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Bridging wastewater and case surveillance reveals the hidden burden of the 2022 mpox outbreak dynamics

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Bridging wastewater and case surveillance reveals the hidden burden of the 2022 mpox outbreak

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Abstract

Transmission models of the 2022 global mpox outbreak relied on case data to infer transmission dynamics despite substantial underascertainment driven by barriers to testing and care. Wastewater-based surveillance (WBS) captures community viral shedding independent of healthcare access, yet how it can be integrated with case data to improve infection estimates remains unclear.

We developed a compartmental model integrating case-notifications, wastewater viral-load, sexual network structure, and vaccination to evaluate how WBS complements case surveillance. Three model variants were fitted and validated using serological data: i) case-only, ii) wastewater-only and iii) combined. The case-only model reproduced incidence but not wastewater dynamics, whereas the wastewater-only model captured viral load trends but overestimated peak incidence. Joint calibration reconciled both data streams, yielding more precise estimates of infection burden, including a peak prevalence of 344 infections (95% CrI: 230-494) and a cumulative incidence of 1,132 (95% CrI: 943-1,349). Model-predicted seroprevalence aligned with that observed among sexual health clinic attendees, providing external validation.

The wastewater-case model revealed infection underascertainment, time-varying contributions of sexual activity groups to wastewater signals and showed that wastewater lead-lag relationships depended on epidemiological and operational conditions. Together, these findings establish integrated wastewater-case modelling as a robust framework for epidemic reconstruction.

1. Introduction

Mpox, an infectious disease caused by the monkeypox virus (MPXV) [1] was declared a public health emergency by the World Health Organization in July 2022 following a global outbreak that began in May of the same year [2]. Transmission during this outbreak, which was driven largely by clade IIb [3], occurred predominantly through close physical and sexual contact with most reported cases identified among gay, bisexual and other men who have sex with men (gbMSM) [4]. The reporting of laboratory-confirmed diagnoses or suspected cases faced major challenges, including social stigma and limited detection due to presymptomatic and asymptomatic transmission, as well as breakthrough infections with milder clinical manifestations [5]. These factors raised concerns that case-based surveillance could underestimate the true scale of transmission [6]. Although serological surveys provide the most direct means of characterizing cumulative infection,they are resource intensive, logistically demanding, often confined to non-representative subpopulations, and cannot be implemented frequently enough to capture rapid changes in transmission during an evolving outbreak [7, 8]. This limitation underscores the need for alternative approaches to accurately characterize the true burden of mpox infection for public health planning.

Wastewater-based surveillance (WBS) offers a complementary data stream to understand mpox transmission because infected individuals shed MPXV DNA regardless of symptoms or healthcare-seeking behaviour [9, 10, 11, 12]. As a result, wastewater aggregates viral material from presymptomatic, asymptomatic, and symptomatic infections, including infected individuals who may never be clinically reported. During the 2022 outbreak, MPXV DNA was detected in wastewater across multiple countries, with strong temporal associations between wastewater viral loads and reported cases [13, 14, 15, 16, 17, 14, 18, 19]. In several settings, wastewater signals appeared earlier than case-based surveillance data or reached levels far exceeding what reported case counts could explain, indicating that a substantial proportion of infections, likely including asymptomatic or untested cases, were not captured by case reporting [17, 14, 18]. Existing WBS studies have been largely descriptive, demonstrating feasibility and correlation, but not quantifying the underlying relationship between wastewater viral load and infection prevalence. This relationship is shaped by several biological and environmental processes, including the timing and magnitude of viral shedding across infection stages [20, 17], the changing distribution of infections across behavioural groups over time [21, 22], delays in reporting of symptomatic cases [5, 6], and transport and decay of viral DNA in sewer networks [14, 11]. Without modelling these processes jointly, it remains unclear how to use wastewater data to estimate underreporting or to interpret wastewater trends in terms of underlying transmission.

Mathematical modelling has become an essential tool for understanding mpox transmission and evaluating the impact of interventions. During the 2022 outbreak, case-based models highlighted how heavy tailed sexual networks among gbMSM sustained early epidemic growth [21] and showed that vaccination and behaviour change contributed to the subsequent decline [23, 22]. As sexual activity shapes exposure risk and the distribution of infections, incorporating behavioural heterogeneity into transmission models can offer additional insight into how infection burden evolves across groups over time. Wastewater data, which reflect viral shedding from all infected individuals regardless of symptoms or healthcare-seeking, provide an

opportunity to examine how these behavioural strata contribute to aggregated viral loads and to explore how group-level dynamics unfold during the course of an outbreak. A small number of theoretical studies have explored mpox wastewater surveillance, such as estimating minimum shedding thresholds for detection [24],but none have combined case-based surveillance data with models that explicitly link transmission dynamics to both wastewater viral signals and reported cases. For other pathogens, particularly SARS-CoV-2, integrating case and wastewater data in mechanistic models has improved estimates of infection burden and reduced bias arising from incomplete reporting [25]. Recent work has highlighted how post-recovery shedding dynamics shape quantitative wastewater epidemiological inferences [26] , while elsewhere wastewater viral loads have even been used to infer total infections and underreporting through model-based inversion of wastewater signals [27]. Extending these approaches to mpox requires capturing multiple interconnected processes: how infections progress and shed viral DNA across stages, how viral material accumulates in wastewater, and how delays in testing, and wastewater transport shape observed signals. A framework that links these processes is needed to interpret wastewater trends in terms of underlying transmission.

The 2022 mpox outbreak in Metro Vancouver (British Columbia, Canada) provides a unique setting for examining the relationship between wastewater signals, reported cases, and underlying infection dynamics, given the concentration of cases within the Lower Mainland and the availability of wastewater measurements across multiple sewershed catchment areas throughout the epidemic. To address these gaps, we developed an integrated mechanistic framework and applied it to the 2022 mpox outbreak in Metro Vancouver, the Lower Mainland of British Columbia (BC), Canada. Our compartmental model links sexual activity group structure, laboratory-confirmed case-based surveillance data, wastewater viral loads, and vaccination scale-up within a unified system, jointly capturing the pathways from infection to viral shedding, case detection, and wastewater transport. This framework enables us to quantify the added value of wastewater surveillance beyond case-based surveillance and to interpret wastewater signals in terms of underlying transmission. In this study, we used the model to compare how case data alone, wastewater data alone, and both combined reconstruct epidemic trajectories, including prevalence and cumulative incidence; to quantify symptomatic underreporting and evaluate how inference changes when wastewater data are incorporated; to estimate a wastewater-informed underascertainment factor that provides a complementary perspective on infections not captured by routine case surveillance; and to examine how infection burden and wastewater contributions vary across sexual activity groups within the gbMSM population. Finally, we explored counterfactual scenarios, including alternative assumptions about vaccination, shedding, and reporting to assess how epidemiological and system-level factors influence the relationship between wastewater signals and reported cases.

Methods and Materials

Data sources

We analyzed wastewater samples collected from five treatment plants in Metropolitan vancouver in the Lower Mainland of BC between June and December 2022. Two samples per week

from each WWTP were processed using three validated MPXV qPCR assays with comparable limits of detection[13]: the CDC-developed G2R_WA and G2R_G assays [28] and a custom assay, G2R_NML developed by the Public Health Agency of Canada's National Microbiology Laboratory (NML)[13] .Viral concentrations were normalized by flow rate and catchment area population to yield viral loads in copies per person per day [29, 30]. These values were log-transformed (log10 copies per capita per day) and used for model fitting.

Daily confirmed mpox cases were obtained from provincial surveillance system . Vaccination data for first and second doses were retrieved from weekly provincial reports, converted to daily counts, and transformed into time-varying vaccination rates.Vaccination was assumed to have been administered to the gbMSM population.

In the model, the gbMSM population was stratified into three sexual activity groups based on the reported number of anal sex partners in the past six months, informed by the empirical distribution observed in behavioural survey data from the Engage Cohort study [31]. Groups were defined as low ($x \leq 4$ partners, 60% of population), medium (x =5–21 partners, 35%), and high activity groups ($x \geq 22$ partners, 5%).

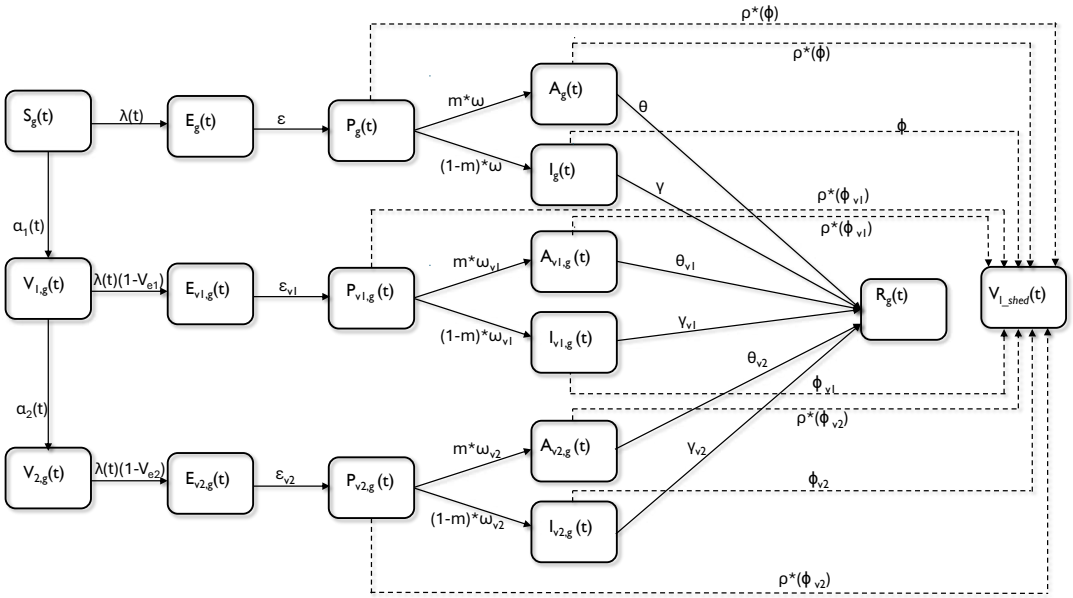


Figure 1: Model framework used across all three model variants (case-only, wastewater-only, and combined), each sharing the same structure but calibrated to different data streams. The model is stratified by sexual activity group (g = low, medium, high), with transmission and transitions defined separately for each group according to the mixing assumptions.The epidemiological states are described in the main text. The dotted lines represent shedding of viral load to wastewater while the solid lines represent movement between states. Individuals move through S (susceptible), E (exposed), P (presymptomatic), A (asymptomatic), I (symptomatic), R (Recovered) states and Vl_shed (viral load), each stratified by vaccination status: unvaccinated, V_1 (1st dose), and V_2 (2nd dose).

Transmission model

We developed a deterministic compartmental model to simulate mpox transmission dynamics among gbMSM in Vancouver, stratified into three behavioral risk groups(g)(Fig. 1). Sexual activity group classification was based on the reported number of recent anal sex partners in the past six months: High-activity: $x \geq 22$ partners (5% of gbMSM; 1305 of 26,100), Medium-activity:x =5–21 partners (35%; 9135 of 26,100), and low-activity: $x \leq 4$ partners (60%; 15,660 of 26,100).

All individuals began in the susceptible compartment (S). Upon exposure, they moved to the exposed compartment (E), representing a latent, non-infectious state. After the latent period, individuals transitioned to a presymptomatic infectious compartment (P). A proportion m of these individuals became asymptomatically infectious (A), while the remaining fraction transitioned to the symptomatically infectious compartment (I). Both A and I individuals subsequently moved into the recovered compartment (R), where they were assumed to be immune. Due to the short duration of the outbreak over the study period, we did not include waning immunity. To better reflect realistic infectious period distributions, both asymptomatic (A) and symptomatic (I) states were modeled using three sequential sub-compartments, to allow for a gamma-distributed duration of infection [32]. The model also incorporated vaccination using two stages: V_1 individuals who received the first vaccine dose and V_2 individuals who received the second dose. Susceptible individuals entered V_1 at daily rates, α_1 derived from empirical vaccination data applied uniformly across sexual activity groups due to the absence of group-specific vaccination uptake data. Transition to V_2 followed administration of a second dose also based on daily uptake rates α_2. A 14-day delay was applied after each dose before vaccine protection was assumed to take effect [33].

We assumed that vaccines are only offered to individuals without any previous mpox symptoms. We implemented a leaky vaccine mechanism where vaccinated individuals retained partial susceptibility to infection based on the dose-specific vaccine effectiveness (ve_1 for first dose, ve_2 for second dose). Once infected, vaccinated individuals progressed through the same disease stages ($E \rightarrow P \rightarrow A/I \rightarrow R$) as unvaccinated individuals. This assumption reflects the absence of robust empirical estimates for stage-specific disease duration or viral shedding conditional on vaccination status, rather than evidence of no biological difference. Potential post-infection effects of vaccination, including reduced viral shedding, were therefore explored through sensitivity analyses.

The model does not explicitly represent reductions in sexual contacts following symptom recognition or diagnosis. Instead, transmission during the symptomatic period is represented through an effective transmission parameter, which captures average transmission dynamics over the course of the outbreak, including the net effects of behavioural change, vaccination, and informal isolation. Full model equations are provided in Supplementary Methods (Section S1).

Wastewater viral load generation

Viral shedding was modelled for presymptomatic (P), asymptomatic (A) and symptomatic (I) stages using empirical viral load data [34]. Shedding was scaled by a fitted parameter(ψ) to

account for uncertainty due to variability in viral decay, sampling efficiency, and transport dynamics within the sewer system. The resulting deposited viral load was propagated through an advection–dispersion–decay framework with an estimated mean transit time $\bar{\tau}$ and dispersion parameter σ to capture sewer travel delays and smoothing effects prior to sampling. Additional details on viral shedding assumptions, wastewater transport dynamics, and sensitivity analyses are provided in Supplementary Methods (Section S2).

Model calibration and inference

We calibrated three model specifications: (i) a case-only model, (ii) a wastewater-only model and (iii) a combined model integrating both data streams. All models were implemented in a Bayesian framework using the "rjags" package with daily time steps. Two Markov chain Monte Carlo (MCMC) chains 50,000 were run with 10,000 burn-in and thinning by 3. Convergence was assessed using trace plots and Gelman-Rubin diagnostics ($\hat{R}$).

Priors for key epidemiological and surveillance parameters were informed by the literature or specified as weakly informative (Table 1). Case counts were modeled using a negative binomial likelihood, while log-transformed wastewater viral loads were modeled using a normal likelihood. Full details of prior specification, likelihood formulations, and model initialization are provided in Supplementary Methods (Section S3).

Estimating underascertainment of mpox infections

Underascertainment of mpox infections was quantified using posterior samples from the combined model, which was jointly constrained by reported case notifications and wastewater viral load. Two complementary measures of underascertainment were defined.

Symptomatic underascertainment was defined as the number of model inferred symptomatic infections per reported case. For each posterior draw, incident symptomatic infections were summed over the study period and divided by the corresponding cumulative number of reported cases. Total infection underascertainment was defined as the number of model inferred infections contributing to transmission and viral shedding (including both symptomatic and asymptomatic infections) per reported case. This quantity was computed analogously using posterior samples from the combined model.

Estimates were summarized using posterior medians and 95% credible intervals.

Scenario analysis

We conducted a series of counterfactual scenario analyses to assess how key epidemiological and surveillance processes influence the temporal alignment between wastewater viral loads and reported cases. All scenarios were simulated using posterior samples from the combined model, with model structure and all non target parameters held constant.

First, to explore uncertainty in post infection viral excretion, we examined reduced shedding among vaccinated individuals by scaling stage-specific shedding rates by 20–80% relative to baseline. Second, to evaluate the impact of sewer-system dynamics, we varied the mean wastewater transit time using epidemiologically plausible values drawn from the posterior distribution

of the fitted model, spanning fast to slow transport scenarios. Third, to assess the role of surveillance timeliness, we varied the mean delay from symptom onset to case reporting using values grounded in the empirical distribution observed in line list data (5, 10, and 14 days).

For each scenario, we quantified (i) predicted case and wastewater trajectories, (ii) the timing and lag between epidemic peaks in cases and wastewater, and (iii) the strength of association between the two signals using an expanding-window correlation, calculated cumulatively from the start of the outbreak through time.

Model validation

To externally assess the plausibility of model predicted infection burden, we compared cumulative incidence estimates with seroprevalence measured in July 2023 among attendees of a sexual health clinic of the Lower Mainland of British Columbia (n = 596). The serosurvey was based on a convenience sample of clinic attendees and was not designed to be representative of the general population

Because seropositivity may reflect either infection or vaccination,validation analyses focused on unvaccinated participants (n = 275) and, separately, on the subset born after 1972 to minimize potential confounding from historic smallpox vaccination. Model predicted seroprevalence was obtained by converting model estimated cumulative incidence into the proportion of the modeled population infected over the study period.

Given differences between the modelled population and the clinic-based sampling frame, serological comparisons were used as an external plausibility check on the magnitude of reconstructed infection burden rather than as a formal calibration target.

Table 1: Description of the model parameters and their sources

Symbol	Description	Value	Prior	Source
$1/\epsilon$, $1/\epsilon_{v1}$, $1/\epsilon_{v2}$	Duration of latent (exposed) period	6.26 days (5.55–6.97)	Gamma(300, 47)	[35]
$1/\omega$, $1/\omega_{v1}$, $1/\omega_{v2}$	Duration of pre-symptomatic infection	2 days	Fixed	[23, 36]
$1/\theta$, $1/\theta_{v1}$, $1/\theta_{v2}$	Duration of asymptomatic infection	14 days (7–21)	Gamma(21, 2)	[37, 38]
$1/\gamma$, $1/\nu_{v1}$, $1/\nu_{v2}$	Duration of symptomatic infection	21 days (14–28)	Gamma(42, 2)	[39, 34]
ρ	Relative infectiousness of asymptomatic and presymptomatic individuals compared to symptomatic	0.776	Fixed	[40]
ϕ_i	Viral load for symptomatic stages	{12.3, 11.5, 10.2} $\log_{10}$ copies/mL	Fixed	[34]
ve_1	Vaccine effectiveness (1 dose)	35.8% (22.1–47.1)	Beta(22.05, 39.56)	[41]
ve_2	Vaccine effectiveness (2 doses)	66.0% (47.4–78.1)	Beta(20.92, 10.77)	[41]
$\alpha_1(t)$	Daily rate of 1st dose vaccination	Estimated	Fixed	BC Vaccination registry
$\alpha_2(t)$	Daily rate of 2nd dose vaccination	Estimated	Fixed	BC Vaccination registry
m	Proportion of Asymptomatic infections	34%(27-43)	Beta(6.8, 13.2)	[37]
β	Probability of transmission per effective contact	Estimated	$\mathcal{N}_{[0,1]}(0.8, 0.1)$	[23]
κ	Mixing probability	Estimated	Beta(40, 2)	[21, 23]
ψ	Scaling factor	Estimated	LogNormal$\big(\log(3\times 10^{-9}), 0.158\big)$	[25]
τ	Mean transit time	Estimated	$\mathcal{N}_{[0.1,10]}(2.5,\ 0.5^2)$	[25]
σ	Sd of mean transit time	Estimated	$\mathcal{N}_{[0.1,1]}(0.3,\ 0.1^2)$	[25]
rf	Reporting fraction	Estimated	Beta(10, 10)	[40]
η	Negative binomial dispersion parameter	Estimated	Gamma(2, 0.5)	Assumed
τ_{ww}	Viral load normal likelihood precision	Estimated	Gamma(2, 1)	Assumed
pop	Catchment area population size	1278020	fixed	BC PEOPLE dataset [42]
$Flowrate$	Volumetric flow rate of WWTPS	fixed	fixed	BC records

Results

Model calibration and fit to cases and wastewater

We developed a deterministic compartmental model of mpox transmission among gbMSM in Metro Vancouver, Canada between June and December 2022 stratified into three sexual activity groups (high, medium, low). The model was calibrated using a Bayesian framework to daily time-series data from (i) case-based surveillance, (ii) wastewater viral load, or (iii) both data streams combined. For each variant, we assessed posterior predictive performance against both observed cases and wastewater, including the data stream not used for calibration, enabling assessment of consistency across surveillance signals (Fig. 2 and Supplementary Fig. S1).

All parameters showed good convergence, with $\hat{R} < 1.01$ and effective sample sizes (ESS) > 200 (Table. S1). The case-only model reproduced the timing and magnitude of reported cases, capturing both epidemic growth and decline (Fig. 2A), and the combined model showed similarly close agreement with observed case counts (Fig. 2C). In contrast, the wastewater-only model captured epidemic timing but overestimated the case peak and underestimated case counts later in the outbreak (Fig. 2B). For wastewater dynamics, both the wastewater-only and combined models closely matched observed viral load trajectories, including the gradual post-peak decline (Fig. 2E–F). The case-only model, which lacked wastewater constraints, showed greater uncertainty and systematically underestimated wastewater concentrations during the epidemic peak (Fig. 2D).

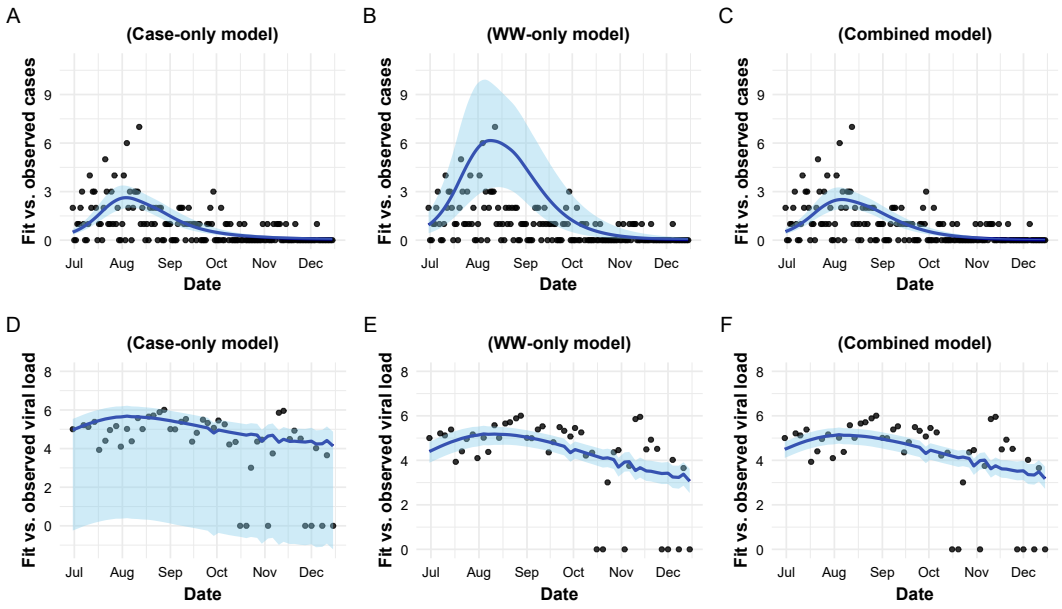


Figure 2: Posterior predictive fits of daily case counts of mpox in 2022 and daily wastewater viral load in log 10 copies per ml across three model types for Vancouver (Canada). A, B and C shows the model fits to reported mpox case counts in Vancouver from June to December 2022 for the case-only, wastewater-only, and combined models, respectively. Blue lines represent posterior median rates, and shaded areas denote 95% credible intervals (CrI). Black points indicate observed data. D, E and F shows corresponding model fits to observed wastewater viral load. The case-only model showed good agreement with case data but failed to reproduce wastewater dynamics, while the wastewater-only model aligned with wastewater observations but overestimated peak case incidence. The combined model was able to capture both data streams consistently.

Epidemic reconstruction under alternative surveillance data streams

We compared how case data, wastewater data, and their integration shaped reconstruction of mpox prevalence, defined as the number of individuals actively infected at a given time, and cumulative incidence, defined as the total number of infections over the outbreak period (Fig. 3). Inferred epidemic size differed markedly by surveillance stream. The case-only model produced the highest burden, with peak prevalence of 546 (95% credible intervals [CrI]:322–675) and cumulative incidence of 1,454 (95% CrI: 1,125–1,731). Estimates were intermediate under the wastewater-only model, with peak prevalence of 423 (95% CrI: 294–542) and cumulative incidence of 1,192 (95% CrI: 1,088–1,281), and lowest under the combined model, which inferred peak prevalence of 344 (95% CrI: 230–494) and cumulative incidence of 1,132 (95% CrI: 943–1,349), with substantially narrower uncertainty. Posterior comparisons indicated an 81% probability that peak prevalence under the combined model was lower than under the wastewater-only model and a 94% probability that it was lower than under the case-only model; corresponding probabilities for cumulative incidence were 70% and 96%, respectively.

To understand these differences, we examined how each data stream constrained key transmission and surveillance parameters (Supplementary Figs. S2–S3). Although all models shared identical structure and priors, the information content of the calibration data differed. Case-based surveillance alone primarily constrained the product of transmission intensity and reporting probability, allowing higher transmission to be offset by lower reporting while still matching observed cases. In contrast, wastewater viral load constrained the total number of infections contributing to community shedding but provided limited information on reporting. Joint calibration restricted this trade-off: the combined model was required to reproduce both observed case counts and wastewater signals, shifting posterior estimates toward lower transmission probabilities and higher reporting fractions. This yielded epidemic reconstructions that were simultaneously consistent with clinical and environmental surveillance data.

Underascertainment of mpox infections

Using the combined model, we quantified the extent to which routine case-based surveillance underestimated mpox infections. We estimated a median of 5.0 symptomatic infections per reported case (95% CrI: 3.9–6.4), indicating substantial fraction of symptomatic infections were not captured by routine surveillance.

When all infections contributing to viral shedding were considered, including symptomatic, asymptomatic, and undiagnosed infections, the estimated underascertainment factor increased to 8.4 total infections per reported case (95% CrI: 6.9–10.2). Together, these findings show that beyond missed symptomatic cases, a large reservoir of infections contributing to wastewater viral load remained invisible to routine case-based surveillance

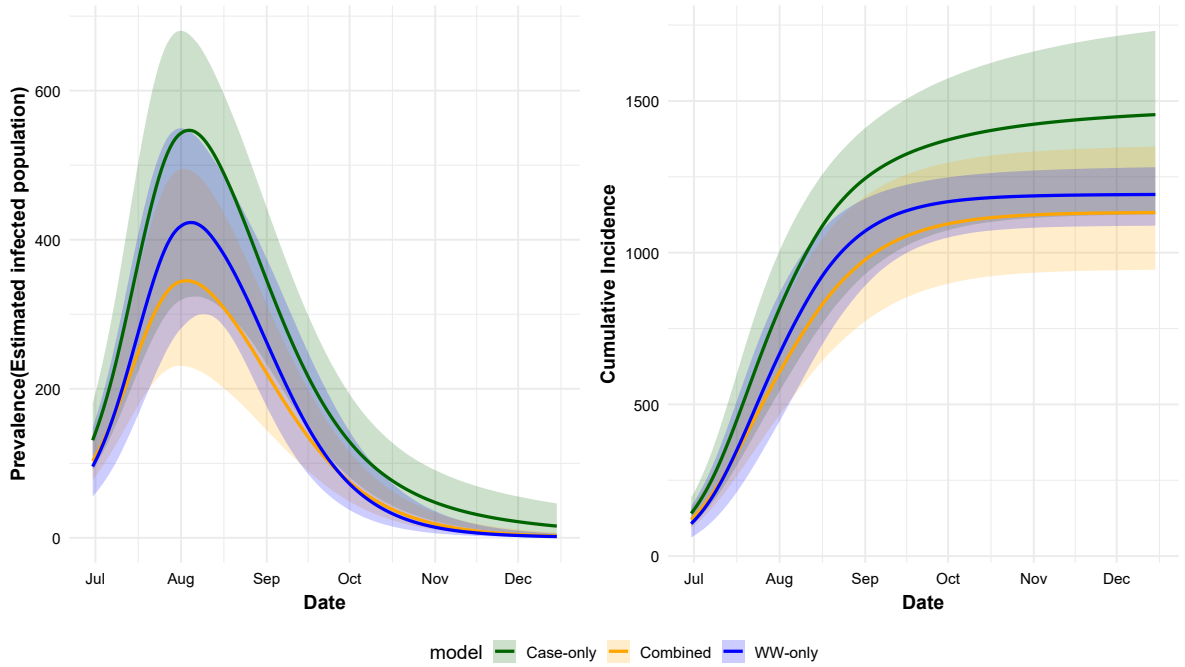


Figure 3: Posterior estimates of mpox prevalence and cumulative incidence in Metro Vancouver(Canada), June-December 2022. The case-only model produced the highest estimates, the wastewater-only model gave intermediate values and the combined model yielded the lowest estimates with narrower uncertainty highlighting sensitivity of epidemic reconstruction to data source. Lines represent posterior median rates, and shaded areas denote 95% credible intervals.

Contribution of sexual activity groups to infection burden and wastewater signal

Using posterior outputs from the combined model, we examined how heterogeneity in transmission across sexual activity groups within the gbMSM population shaped the aggregate wastewater signal and how these contributions evolved over the course of the outbreak. The population was stratified into three behavioural groups based on reported numbers of anal sex partners in the past six months: high ($x \geq 22$ partners, 5%), medium (x =5–21 partners, 35%) and low ($x \leq 4$ partners).

Early in the outbreak, the high activity group accounted for nearly all model-predicted wastewater viral load, contributing 95% of the signal in July 2022 (Fig. 4A). As transmission declined in this group and spread to individuals with fewer partners, the contribution of the medium activity group increased steadily and surpassed that of the high activity group by November, accounting for 65% of the wastewater signal, while the low activity group consistently contributed $< 5\%$. Model-derived estimates of infectious individuals mirrored these patterns (Fig. 4C). At the epidemic peak in August 2022, the high activity group reached an estimated 300 infectious individuals (95% CrI: 186–436), representing 23% of its population, over 100-fold higher than in the medium (11; 95% CrI: 02–34; 0.01%) and low activity groups (2; 95% CrI: 1–6;$< 0.001\%$).

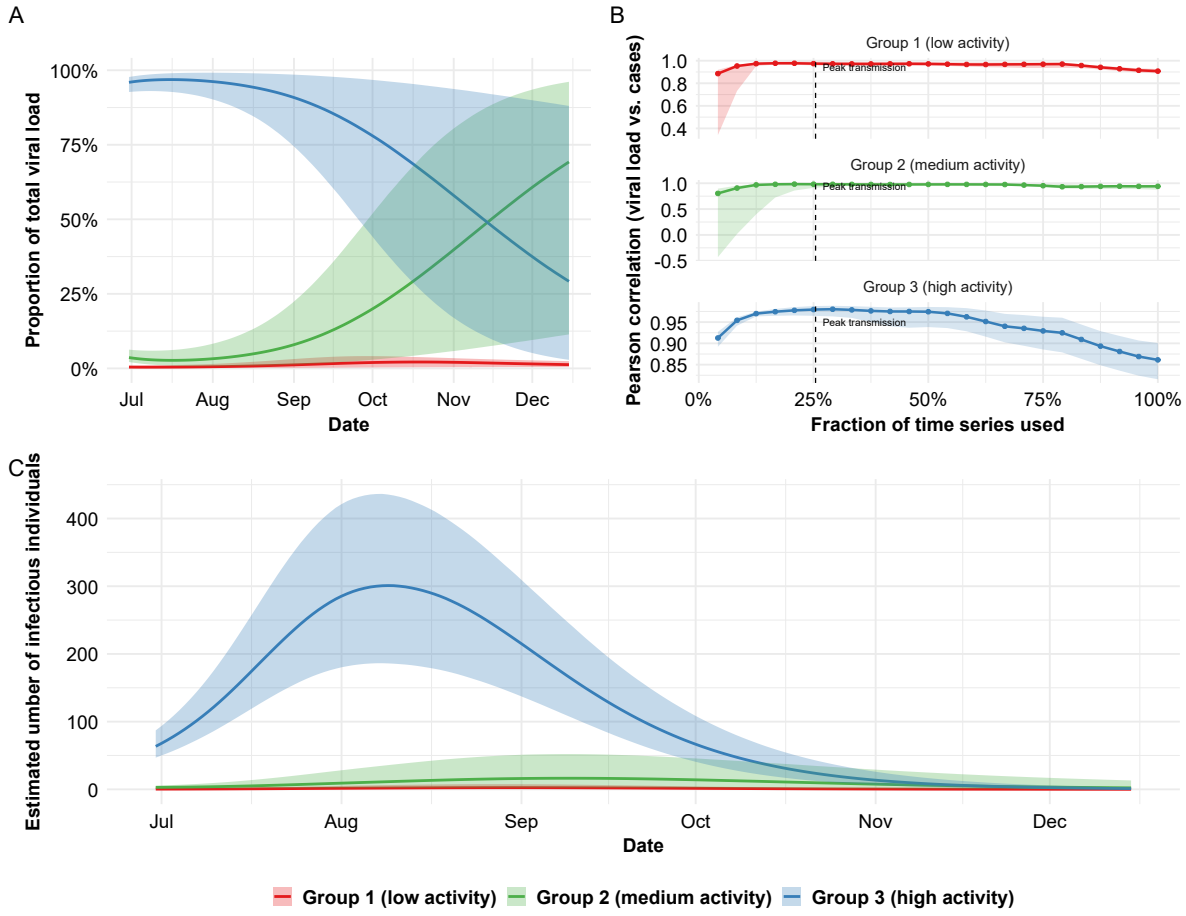


Figure 4: Contribution of sexual activity groups to mpox wastewater viral load and infection dynamics in 2022 in Vancouver (Canada). (A) Proportion of total wastewater viral load attributable to each group over time. (B) Pearson correlation between predicted wastewater viral load and reported cases by group across the epidemic with dashed lines indicating timing of peak transmission. (C) Estimated number of infectious individuals by group. Lines represent posterior median rates, and shaded areas denote 95% credible intervals.

We assessed temporal alignment between wastewater viral load and cases within each group using sliding-window correlations (Fig. 4B). In the high activity group, correlations remained high ($r > 0.9$) during epidemic growth and peak, but declined toward the end as infections decreased rapidly and wastewater signals decayed more gradually. Correlations were also high in the medium and low activity groups for much of the epidemic, although they were partly driven by extended periods of near-zero infections and minimal wastewater contribution.

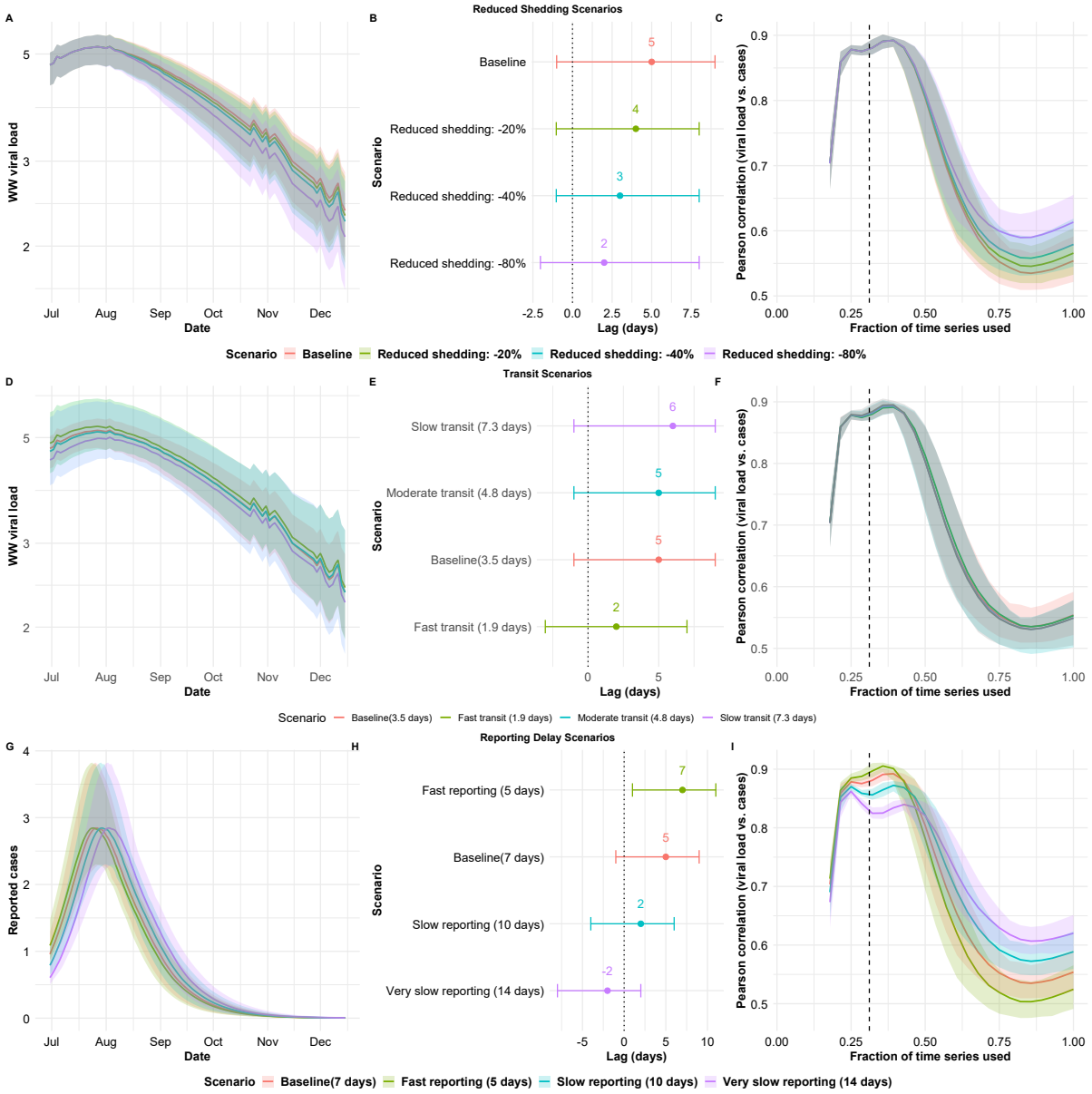


Figure 5: Effect of key alternative scenarios on predicted mpox viral load/cases, peak lag (positive implies cases peak earlier) and correlation with daily reported cases in 2022 in Metro Vancouver (Canada) from the combined model. Rows show reduced shedding, longer /shorter WW transit time, and reporting delays. Left: predicted normalized viral load or reported cases (median, 95% CrI). Middle: lag (days) at peak with the median and credible intervals represented as points and bars. Right: correlation with reported cases over the epidemic . Baseline in orange

Sensitivity of case-wastewater alignment to shedding, transit time, and reporting delays

We evaluated how epidemiological and operational factors shape the temporal alignment between wastewater viral load and reported mpox cases in the combined model (Fig. 5). Specifically, we examined the effects of reduced viral shedding among vaccinated individuals, variation in mean wastewater transit time, and delays between symptom onset and case reporting. For each scenario, we compared predicted case and wastewater trajectories, peak timing, and correlations between the two signals over the course of the epidemic.

Reduced shedding among vaccinated individuals (Fig. 5A-C)

Reducing viral shedding among vaccinated individuals modestly attenuated the wastewater signal, with peak viral load reduced by 6% under a 20% reduction and 12% under an 80% reduction. In the baseline scenario, reported cases peaked about five days before wastewater; under the strongest shedding reduction, this lag shortened to two days. Despite these shifts in magnitude and timing, correlations between wastewater and cases remained high throughout the epidemic ($r > 0.8$), with slightly stronger correlations late in the outbreak as reduced shedding dampened noise in the wastewater signal.

Wastewater transit time (Fig. 5D-F)

Varying mean wastewater transit time altered the timing of wastewater peak relative to cases. Shorter transit times increased temporal proximity between the two signals, whereas longer transit times primarily attenuated wastewater magnitude without substantially changing epidemic timing. Across scenarios spanning fast (1.9 days) to slow (7.3 days) transit, cases generally peaked before wastewater, but the estimated lag decreased to two days under fast transit and increased to six days under slow transit. Correlation profiles were broadly similar across scenarios, indicating that hydrodynamic processes can shift lead-lag relationships, particularly under faster transit, without substantially degrading overall signal alignment.

Reporting delays (Fig. 5G-I)

Reporting delay scenarios, anchored in empirically observed delays from line list data, had the strongest effect on temporal alignment. Short delays (5 days) accentuated the lead of cases relative to wastewater, whereas longer delays (10-14 days) progressively reduced this lead and, under the longest delays, resulted in wastewater peaking slightly before cases. Correlations remained high during epidemic growth and peak across all scenarios ($r = 0.85$–0.9), but diverged during the decline. Short delays produced sharper drops in reported cases relative to wastewater, whereas longer delays smoothed case trajectories and preserved closer alignment with wastewater signals in the epidemic tail.

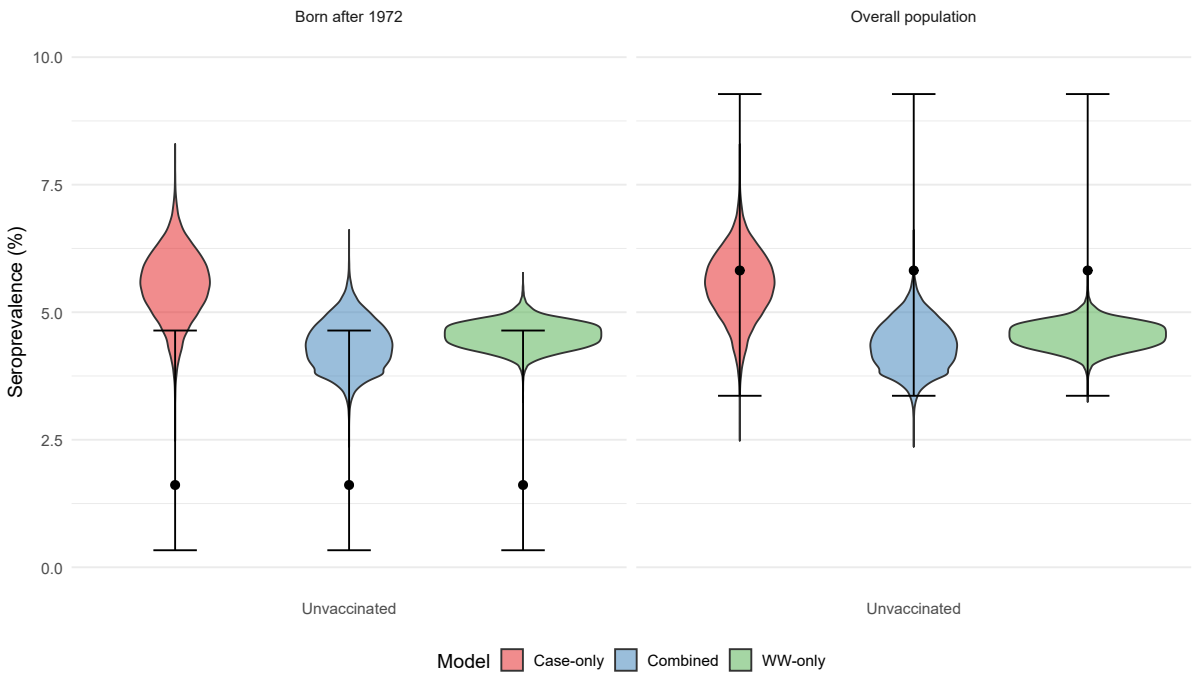


Figure 6: Comparison of model-predicted seroprevalence with observed seroprevalence from unvaccinated attendees of a sexual health clinic in July 2023 in the Lower Mainlands of British Columbia (Canada). Violin plots show the posterior distribution of predicted seroprevalence (cumulative infections / population) from the case-only (red), combined (blue), and wastewater-only (green) models. Black points and vertical lines represent the observed seroprevalence and exact binomial 95% confidence intervals from the serosurvey. Results are shown for the overall gbMSM population (right) and the subset born after 1972 (left), who are unlikely to have immunity from historic smallpox vaccination

External validation using seroprevalence data

We validated model-estimated infection burden by comparing predicted cumulative incidence with seroprevalence measured in July 2023 among attendees of a sexual health clinic in the Lower Mainland of British Columbia. Because seropositivity may reflect either prior infection or vaccination, analyses focused on unvaccinated participants and, separately, on those born after 1972, who are unlikely to have residual immunity from historic smallpox vaccination.

Across all three model variants, predicted seroprevalence among unvaccinated individuals closely aligned with observed seroprevalence from the clinic based survey (Fig. 6). Median model-predicted seroprevalence was 5.6% (95% CrI:4.2–6.8%) for the case-only model, 4.6% (95% CrI:3.9–5.2%) for the wastewater-only model, and 4.3% (95% CrI:3.4–5.3%) for the combined model, compared with an observed seroprevalence of 5.8% (95% CI:3.4–9.3%).

Among unvaccinated participants born after 1972, observed seroprevalence was lower (1.6%; 95% CI:0.3–4.6%) and overlapped the lower bounds of the model-predicted credible intervals across all three variants. Together, these findings indicate that model-inferred cumulative incidence was broadly consistent with independent serological evidence, supporting the plausibility of infection burden estimates derived from case data, wastewater data, and their integration.

Discussion

Accurately quantifying the population-level burden and risk of mpox infections is challenging, as stigma, care-seeking barriers, and presymptomatic or asymptomatic transmission can bias case-based surveillance. Wastewater-based surveillance offers a complementary, population-wide signal independent of healthcare access, but cannot on its own distinguish who is infected or directly quantify infections. By integrating wastewater viral load and laboratory-confirmed case-based surveillance data within a single transmission model, we leveraged the strengths of both systems. Linking infection, viral shedding, case detection, and wastewater transport allowed wastewater data to constrain total infections contributing to shedding, while case data informed the subset that were diagnosed and reported. This joint framework resolved discrepancies that arose when each data stream was analysed in isolation, constrained key epidemiological parameters, and produced more consistent reconstructions of transmission dynamics. Integrating both streams reduced uncertainty in peak prevalence and cumulative incidence and yielded infection burden estimates supported by independent seroprevalence data among unvaccinated individuals. Importantly, this approach enabled quantification of underascertainment in routine surveillance and revealed infections not apparent from case-based surveillance data alone. Together, these findings demonstrate the added value of wastewater surveillance beyond case reporting and show how combining multiple surveillance signals improves outbreak reconstruction for pathogens with substantial underascertainment [43].

Our analyses showed that integrating case-based surveillance with wastewater data substantially improved reconstruction of mpox transmission dynamics. Models calibrated to a single data stream yielded divergent epidemic trajectories, whereas joint calibration constrained both infection burden and reporting processes, producing reconstructions consistent with clinical and environmental surveillance and characterised by narrower uncertainty. The combined frame-

work further indicates that routine case-based surveillance substantially underestimated mpox infections during the 2022 outbreak, including symptomatic infections. Multiple symptomatic infections occurred for each reported case, consistent with stigma, delayed care seeking, limited testing access, and mild symptom presentation [38, 44, 45]. Wastewater data also revealed a larger pool of infections contributing to community viral shedding beyond those captured by clinical surveillance, including asymptomatic, presymptomatic, and undiagnosed infections. This aligns with SARS-CoV-2 wastewater studies showing that signals integrate infections across the clinical spectrum and imply infection burdens several-fold higher than reported cases [25, 27]. Together, these findings reinforce the complementary roles of wastewater and case surveillance. While case data remain essential for monitoring clinically apparent disease, wastewater provides a population-wide lens on hidden transmission. Integrating both streams therefore offers a more complete and resilient framework for epidemic reconstruction, particularly for infections characterised by substantial underascertainment [46, 47].

Transmission early in the outbreak was concentrated among a small group of highly connected individuals, producing a wastewater signal dominated by this group. As transmission declined within this core population and spread to individuals with fewer partners, the dominant contributors to viral shedding shifted. As wastewater reflects infections regardless of clinical detection, signals can remain elevated even as transmission decreases in the initially dominant group. Here, rising contributions from the medium activity group accompanied a rapid decline among the highest activity group, indicating redistribution of transmission rather than epidemic resolution. Our findings align with prior work showing that mpox transmission is concentrated in highly connected subpopulations but evolves as susceptibility is depleted [21, 40, 48, 49]. They reinforce evidence that early vaccination and intensified case finding in core groups are critical for outbreak control and that, as transmission diffuses, interventions should target broader segments of gbMSM populations. More broadly, our results illustrate how group-structured modelling can inform targeted surveillance and optimize intervention timing for mpox and other network-driven infections.

Counterfactual analyses showed that the temporal relationship between wastewater viral load and reported mpox cases was shaped by biological, infrastructural, and surveillance processes. Changes in viral shedding following vaccination, variation in wastewater transport, and delays in case reporting influenced how closely wastewater and case signals aligned, underscoring that lead-lag relationships were not intrinsic to wastewater surveillance but emerged from system dynamics. Reduced shedding among vaccinated individuals attenuated wastewater signals and partially decoupled wastewater trends from reported incidence. Although direct evidence for vaccine effects on mpox shedding remains limited [50], similar dynamics have been observed for SARS-CoV-2, where vaccination altered wastewater-case relationships depending on disease severity and care-seeking behaviour [51, 52]. Together, these findings suggest that vaccination can reshape how wastewater reflects transmission, with the direction and magnitude of this effect depending on shedding kinetics, clinical severity, and surveillance context.

Hydrodynamic processes also influenced wastewater-case alignment by shifting the timing of wastewater peak relative to cases, particularly under faster transit conditions. However, correlation profiles remained broadly similar across transit scenarios, indicating that while hy-

drodynamics can alter lead-lag relationships, they do not substantially degrade overall signal alignment [25, 46]. By contrast, reporting delays exerted the strongest influence on temporal alignment. Changes in testing and notification practices determined whether wastewater appeared to lead or lag case data, showing that wastewater has no fixed temporal advantage over case-based surveillance [53, 54]. Instead, relative timing reflects the interaction between shedding kinetics, behaviour, and health-system processes, making these operational factors essential when using wastewater data for outbreak monitoring and public health decision-making [26].

Comparison with independent serological data provided an external plausibility check on reconstructed infection burden. The consistency between model-inferred cumulative incidence and observed seroprevalence supports the overall scale of infections estimated from case data, wastewater data, and their integration, lending confidence to the combined surveillance framework. Interpretation remains constrained by the clinic-based sample, limited size, potential inclusion of vaccine-derived antibodies, and the delay between the outbreak and the July 2023 serosurvey. Despite these limitations, the agreement between modelled infection burden and observed seroprevalence suggests that the inferred epidemic size is epidemiologically plausible. Serology-based validations have similarly been used to benchmark epidemic size estimates for other pathogens. For example, Salje et al.[55] confirmed that model inferred SARS-CoV-2 infections in France matched observed seroprevalence (0–3% observed vs 1–3% modelled) underscoring the value of independent serological benchmarks to strengthen confidence in modelled estimates.

Our model has several limitations that point to directions for future work. First, wastewater transport was represented using a simple advection–dispersion framework [25] that captures average transit time and signal smoothing but does not resolve heterogeneity within sewer networks [46]. Although local variation may affect short-term fluctuations, this simplification is unlikely to materially influence inference on epidemic-scale dynamics. Second, stage-specific shedding rates were fixed because of limited empirical data, potentially under-representing individual-level heterogeneity. We also did not model differences in disease progression or post-infection shedding by vaccination status. While vaccination reduces susceptibility and severity, evidence on its effects on mpox shedding kinetics remains limited; we therefore explored this uncertainty through targeted sensitivity analyses. Third, transmission was represented using an effective parameter rather than explicitly modelling behavioural changes such as early self-isolation after symptom onset. Such behaviours, widely reported during the 2022 outbreak, could reduce onward transmission without proportionally reducing wastewater shedding. Incorporating these mechanisms could refine estimates of epidemic timing and improve interpretation of case-wastewater alignment. Finally, wastewater surveillance for mpox remains an emerging field with limited empirical validation linking viral concentrations to infection prevalence. Although our framework integrates wastewater and case data and was supported by independent serological comparisons, further empirical studies are needed to refine shedding parameters, improve calibration, and reduce uncertainty in future applications.

This study provides, to our knowledge, the first mechanistic framework linking reported cases and wastewater viral load for mpox, clarifying how these surveillance streams complement one another. By jointly modelling transmission, viral shedding, case detection, and wastewater

transport, we demonstrate that integrating wastewater with case data resolves systematic biases inherent in single-stream analyses and yields more precise, epidemiologically coherent estimates of infection burden supported by independent serology. Wastewater data constrain epidemic scale independently of healthcare-seeking behaviour, revealing substantial underascertainment invisible to routine case surveillance and clarifying shifts in transmission across sexual activity groups. Counterfactual analyses further show that wastewater does not have a fixed lead or lag relative to cases, but reflects underlying epidemiological and operational conditions. Beyond mpox, this framework provides a blueprint for integrating multi-stream surveillance data to improve situational awareness, guide targeted interventions, and strengthen early warning for underascertained infections.

Data availability

The mpox case-based surveillance, wastewater and vaccination coverage datasets that support the findings of this study are not openly available and may be available from the corresponding author upon reasonable request. Data are in controlled access storage at the British Columbia Centre for Disease Control.

Code availability

All analyses were performed in R. The code supporting this study is openly available at: `https://github.com/CarolineNM/mpox25b`.

Author contribution

C.M. developed the methodology, conducted the formal analysis, and wrote the original draft of the manuscript. A.M.N. and N.A.P contributed to wastewater data curation, validation and manuscript review and editing. A.C.M. and A.N.J. contributed to serological data curation,validation and manuscript review and editing.C.G.X, K.A.T., V.R., K.B. and M.G. contributed to case surveillance data curation, validation, and manuscript review and editing. N.C.K. and C.S.M. contributed to wastewater data curation, manuscript review and editing. M.M.-G., S.M., contributed to methodology, resources, and provided guidance on study design and analysis. H.S. and M.A.I. supervised the study and contributed to conceptualization, methodology, resources, and funding acquisition. All authors contributed to interpretation of the results, reviewed the manuscript, and approved the final version.

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Competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

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