My analyses of empirical data from the *Engage Cohort Study* (*Engage*) suggest that GBM could have modified their sexual behaviours during the mpox outbreaks, but my results were highly uncertain. Using these empirical results as a prior distribution in the dynamic model, I found that declines in partner numbers could have averted 10%-15% of cases across cities. Contact tracing/isolation of 20% of sexual contacts of reported cases could have averted 14% of new infections across cities. First-dose vaccination was most influential in curbing mpox transmission, respectively averting 21%, 22%, and 39% new infections in Montréal, Toronto, and Vancouver. The higher fraction of cases averted in Vancouver is due to its relative earlier implementation with respect to the start of the outbreak in that city. This finding underscores the importance of early interventions, including immunization. Finally, contact tracing/isolation and vaccination were implemented rather swiftly in Canada as the COVID-19 pandemic increased public health staffing for case investigations, contact tracing, and logistics of mass vaccination [156]. In the current funding landscape and shifting public health priorities [156,157], sustaining nimble rapid response teams within local public health units is warranted.

6.2 Strengths and limitations

The results of my thesis should be interpreted considering several limitations. First, I used self-reported data from the *Engage* participants, which could be subject to social desirability bias. For example, stigmatized sexual behaviours might have been underreported. Nonetheless, the use of anonymous self-administered questionnaires could have reduced such biases. Second, in both manuscripts, I used sexual partner numbers as a primary measure of GBM's sexual activities and to parameterize contact rates in the mathematical models. Other behavioural attributes, such as type of sex acts, frequency of sex in a partnership, and condom use, were not considered. Nevertheless, the sexual partner numbers variable was the most complete of all among the *Engage* participants, whereas frequency and condom use attributes were only captured for the most recent 5 sexual partners in the P6M. Third, since the distribution of the sexual partnerships over the 6-month recall period in the *Engage Cohort Study*, we assumed partnerships were uniformely distributed over that period and we did not account for concurrency between partnerships. The latter is unlikely to greatly affect our inferences since most parternships were casual, but we could still have underestimated the modeled transmission probabilities. Fourth, inverse probability of censoring weights (IPCW) was used to adjust for loss to follow-up (LTFU) in both manuscripts. However, unmeasured variables related to both the outcome (sexual activity) and LTFU could mean that attrition bias may have not been fully adjusted for. Finally, the results from both manuscripts depended on surveillance data published in reports and the level of disaggregation (by age, city, HIV status) required for model calibration was sometimes coarse. Local public health authorities should be further incentivized to make accessible detailed stratifications of the aggregated surveillance data they collect, following established best practices that preserve anonymity of cases.

This study boasts several strengths. First, for both manuscripts, I leveraged a large, longitudinal, population-based survey of the GBM population in the three cities. To my knowledge, it is the best data available for GBM in the three cities. I applied RDS-II and IPCW to ensure representativeness of the study population and generalizability of my results to all GBM in Montréal, Toronto, and Vancouver. Second, the mathematical models in both manuscripts considered stratifications and mixing by detailed sexual activity groups that were informed by empirical data. This granularity increases the validity of the model, given the critical role played

by heterogenous sexual activities in mpox transmission [12]. Manuscript 2 included further stratifications by age groups and HIV status, as well as sexual mixing by age and HIV status, which better reflected mpox's epidemiological characteristics [9]. Finally, parameter uncertainty was considered in both manuscripts using an efficient Bayesian sampling importance resampling algorithm for model calibration, ensuring computational efficiency and robustness of the findings by appropriately propagating key uncertainties to the modeled outputs.

6.3 Areas for further research

This thesis improves our understanding of the 2022-2023 mpox outbreak in Canada, yet knowledge gaps remain. As communicable diseases continue to pose threats to the health of populations globally [153], studying the impact of international travel and case importations will be relevant for control of mpox and other pathogens. Additional research is needed to understand the risk of resurgence given some uncertainties related to the duration of both naturally-acquired and vaccine-derived immunity, relatively low coverage of the second-dose vaccination, and turnover between low and high sexual activity groups. Finally, exploring the impact of mpox interventions among various age groups and PLHIV, which could be achieved using the current model, will inform targeted strategies and optimize allocation of surveillance resources.

Chapter 7

Conclusion

GBM's sexual partner numbers decreased during the COVID-19 pandemic in Montréal, Toronto, and Vancouver. After travel-related restrictions were lifted, sexual activity rebounded slightly but remained below pre-pandemic levels at the onset of the 2022-2023 mpox outbreak. Mpox's transmission potential was high among GBM with high sexual partner numbers, but the high sexual activity groups were quickly saturated, resulting in the cumulative incidence of ≤1% among the whole GBM population of the three largest Canadian cities. Even though the epidemic downturn would have occurred without interventions, GBM's reduction in the numbers of sexual partners during the mpox outbreak and contact tracing/isolation of case contacts might have contributed to accelerating it. First-dose vaccinations still averted a large number of cases.

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