RESEARCH ARTICLE

Real-time forecasting the trajectory of monkeypox outbreaks at the national and global levels, July–October 2022

Amanda Bleichrodt[†], Sushma Dahal[†], Kevin Maloney, Lisa Casanova, Ruiyan Luo and Gerardo Chowell[*]

Abstract

Background   Beginning May 7, 2022, multiple nations reported an unprecedented surge in monkeypox cases. Unlike past outbreaks, differences in affected populations, transmission mode, and clinical characteristics have been noted. With the existing uncertainties of the outbreak, real-time short-term forecasting can guide and evaluate the effectiveness of public health measures.

Methods   We obtained publicly available data on confirmed weekly cases of monkeypox at the global level and for seven countries (with the highest burden of disease at the time this study was initiated) from the Our World in Data (OWID) GitHub repository and CDC website. We generated short-term forecasts of new cases of monkeypox across the study areas using an ensemble n-sub-epidemic modeling framework based on weekly cases using 10-week calibration periods. We report and assess the weekly forecasts with quantified uncertainty from the top-ranked, second-ranked, and ensemble sub-epidemic models. Overall, we conducted 324 weekly sequential 4-week ahead forecasts across the models from the week of July 28th, 2022, to the week of October 13th, 2022.

Results   The last 10 of 12 forecasting periods (starting the week of August 11th, 2022) show either a plateauing or declining trend of monkeypox cases for all models and areas of study. According to our latest 4-week ahead forecast from the top-ranked model, a total of 6232 (95% PI 487.8, 12,468.0) cases could be added globally from the week of 10/20/2022 to the week of 11/10/2022. At the country level, the top-ranked model predicts that the USA will report the highest cumulative number of new cases for the 4-week forecasts (median based on OWID data: 1806 (95% PI 0.0, 5544.5)). The top-ranked and weighted ensemble models outperformed all other models in short-term forecasts.

Conclusions   Our top-ranked model consistently predicted a decreasing trend in monkeypox cases on the global and country-specific scale during the last ten sequential forecasting periods. Our findings reflect the potential impact of increased immunity, and behavioral modification among high-risk populations.

Keywords   Monkeypox, Real-time forecasts, Mathematical model, Sub-epidemic, Ensemble model, Global, Country level

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Background

On May 7th, 2022, a case of monkeypox (mpox) with recent travel to Nigeria was reported in England [1, 2]. Shortly after, the Centers for Disease Control and Prevention (CDC) identified a case of monkeypox in Massachusetts on May 15th, 2022 [3]. Since then, multiple nations, including the U.S., have reported a surge in monkeypox

Bleichrodt *et al. BMC Medicine*   (2023) 21:19

Page 2 of 20

cases, mostly among males within the communities of gay, bisexual, and other men who have sex with men (MSM) [4–6]. The World Health Organization (WHO) declared monkeypox a global health emergency on July 23rd, 2022 [7]. As of November 23rd, 2022, over 79,900 monkeypox cases have been reported in non-endemic countries, especially in the USA, Spain, and Brazil, during the ongoing outbreak [8]. Given that this is an emerging infection in non-endemic countries, with little historical information about how outbreaks might unfold, mathematical models can help generate real-time forecasts of the trajectory of the epidemics and guide public health measures appropriate for a given geographic setting.

Monkeypox is an endemic zoonotic virus in Africa, most similar in clinical presentation to the Variola (Smallpox) virus [9]. Both are part of the *Orthopoxvirus* genus, which includes other viruses such as cowpox and Vaccinia virus—used in smallpox vaccines [9, 10]. Monkeypox symptoms include, but are not limited to, flu-like symptoms followed by a raised rash on the face and extremities. The incubation period is usually 6–13 days, with a symptomatic period ranging from 2 to 4 weeks [9]. Fortunately, monkeypox is not an airborne pathogen. Instead, transmission is mainly driven by prolonged close contact with infected individuals or direct contact with skin lesions, respiratory secretions, or recently contaminated objects—a feature that may facilitate control through basic public health measures [9].

The ability to forecast country-specific epidemic trajectories is particularly useful in an outbreak like this, which paints a unique epidemiological picture compared to past outbreaks within both endemic and non-endemic countries [4, 6, 11, 12]. For instance, sexual and intimate contact, specifically between men, has driven the great majority of infections [5, 13, 14]. Likewise, over 98% of cases in the USA and Spain are male, and most have identified as MSM [13, 15]. Cases of the ongoing outbreak are less likely to report prodromal symptoms, and rash occurs most frequently in the genital region [4, 13]. The scale of community spread is unprecedented [16].

While much has been learned about the epidemiology of this emerging outbreak during the last few months, substantial uncertainties remain about the effect of several variables on the epidemic trajectory, including the frequency and role of asymptomatic individuals, the role of pre-existing immunity from previous smallpox immunization campaigns, and the efficacy of available vaccines [17]. In this context, semi-mechanistic growth models are especially suitable for conducting short-term forecasts to guide response efforts and evaluate the impact of control measures, including behavior changes that mitigate transmission rates, contact tracing, and vaccination, on growth

trends [18]. Previous real-time forecasting studies have employed a variety of mathematical models in the context of influenza, SARS, Ebola, and COVID-19 [19–23]. Here, we employ an ensemble sub-epidemic modeling framework to characterize epidemic trajectories that result from sub-epidemics aggregation through an optimization process [19]. This framework has yielded competitive performance in short-term forecasts of various infectious disease outbreaks [19, 23]. In this study, we generate 4-week ahead forecasts of laboratory-confirmed cases of monkeypox in near real-time at the global level and for nations that have reported the great majority of the cases: Brazil, Canada, England, France, Germany, Spain, and the USA. We also evaluate the model fit and performance of the forecasts based on the mean absolute error (MAE), mean square error (MSE), 95% prediction interval coverage (PI), and weighted interval score (WIS).

Methods
Data
We obtained weekly updates of the daily confirmed monkeypox cases by reporting date from publicly available sources by the CDC and the Our World in Data (OWID) GitHub repository [24, 25]. At the global level and for countries that have reported the great majority of the cases, including Brazil, Canada, England, France, Germany, Spain, and the USA, we retrieved daily case series from the GitHub Our World in Data (OWID) repository [8, 25]. We reported forecasts based on CDC and OWID team data for the USA. The CDC and OWID data sources define a confirmed case as a person with a laboratory-confirmed case of monkeypox [26, 27]. Data were downloaded every Wednesday evening from the CDC and every Friday afternoon from the GitHub Our World in Data (OWID) repository from the week of July 28th, 2022, through the week of October 13th, 2022. For the week of July 28th, 2022, data posted by the OWID team on August 9th, 2022, was used to produce the forecast as it was the earliest data available.

The *n*-sub-epidemic modeling framework
A detailed description of our modeling framework is given in ref. [19]. In this n-sub-epidemic modeling framework, epidemic trajectories are modeled as the aggregation of overlapping and asynchronous sub-epidemics. A sub-epidemic follows the 3-parameter generalized-logistic growth model (GLM), which has displayed competitive performance [28–30]. This model is given by the following differential equation:

$$\frac{dC(t)}{dt} = C'(t) = rC^p(t)\left(1 - \frac{C(t)}{K_0}\right),$$

where $C(t)$ denotes the cumulative number of cases at time t and $\frac{dC(t)}{dt}$ describes the curve of daily cases over time t. The parameter r is positive, denoting the growth rate per unit of time, K_0 is the final outbreak size, and $p \in [0,1]$ is the "scaling of growth" parameter which allows the model to capture early sub-exponential and exponential growth patterns. If $=0$, this equation describes a constant number of new cases over time, while $p = 1$ indicates that the early growth phase is exponential. Intermediate values of p ($0 < p < 1$) describe early sub-exponential (e.g., polynomial) growth dynamics.

An n-sub-epidemic trajectory comprises n overlapping sub-epidemics and is given by the following system of coupled differential equations:

$$\frac{dC_i(t)}{dt} = C_i'(t) = A_i(t) r_i C_i^{p_i}(t) \left(1 - \frac{C_i(t)}{K_{0i}}\right),$$

where $C_i(t)$ tracks the cumulative number of cases for sub-epidemic i, and the parameters that characterize the shape of the ith sub-epidemic are given by (r_i, p_i, K_{0i}), for $i = 1, ..., n$. Thus, the 1-sub-epidemic model is equivalent to the generalized growth model described above. When $n > 1$, we model the onset timing of the $(i+1)_{th}$ sub-epidemic, where $(i+1) \leq n$, by employing an indicator variable given by $A_i(t)$ so that the $(i+1)_{th}$ sub-epidemic is triggered when the cumulative curve of the i_{th} sub-epidemic exceeds C_{thr}.

The $(i+1)_{th}$ sub-epidemic is only triggered when $C_{thr} \leq K_{0i}$. Then, we have:

$$A_i(t) = \begin{cases} 1, C_{i-1}(t) > C_{thr} \\ 0, Otherwise \end{cases} \quad i = 2, \ldots n,$$

where $A_1(t) = 1$ for the first sub-epidemic. Hence, the total number of parameters that are needed to model an n-sub-epidemic trajectory is given by $3n+1$. The initial number of cases is given by $C_1(0) = I_0$, where I_0 is the initial number of cases in the observed data. The cumulative curve of the n-sub-epidemic trajectory is given by:

$$C_{tot}(t) = \sum_{i=1}^{n} C_i(t).$$

Hence, this modeling framework is suitable for diverse epidemic patterns including those characterized by multiple peaks.

Parameter estimation for the n-sub-epidemic model

The time series of new weekly monkeypox cases are denoted by:

$y_{t_j} = y_{t_1}, y_{t_2}, \ldots, y_{t_{n_d}}$ where $j = 1, 2, ..., n_d$

Here, t_j are the time points for the time series data, n_d is the number of observations. Using these case series, we estimate a total of $3n+1$ model parameters, namely $\Theta = (C_{thr}, r_1, p_1, K_{01}, ..., r_n, p_n, K_{0n})$. Let $f(t, \Theta)$ denote the expected curve of new monkeypox cases of the epidemic's trajectory. We can estimate model parameters by fitting the model solution to the observed data via non-linear least squares [31] or via maximum likelihood estimation assuming a specific error structure [32]. For nonlinear least squares, this is achieved by searching for the set of parameters $\hat{\Theta}$ that minimizes the sum of squared differences between the observed data $y_{t_j} = y_{t_1}, y_{t_2}, \ldots, y_{t_{n_d}}$ and the model mean $f(t, \Theta)$. That is, $\Theta = (C_{thr}, r_1, p_1, K_{01}, ..., r_n, p_n, K_{0n})$ is estimated by $\hat{\Theta} = \text{argmin} \sum_{j=1}^{n_d} \left(f(t_j, \Theta) - y_{t_j}\right)^2$.

We quantify parameter uncertainty using a bootstrapping approach described in [33], which allows the computation of standard errors and related statistics in the absence of closed-form solutions. To that end, we use the best-fit model $f\left(t, \hat{\Theta}\right)$ to generate B-times replicated simulated datasets of size n_d, where the observation at time t_j is sampled from a normal distribution with mean $f\left(t_j, \hat{\Theta}\right)$ and variance $\frac{\sum_{j=1}^{n_d} \left(f\left(t_j, \hat{\Theta}\right) - y_{t_j}\right)^2}{n_d - (3n+1)}$. Then, we refit the model to each B simulated dataset to re-estimate each parameter. The new parameter estimates for each realization are denoted by $\hat{\Theta}_b$ where $b = 1, 2, ..., B$. Using the sets of re-estimated parameters $\left(\hat{\Theta}_b\right)$, the empirical distribution of each estimate can be characterized, and the resulting uncertainty around the model fit can similarly be obtained from $f\left(t, \hat{\Theta}_1\right), f\left(t, \hat{\Theta}_2\right), \ldots, f\left(t, \hat{\Theta}_B\right)$. We run the calibrated model forward in time to generate short-term forecasts with quantified uncertainty.

Selecting the top-ranked sub-epidemic models

We used the AIC_c values of the set of best fit models based on one and two subepidemics to select the top-ranked sub-epidemic models. We ranked the models from best to worst according to their AIC_c values, which is given by [34, 35]:

$$AIC_c = n_d \log(SSE) + 2m + \frac{2m(m+1)}{n_d - m - 1}$$

where $SSE = \sum_{j=1}^{n_d} \left(f\left(t_j, \hat{\Theta}\right) - y_{t_j}\right)^2$, $m = 3n+1$ is the number of model parameters, and n_d is the number of data points. Parameters from the above formula for AIC_c are estimated from the nonlinear least-squares fit, which implicitly assumes normal distribution for error.

Bleichrodt *et al. BMC Medicine*   (2023) 21:19

Page 4 of 20

Table 1 Mean performance metrics of the forecasts generated by the sub-epidemic models

	Model	Brazil	Canada	England	France	Germany	Spain	US (OWID)	US (CDC)	World
Mean absolute error (MAE)	Top-ranked	**377.90**	**20.13**	**38.36**	119.13	**21.31**	**76.59**	1485.54	**1169.67**	1056.77
	2nd ranked	749.38	25.41	46.50	**105.15**	42.28	154.15	**892.71**	2597.93	1403.50
	Ensemble (Weighted)	**377.90**	**20.13**	**38.36**	119.13	**21.31**	**76.59**	1485.54	**1169.67**	1056.77
	Ensemble (Unweighted)	408.27	22.04	39.80	107.87	23.22	108.64	1085.13	1325.64	**1015.21**
Mean square error (MSE)	Top-ranked	**383,525.66**	1468.89	**3833.80**	45,724.96	**806.13**	**12,347.01**	6,071,637.86	**5,346,637.83**	2,204,026.11
	2nd ranked	2,413,843.43	1420.74	4436.03	**37,874.07**	3591.54	45,935.30	**1,366,006.66**	57,778,292.62	3,512,916.37
	Ensemble (Weighted)	**383,525.66**	1468.89	**3833.80**	45,724.96	**806.13**	**12,347.01**	6,071,637.86	**5,346,637.83**	2,204,026.11
	Ensemble (Unweighted)	485,613.55	**1405.55**	3889.00	41,981.04	869.00	29,812.68	2,087,350.98	7,742,719.36	**1,757,084.06**
Percent coverage of the 95% prediction interval (PI)	Top-ranked	68.75	**87.50**	90.63	87.50	**100.00**	**100.00**	71.88	56.25	84.38
	2nd ranked	68.75	81.25	**93.75**	**90.63**	93.75	93.75	**87.50**	**75.00**	**90.63**
	Ensemble (Weighted)	68.75	**87.50**	90.63	87.50	**100.00**	**100.00**	71.88	56.25	84.38
	Ensemble (Unweighted)	**75.00**	**87.50**	90.63	**90.63**	96.88	**100.00**	**93.75**	**75.00**	**93.75**
Weighted Interval Score (WIS)	Top-ranked	276.22	16.42	26.48	98.80	13.74	55.81	1021.17	893.27	677.85
	2nd ranked	496.21	19.32	32.37	91.24	27.84	105.07	799.28	1568.86	834.45
	Ensemble (Weighted)	276.22	16.42	26.48	98.80	13.74	55.81	1021.17	893.27	677.85
	Ensemble (Unweighted)	337.07	17.28	28.36	92.81	17.40	68.06	708.94	1027.57	669.14

The mean performance metrics of the forecasts generated by the sub-epidemic models' performance across 8 sequential forecasting periods (Week of July 28th through the week of September 15th, 2022) for each geographical area. Only weeks in which observed case data was available are included. Values highlighted in bold correspond to best performing model for a given geographical region and metric

Bleichrodt *et al. BMC Medicine*   (2023) 21:19

Page 5 of 20

Constructing ensemble n-sub-epidemic models

We generate ensemble models from the weighted combination of the highest-ranking sub-epidemic models as deemed by the AIC_{c_i} for the ith ranked model where $AIC_{c_1} \leq \cdots \leq AIC_{c_I}$ and $i = 1, ..., I$. An ensemble derived from the top-ranking I models is denoted by Ensemble(I). Thus, Ensemble (2) refers to the ensemble model generated from the weighted combination of the top-ranking 2 sub-epidemic models. We compute the weight w_i for the ith model, $i = 1, ..., I$, where $\sum w_i = 1$ as follows:

$w_i = \frac{l_i}{l_1 + l_2 + \cdots + l_I}$ for all $i = 1, 2, ..., I$,

where l_i is the relative likelihood of model i, which is given by $l_i = e^{((AIC_{min} - AIC_i)/2)}$ [36], and hence $w_I \leq ... \leq w_1$. The prediction intervals based on the ensemble model can be obtained using a bootstrap approach similar as before. We employed the first-ranked and the
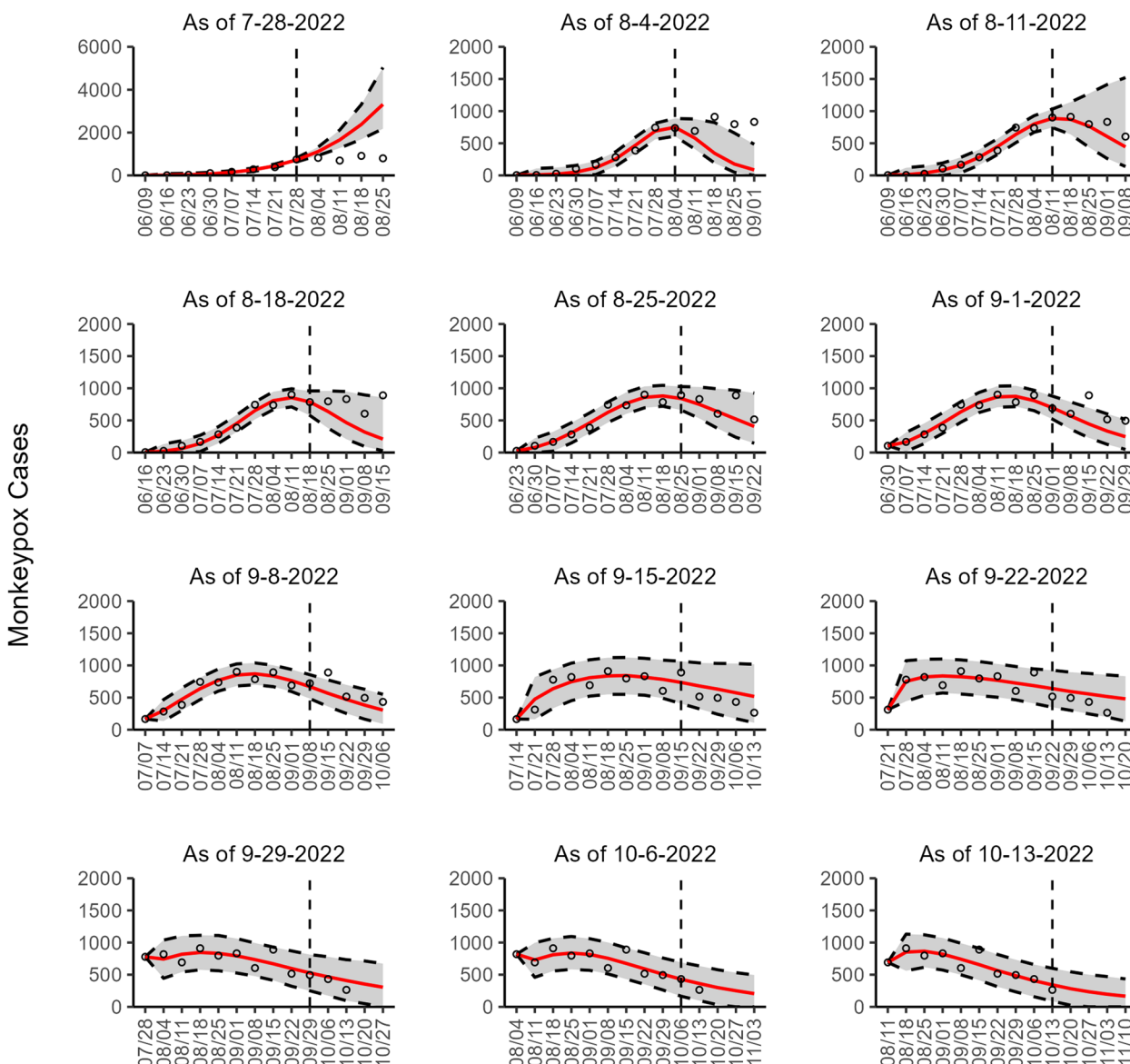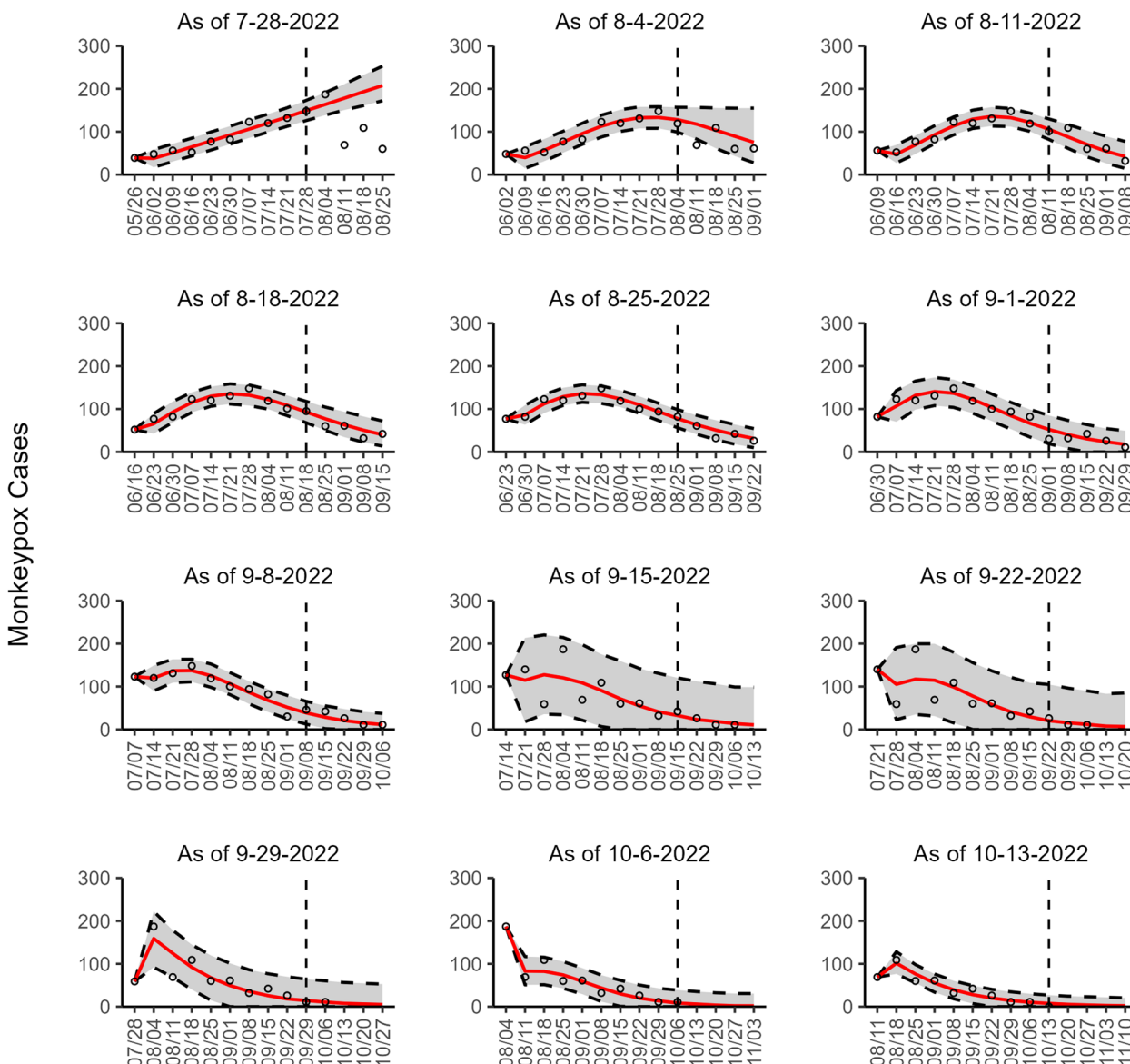

Fig. 1 The overlayed forecasted and reported monkeypox cases for the weeks of 7/28/2022 through the week of 10/13/2022 for Brazil. The forecasts are derived from the weighted ensemble sub-epidemic model using 10-week calibration data, and the reported cases are obtained from the OWID GitHub [25]. The black circles to the left of the vertical line represent the reported cases as of the Friday of the forecast period; the solid red line corresponds to the best fit model; the dashed black lines correspond to the 95% prediction intervals. The black circles to the right of the vertical line represent the reported case counts (as of 10/21/2022) for the corresponding date. The vertical dashed black line indicates the start of the forecast period. For the week of 7/28/2022, data posted by the OWID team on 8/9/2022 was used to produce the forecast as it was the earliest version of data available

Bleichrodt *et al. BMC Medicine*   (2023) 21:19

Page 6 of 20

second-ranked models to derive the ensemble forecasts. AIC_c values of the top models for the most recent forecast can be found in figure 1s (Additional file 1) [24, 25].

Forecasting strategy

Using a 10-week calibration period for each model, we have conducted 324 real-time weekly sequential 4-week ahead forecasts across studied areas and models (week of July 28th–week of October 13th, 2022) thus far. At

the national and global levels, we also report forecasting performance metrics for 8 sequential forecasting periods covering the weeks of July 28th, 2022, through September 15, 2022, for which data was available to assess the 4-week ahead forecasts. We also compare the predicted cumulative cases for the 4-week forecasts across models for a given setting. Cumulative cases for a given model were calculated as the sum of median number of new cases predicted during the 4-week forecast. Forecasts
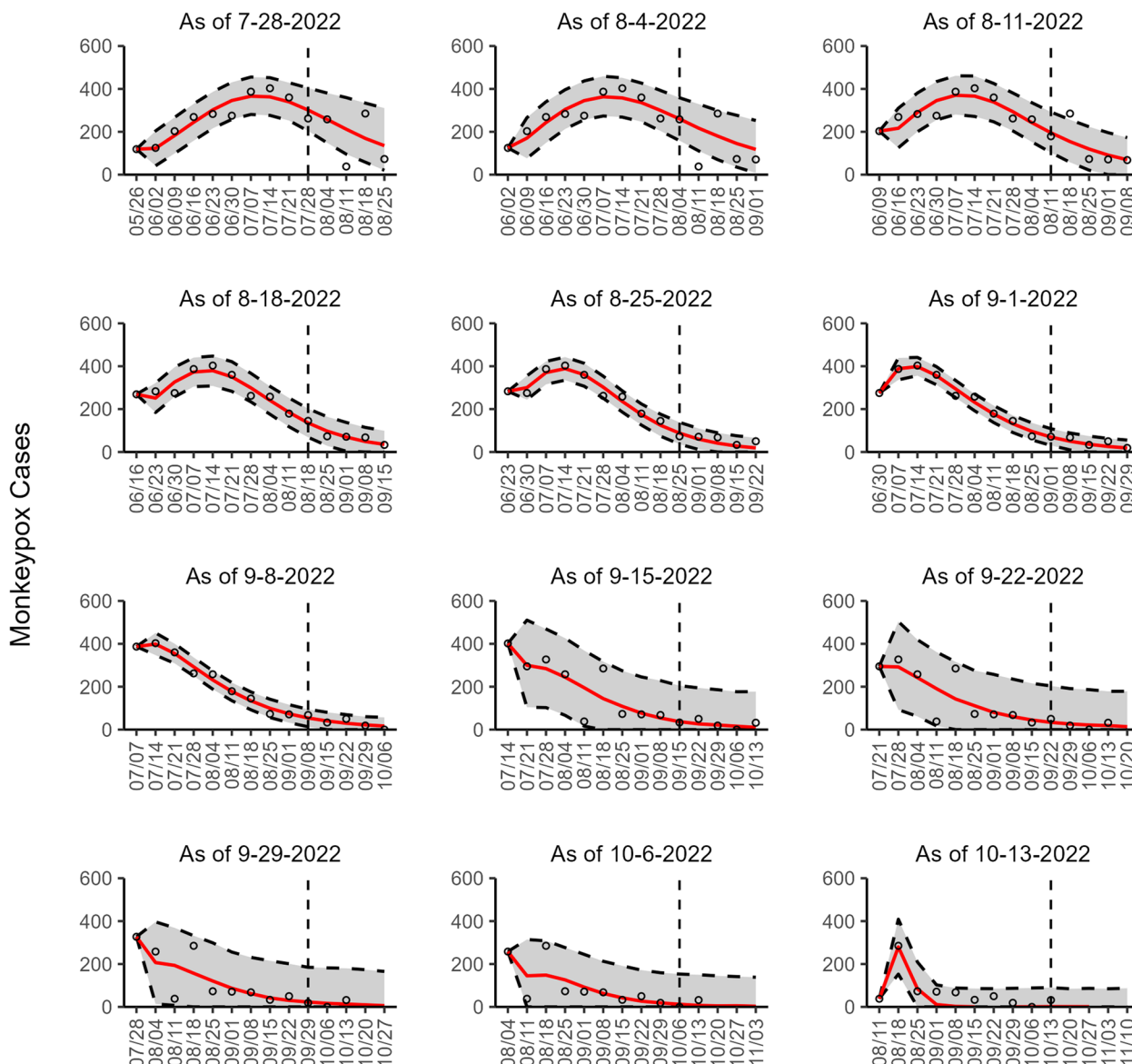

Fig. 2 The overlayed forecasted and reported monkeypox cases for the weeks of 7/28/2022 through the week of 10/13/2022 for Canada. The forecasts are derived from the weighted ensemble sub-epidemic model using 10-week calibration data, and the reported cases are obtained from the OWID GitHub [25]. The black circles to the left of the vertical line represent the reported cases as of the Friday of the forecast period; the solid red line corresponds to the best fit model; the dashed black lines correspond to the 95% prediction intervals. The black circles to the right of the vertical line represent the reported case counts (as of 10/21/2022) for the corresponding date. The vertical dashed black line indicates the start of the forecast period. For the week of 7/28/2022, data posted by the OWID team on 8/9/2022 was used to produce the forecast as it was the earliest version of data available

Bleichrodt *et al. BMC Medicine*   (2023) 21:19

Page 7 of 20

were evaluated using data reported during the week of October 13th, 2022.

Performance metrics

Across geographic areas, we assessed the quality of our model fit and performance of the short-term forecasts for each model by using four standard performance metrics: the mean squared error (MSE) [37], the mean absolute error (MAE) [38], the coverage of the 95% prediction interval (PI) [37], and the weighted interval score (WIS) [20, 39]. While MSE and MAE assess the average deviations of the mean model fit to the observed data, the coverage of the 95% PI and the weighted interval score consider the uncertainty of the forecasts.

Fig. 3 The overlayed forecasted and reported monkeypox cases for the weeks of 7/28/2022 through the week of 10/13/2022 for England. The forecasts are derived from the weighted ensemble sub-epidemic model using 10-week calibration data, and the reported cases are obtained from the OWID GitHub [25]. The black circles to the left of the vertical line represent the reported cases as of the Friday of the forecast period; the solid red line corresponds to the best fit model; the dashed black lines correspond to the 95% prediction intervals. The black circles to the right of the vertical line represent the reported case counts (as of 10/21/2022) for the corresponding date. The vertical dashed black line indicates the start of the forecast period. For the week of 7/28/2022, data posted by the OWID team on 8/9/2022 was used to produce the forecast as it was the earliest version of data available

Bleichrodt *et al. BMC Medicine*   (2023) 21:19

Page 8 of 20

Results

Performance of forecasts

Table 1 summarizes the mean forecasting performance metrics of the models by geographic area. Figures 2s-10s (Additional file 1), and tables 1s-4s (Additional file 2) show the forecasting performance metrics for each of the 8 sequential forecasts. Regarding the average MAE, MSE, and WIS across forecasting periods, the first-ranked and weighted ensemble models outperformed the other

models for most studied areas except for France, the USA (OWID), and the global level (Table 1; Additional file 2: Table 5s). The individual MAE, MSE, and WIS values for each of the eight sequential forecasts evaluated are shown in tables 1s, 2s, and 4s, respectively (Additional file 2).

Regarding the 95% PI coverage, most models had similar coverage value across the 8 sequential forecasts. For example, in Canada, France, England, and Germany, all four models had the same 95% PI coverage in 7 of 8
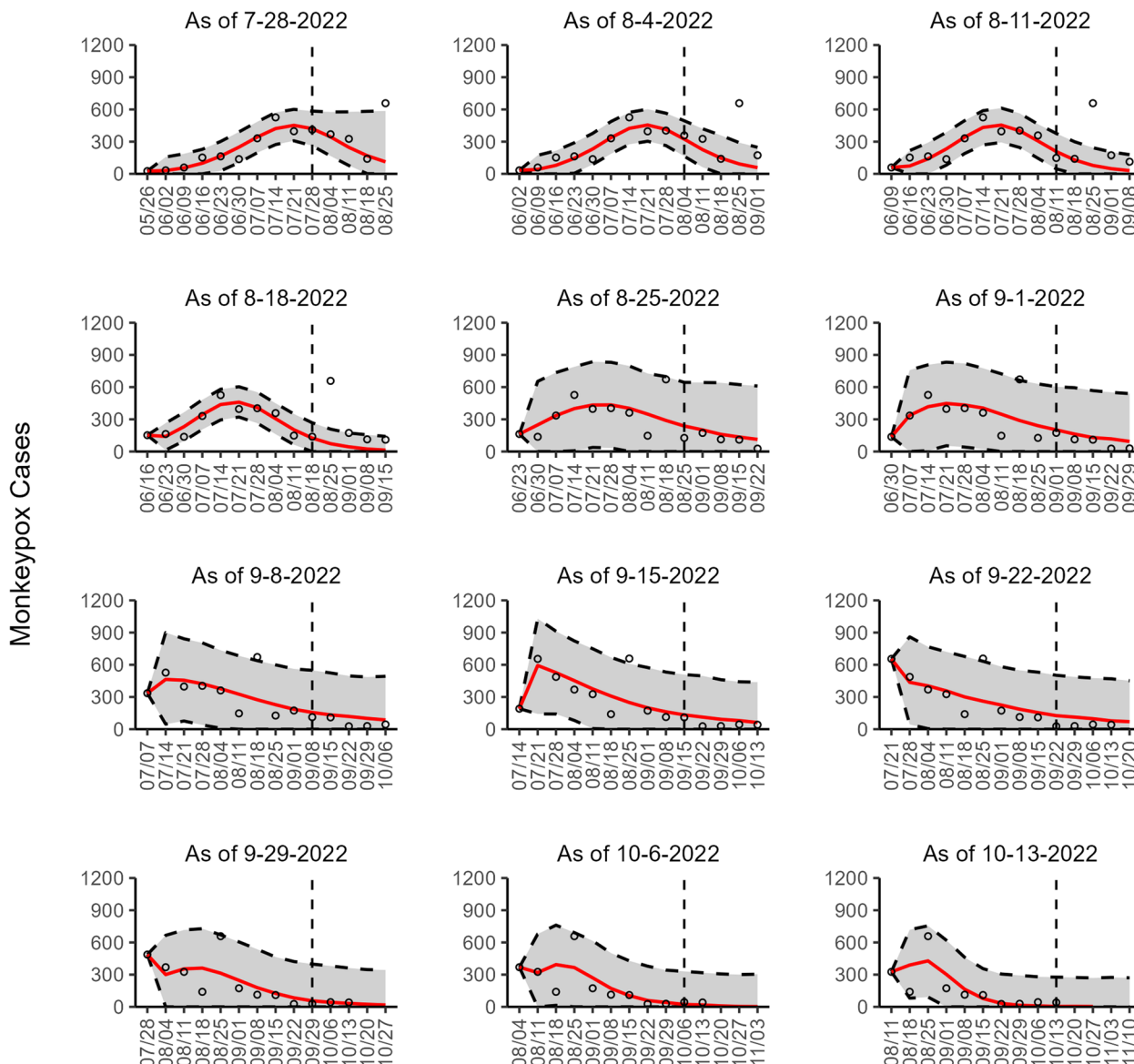
Fig. 4 The overlayed forecasted and reported monkeypox cases for the weeks of 7/28/2022 through the week of 10/13/2022 for France. The forecasts are derived from the weighted ensemble sub-epidemic model using 10-week calibration data, and the reported cases are obtained from the OWID GitHub [25]. The black circles to the left of the vertical line represent the reported cases as of the Friday of the forecast period; the solid red line corresponds to the best fit model; the dashed black lines correspond to the 95% prediction intervals. The black circles to the right of the vertical line represent the reported case counts (as of 10/21/2022) for the corresponding date. The vertical dashed black line indicates the start of the forecast period. For the week of 7/28/2022, data posted by the OWID team on 8/9/2022 was used to produce the forecast as it was the earliest version of data available

forecasts, with lower coverage value during early forecasting periods (25 to 75%) and higher coverage value during later forecasting periods (100%) (Additional file 2: Table 3s). Across 72 forecasts involving all study areas (2 datasets for the U.S.), 54.17% (39/72) of the 95% PI coverage was 100% for all four models. In general, the 95% PI coverage improved during the declining phase compared to the earlier periods (Additional file 1: Figs. 2s-10s). Figures 1, 2, 3, 4, 5, 6, 7, 8, and 9 show the forecasts for the
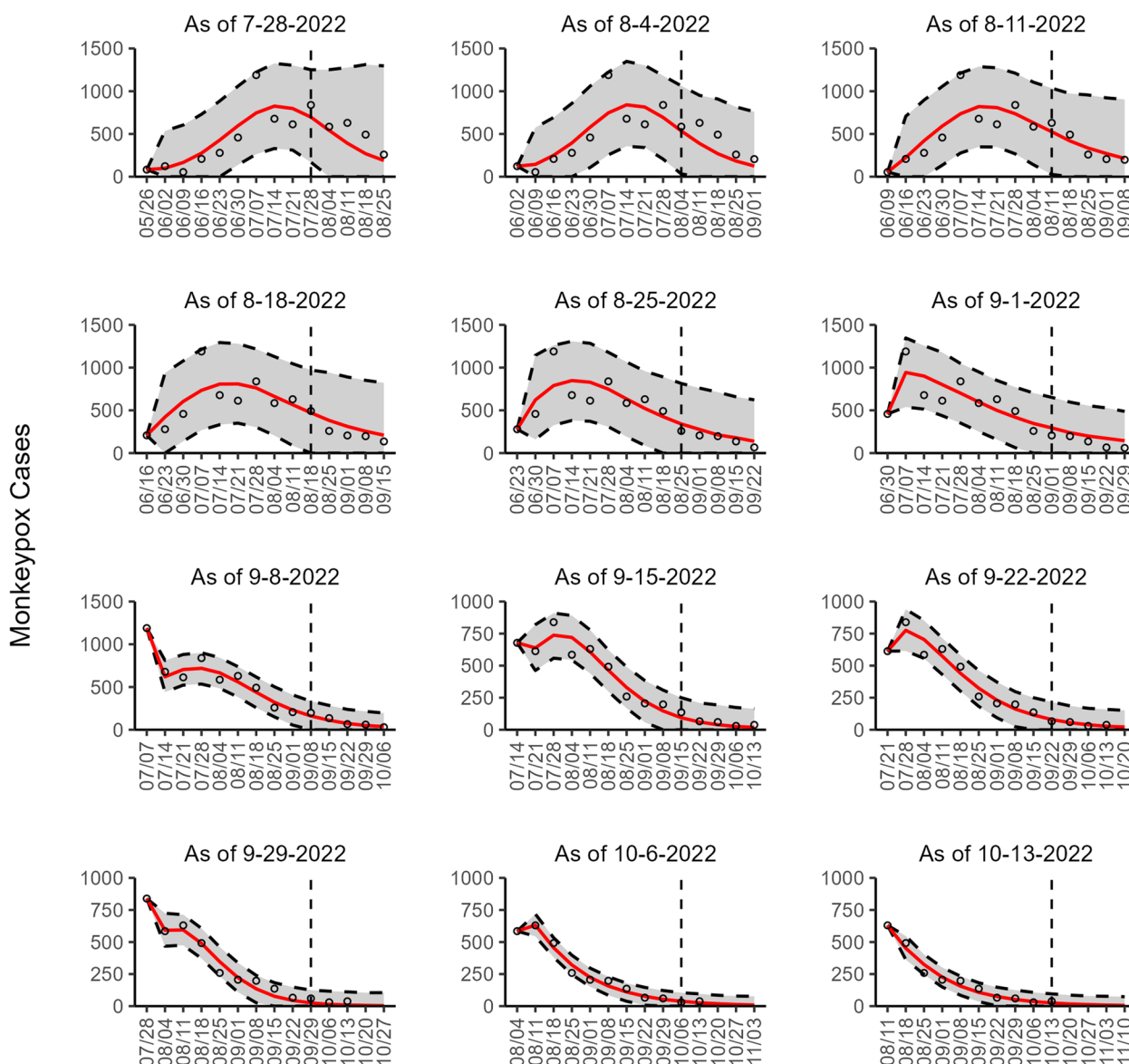
weighted ensemble model for each study area while the forecasts from the top-ranked and second-ranked models are given in supplementary figures (Additional file 1: Figs. 11s-28s).

Performance of the model fit

The mean calibration performance metrics are shown in table 6s (Additional file 2). Overall, the sub-epidemic models yielded good fits for the 10-week calibration
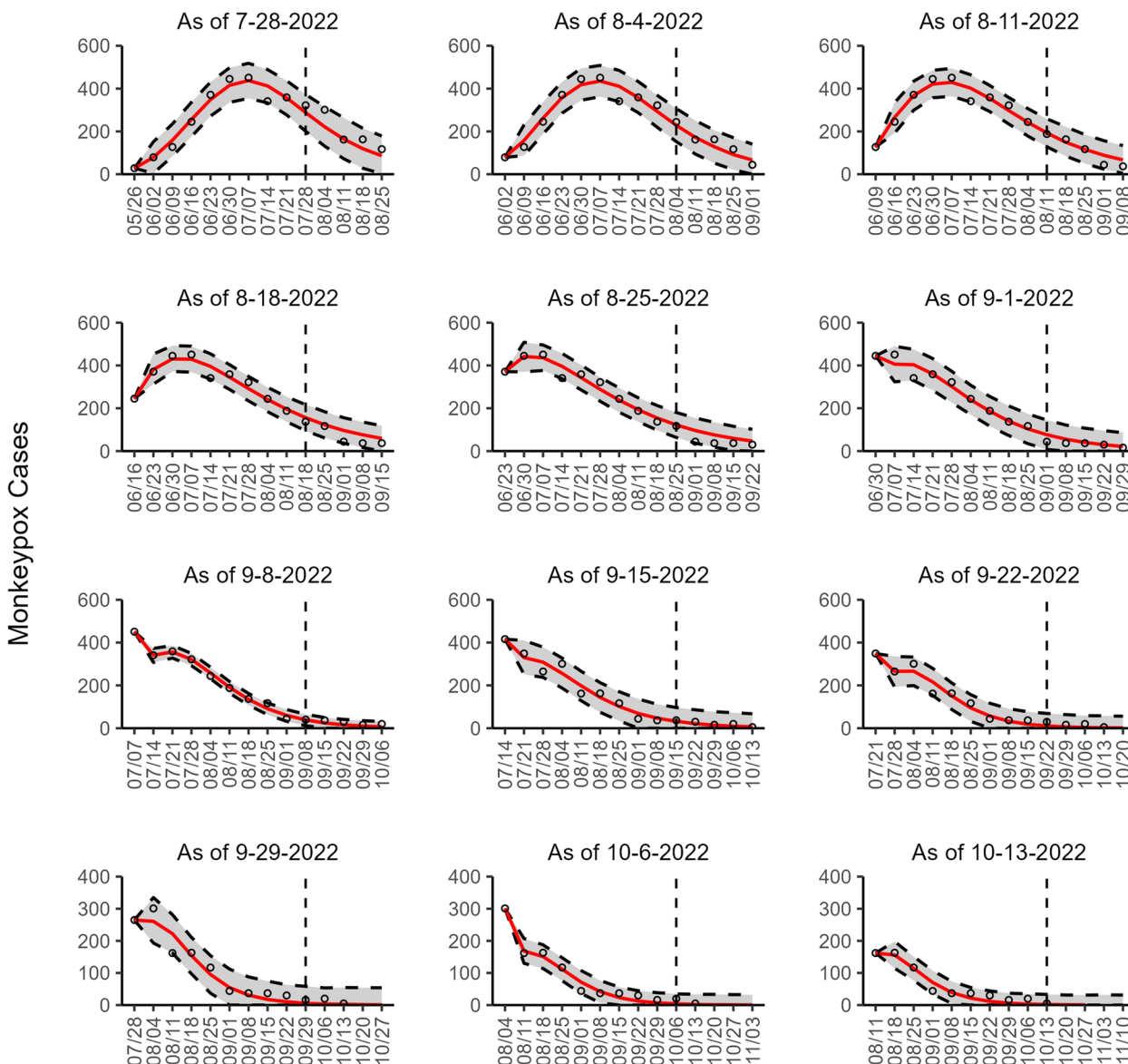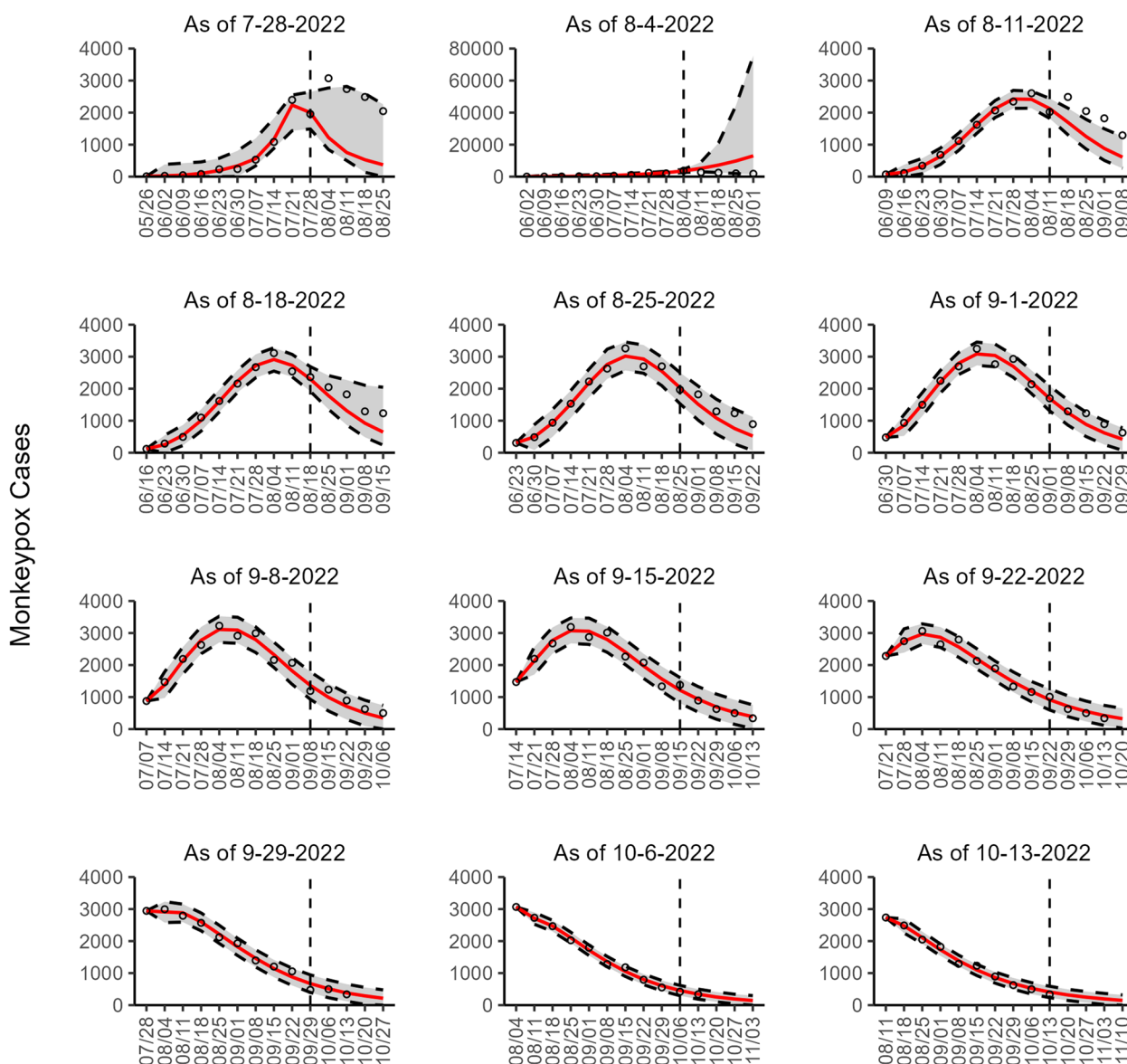

Fig. 5 The overlayed forecasted and reported monkeypox cases for the weeks of 7/28/2022 through the week of 10/13/2022 for Germany. The forecasts are derived from the weighted ensemble sub-epidemic model using 10-week calibration data, and the reported cases are obtained from the OWID GitHub [25]. The black circles to the left of the vertical line represent the reported cases as of the Friday of the forecast period; the solid red line corresponds to the best fit model; the dashed black lines correspond to the 95% prediction intervals. The black circles to the right of the vertical line represent the reported case counts (as of 10/21/2022) for the corresponding date. The vertical dashed black line indicates the start of the forecast period. For the week of 7/28/2022, data posted by the OWID team on 8/9/2022 was used to produce the forecast as it was the earliest version of data available

Fig. 6 The overlayed forecasted and reported monkeypox cases for the weeks of 7/28/2022 through the week of 10/13/2022 for Spain. The forecasts are derived from the weighted ensemble sub-epidemic model using 10-week calibration data, and the reported cases are obtained from the OWID GitHub [25]. The black circles to the left of the vertical line represent the reported cases as of the Friday of the forecast period; the solid red line corresponds to the best fit model; the dashed black lines correspond to the 95% prediction intervals. The black circles to the right of the vertical line represent the reported case counts (as of 10/21/2022) for the corresponding date. The vertical dashed black line indicates the start of the forecast period. For the week of 7/28/2022, data posted by the OWID team on 8/9/2022 was used to produce the forecast as it was the earliest version of data available

periods. In terms of the mean MAE, the second-ranked model performed better than the other models in all the study areas. Likewise, the second-ranked model outperformed other models in terms of mean MSE in all the study areas except Canada. In terms of mean WIS, the unweighted ensemble model performed better than the other 55.5% of the time. The coverage of the 95% PI coverage was consistently 100% across models and study areas except for France, where for the recent two forecast periods, the top-ranked and the weighted ensemble models reached 90% coverage. The performance metrics for each sequential calibration period are shown in tables 7s-10s (Additional file 2) and figures 29s-37s (Additional file 1).
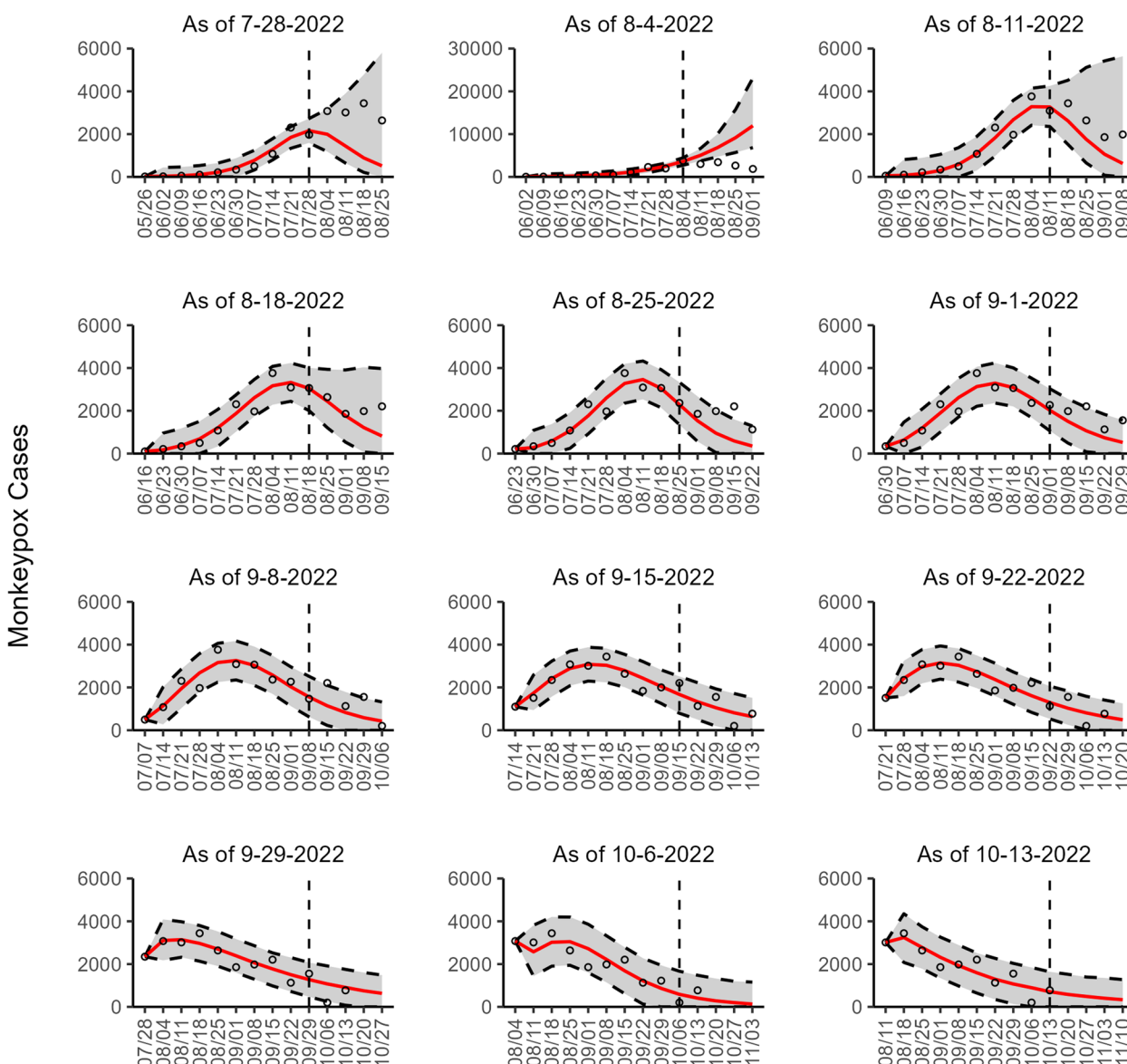
Fig. 7 The overlayed forecasted and reported monkeypox cases for the weeks of 7/28/2022 through the week of 10/13/2022 for the USA. The forecasts are derived from the weighted ensemble sub-epidemic model using 10-week calibration data, and the reported cases are obtained from the CDC [24]. The black circles to the left of the vertical line represent the reported cases as of the Wednesday of the forecast period; the solid red line corresponds to the best fit model; the dashed black lines correspond to the 95% prediction intervals. The black circles to the right of the vertical line represent the reported case counts (as of 10/21/2022) for the corresponding date

Global forecasts

Based on the global trend, our latest 4-week ahead forecasts from the three models continue to support a significant slowdown in the growth rate of monkeypox (Figs. 10, 11, and 12). Our most recent forecasts for the week of October 13th, 2022, predict a short-term decline in the number of new cases reported worldwide. According to our latest forecasts from the top-ranked model and weighted ensemble model, a total of 6232 (95% PI

487.8, 12,468.0 and 95% PI 492.8, 12,463.1) cases could be added globally during the 4 weeks from October 20th to the week of November 10, 2022 (Table 2; Additional file 2: Table 12s).

The uncertainty of the cumulative predicted median cases was higher for the second-ranked model compared to the top-ranked and ensemble models for most forecasts. For example, for Brazil, the 95% prediction interval for the cumulative median forecasts generated
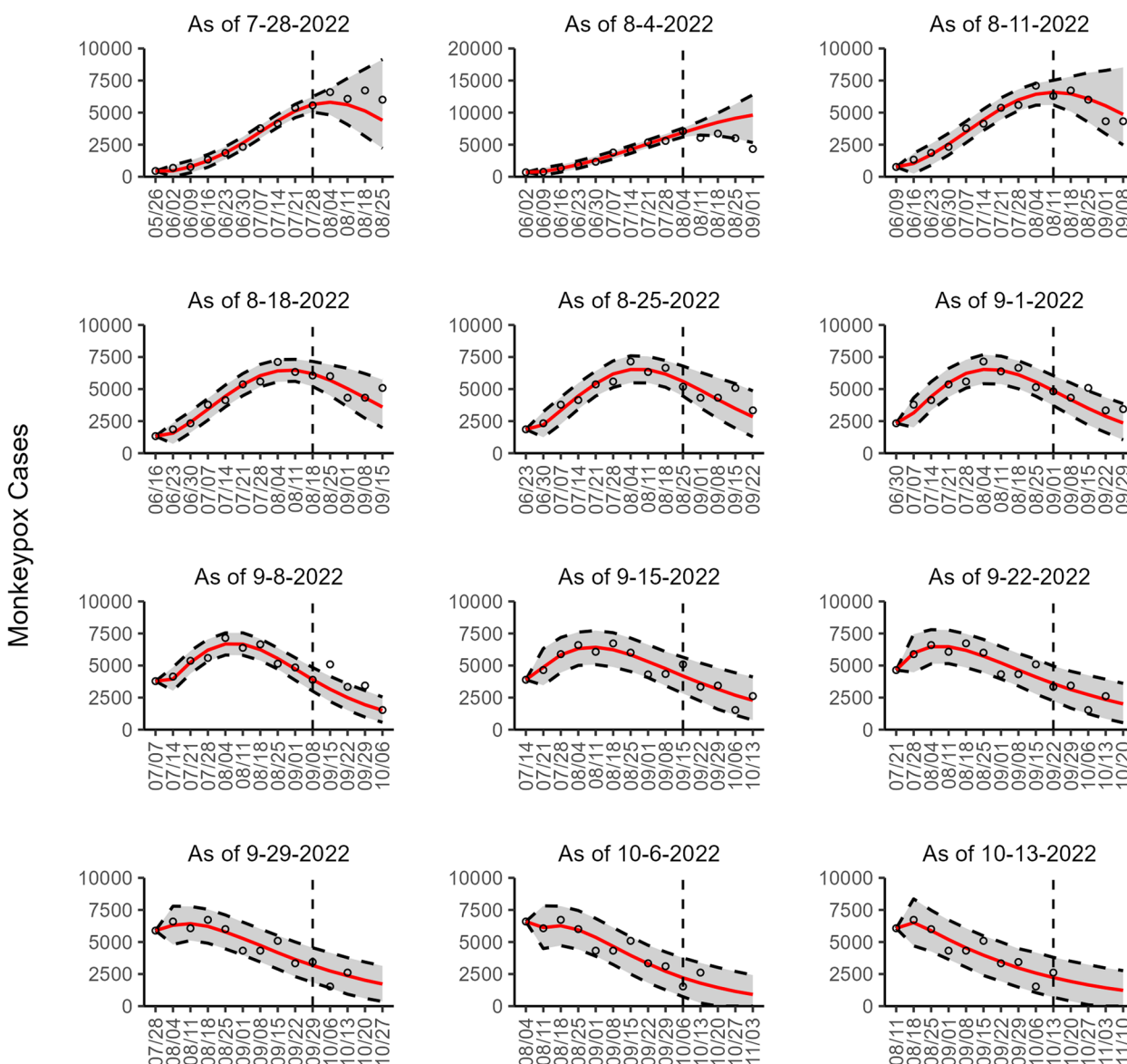
Fig. 8 The overlayed forecasted and reported monkeypox cases for the weeks of 7/28/2022 through the week of 10/13/2022 for the USA. The forecasts are derived from the weighted ensemble sub-epidemic model using 10-week calibration data, and the reported cases are obtained from the OWID GitHub [24]. The black circles to the left of the vertical line represent the reported cases as of the Friday of the forecast period; the solid red line corresponds to the best fit model; the dashed black lines correspond to the 95% prediction intervals. The black circles to the right of the vertical line represent the reported case counts (as of 10/21/2022) for the corresponding date. The vertical dashed black line indicates the start of the forecast period. For the week of 7/28/2022, data posted by the OWID team on 8/9/2022 was used to produce the forecast as it was the earliest version of data available

during the week of August 25, 2022, was 1288 to 3903 for the top-ranked model and ensemble model compared to 1038 to 27,926 for the second-ranked model (Additional file 1: Figs. 41s, Table 2, Additional file 2: Table 11s). The cumulative predicted median number of cases for each of the models across 12 sequential forecasting weeks for all study areas are shown in Table 2 (top-ranked model), table 11s (Additional file 2) (second-ranked model),

table 12s (Additional file 2) (weighted ensemble model), table 13s (Additional file 2) (unweighted ensemble model), and figures 38s-46s (Additional file 1).

Country-level forecasts

Our most recent forecasts from the top-ranked, second-ranked, and the corresponding ensemble sub-epidemic model support a continued declining trend for

Bleichrodt *et al. BMC Medicine*   (2023) 21:19

Page 13 of 20

Fig. 9 The overlayed forecasted and reported monkeypox cases for the weeks of 7/28/2022 through the week of 10/13/2022 for the World. The forecasts are derived from the weighted ensemble sub-epidemic model using 10-week calibration data, and the reported cases are obtained from the OWID GitHub [25]. The black circles to the left of the vertical line represent the reported cases as of the Friday of the forecast period; the solid red line corresponds to the best fit model; the dashed black lines correspond to the 95% prediction intervals. The black circles to the right of the vertical line represent the reported case counts (as of 10/21/2022) for the corresponding date. The vertical dashed black line indicates the start of the forecast period. For the week of 7/28/2022, data posted by the OWID team on 8/9/2022 was used to produce the forecast as it was the earliest version of data available

each of the seven countries (Figs. 10 and 12). However, the upper 95% PI of the forecast for Brazil derived from the second-ranked sub-epidemic model, albeit with substantially reduced statistical support, indicates the possibility of a further increasing trend in the number of new cases starting late October 2022 (Fig. 11). Out of a total of 324 forecasts generated from the week of July 28th through the week of October 13th 2022, for

all study areas across the three models, 306 (94.4%) forecasts showed a declining trend of monkeypox cases (Figs. 1, 2, 3, 4, 5, 6, 7, 8, and 9; Additional file 1: Figs.11s-28s).

The USA exhibited a slow increase in cases from late May 2022 until late June 2022, followed by a rapid increase, peaking during early to mid-August 2022. According to our latest forecasts from the weighted
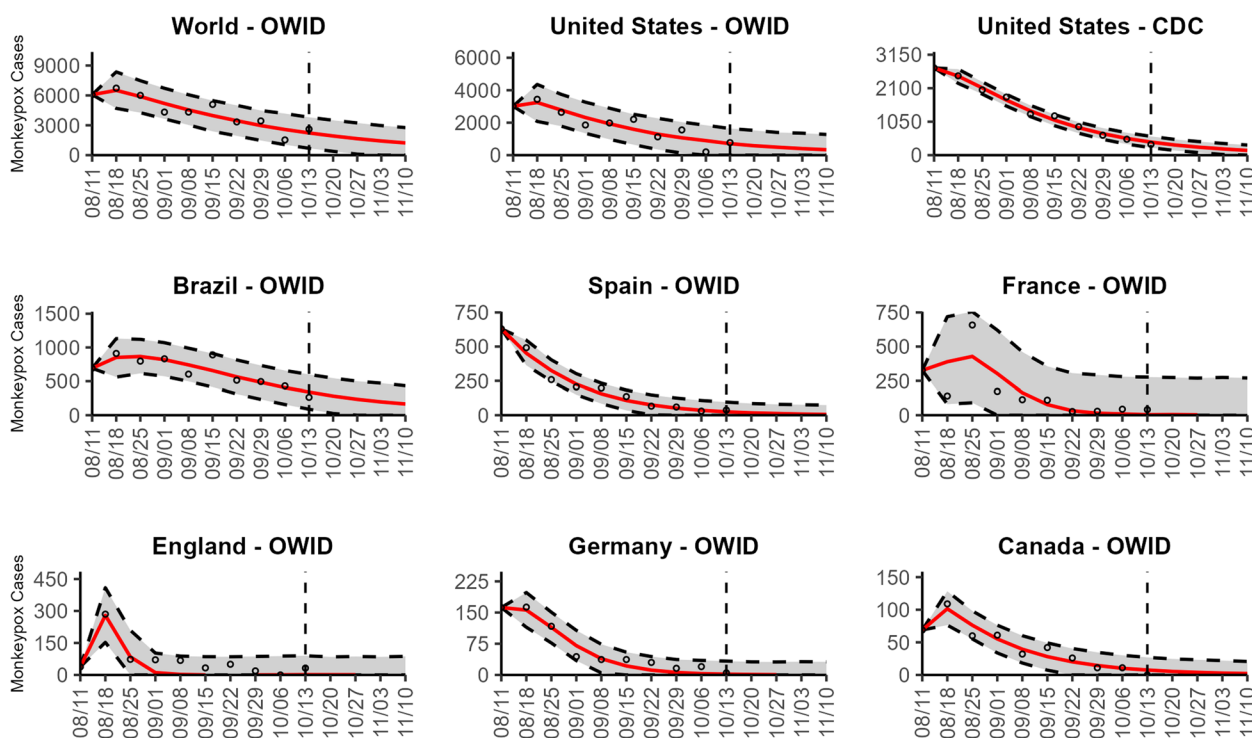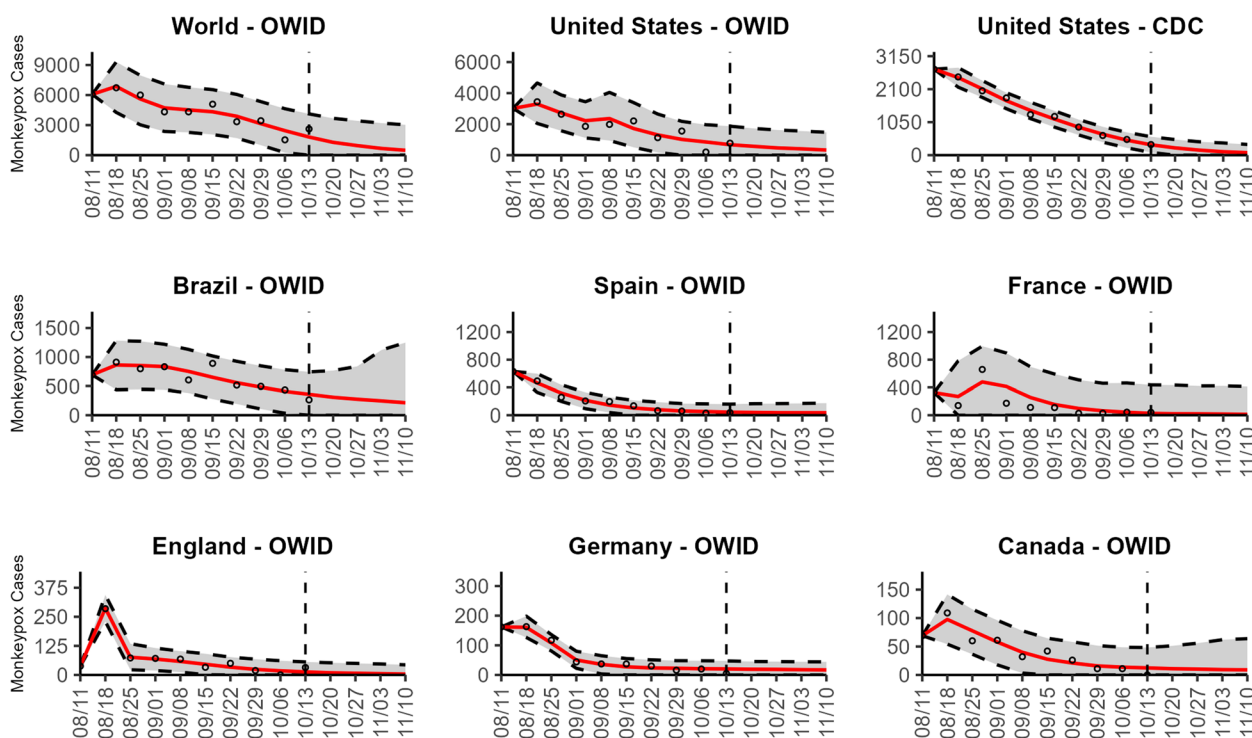
Fig. 10 The latest 4-week ahead forecasts of reported monkeypox cases for the week of 10/13/2022 derived from the top-ranked sub-epidemic model based on weekly cases using 10-week calibration data. The black circles to the left of the vertical line represent the reported cases as of the Wednesday (CDC forecast) or Friday (OWID forecast) of the forecast period; the solid red line corresponds to the best fit model; the dashed black lines correspond to the 95% prediction intervals. The vertical dashed black line indicates the start of the forecast period

ensemble model, a maximum of 1604 and 554 cases could be added from the week of October 20th to the week of November 10, 2022, in the USA based on the CDC data and the OWID data, respectively (Additional file 2: Table 12s; Additional file 1: Figs. 39s, 40s). The uncertainty of the predictions based on OWID data is higher than those based on the CDC data (Figs. 10, 11, and 12; Additional file 1: Figs. 30s, 40s).

The epidemic curve peaked earliest in Germany in late June 2022. Two weeks later, in mid-July, the epidemic peaked in England. However, the epidemics in the USA and Brazil seem to have peaked later, during early August and mid-August, respectively. For Brazil, the top-ranked model predicted the possibility of adding a median of 879 cases (95% PI 25, 1952) during the 4 weeks until November 10, 2022 (Table 2; Additional file 1: Fig. 41s). Similarly, based on the top-ranked model, Germany and England could each add a median 1.5 (95% PI 0, 126) and 2.7 (95% PI 0, 343) cases, respectively, between the week of October 20 to November 10, 2022 (Table 2; Additional file 1: Figs. 42s, 43s). Likewise, for France, Spain, and Canada, the number of cases peaked during the week of July 14–July 21, 2022, followed by a decline in the number of reported

new cases. During the most recent 4-week ahead forecast, the top-ranked model predicted very few cases (in terms of median value) of monkeypox in France (median 10, 95% PI 0, 1088), Spain (median 43, 95% PI 0, 316), and Canada (median 14, 95% PI 0, 90) (Table 2; Additional file 1: Figs. 44s, 45s, 46s).

It is reassuring that the cumulative number of new cases predicted for the weeks of September 29th, October 6th, and October 13th, 2022, show a declining pattern for Germany, France, and England, indicating a significant reduction in the growth rate (Table 2; Additional file 1: Figs. 42s- 44s). For Brazil, the pattern in the number of cumulative cases in 4-week ahead predictions has consistently declined from the week of September 15 to the week of October 13 (from 2402 to 879, 63.4% decline) (Table 2; Additional file 1: Fig. 41s). For the forecasts generated during the last 3 weeks (September 29th, October 6th, and October 13th), the predicted median cumulative cases remain below 50 for Canada and England, below 10 for Germany, and below 70 for Spain, suggesting that the trend is stabilizing at low case numbers (Table 2; Additional file 1: Figs. 42s, 43s, 45s, 46s). Table 2, tables 11s-13s (Additional file 2), and figures 38s-46s (Additional file 1) summarize the forecasting results for each model.
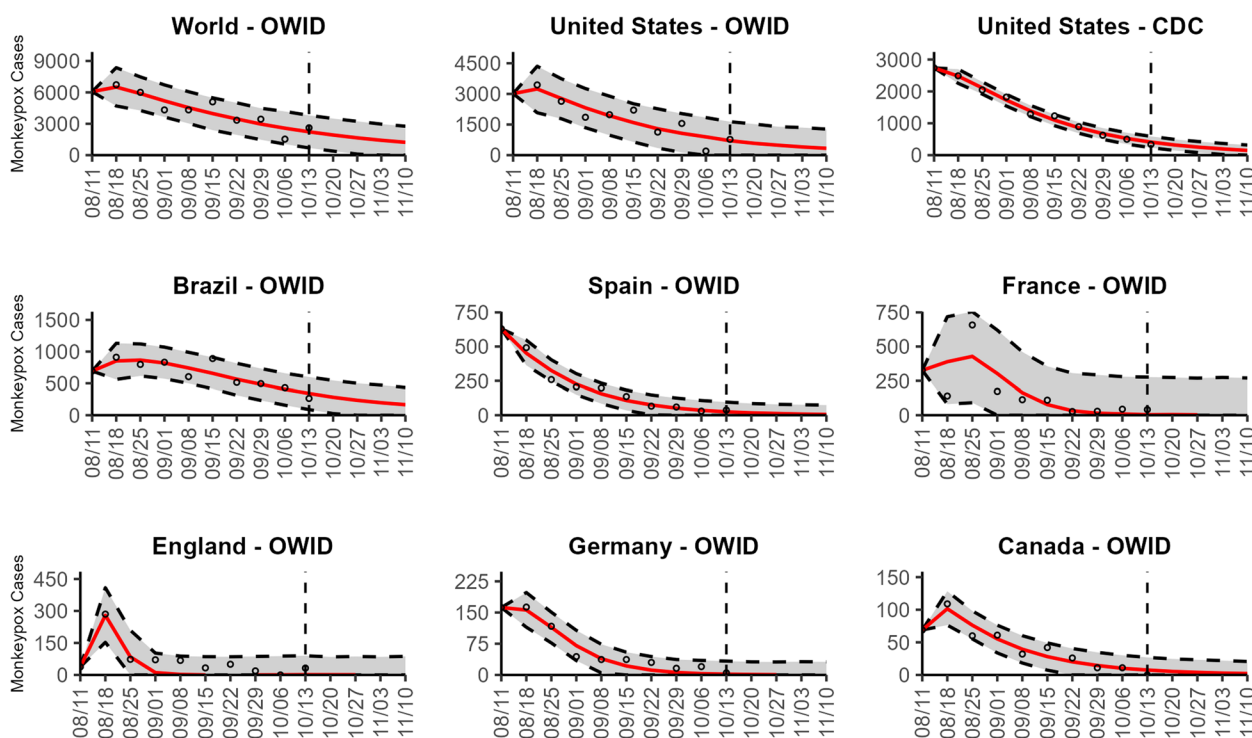
Fig. 11 The latest 4-week ahead forecasts of reported monkeypox cases for the week of 10/13/2022 derived from the second- ranked sub-epidemic model based on weekly cases using 10-week calibration data. The black circles to the left of the vertical line represent the reported cases as of the Wednesday (CDC forecast) or Friday (OWID forecast) of the forecast period; the solid red line corresponds to the best fit model; the dashed black lines correspond to the 95% prediction intervals. The vertical dashed black line indicates the start of the forecast period

Our forecast for the USA can be found in our GitHub repository [40] and on our webpage [41].

Discussion

We report results from short-term (4 weeks ahead) forecasts of monkeypox cases using a sub-epidemic modeling framework for the world and seven countries that, at the time this study began, had reported the great majority of cases. Our forecasts continue to support an overall declining trend in the number of new cases of monkeypox at the global and country-specific levels. Based on the top-ranked model and weighted ensemble model, we predict that during the next 4 weeks (the week of October 20th, 2022, through the week of November 10, 2022), a total 6232 (95% PI 487.8, 12,468.0, and 95% PI 492.8, 12,463.1) cases of monkeypox could be added globally. At the country level, our top-ranked model indicates that the highest number of new cases will be reported in the USA (OWID data) (median 1806, 95% PI 0, 5545) followed by Brazil (median 879, 95% PI 25, 1952) and Spain (median 43, 95% PI 0, 316). Overall, our models have performed reasonably well across study areas. The top-ranked and weighted ensemble model outperformed other models on average in forecasting performance. Our results offer valuable information to policymakers to

guide the continued allocation of resources and inform mitigation efforts. More broadly, findings suggest that the epidemic could be brought under near-complete control in some regions should public health measures continue to be sustained, especially among the high-risk groups [42–44]. Indeed, a core group of higher-risk people is thought to disproportionately contribute to transmission and thereby sustain sexually transmitted infection (STI) epidemics. Monkeypox is inherently different from other STIs like HIV, which has a lifelong duration, or bacterial STIs, which can be acquired repeatedly. Cases may decline rapidly as immunity increases among core group members, either due to infection or vaccination. Without a core group driving the epidemic, monkeypox may become endemic with low transmission levels [45–47]. The current monkeypox outbreak is unprecedented in size and geographic scope. As of November 23rd, 2022, a total of 110 countries globally have reported monkeypox cases at 80,899 [8]. Only seven countries have historically reported monkeypox cases indicating that more than 93% of the countries reporting cases are non-endemic to monkeypox [8]. Our latest short-term forecasts from top-ranked models and weighted ensemble models conducted in near real-time indicate a clear, continued slow down in the number of new cases globally and in each

Fig. 12 The latest 4-week ahead forecasts of reported monkeypox cases for the week of 10/13/2022 derived from the weighted ensemble sub-epidemic model based on weekly cases using 10-week calibration data. The black circles to the left of the vertical line represent the reported cases as of the Wednesday (CDC forecast) or Friday (OWID forecast) of the forecast period; the solid red line corresponds to the best fit model; the dashed black lines correspond to the 95% prediction intervals. The vertical dashed black line indicates the start of the forecast period

country included in the study. This mirrors the recent continental declines in cases reported for Europe and the Americas [43, 48, 49].

Findings support the significant impact of current measures to contain the outbreak in different areas. For example, in the USA, the primary strategy has been a combination of increasing education around monkeypox (e.g., symptoms, transmission), encouraging practices that reduce potential close contacts and increasing access to vaccination and testing for high-risk groups [50–52]. Although supply-chain shortages impacted early vaccine access, as of August 26th, 2022, the availability of monkeypox vaccines had increased to sufficient levels to combat the outbreak. The racial disparities in access to vaccines that arose in late August are continuing to persist [53–55] though some progress has been made in improving the monkeypox vaccination among racial and ethnic minority groups in the USA. For example, according to a recent morbidity and mortality weekly report (MMWR), between May 22–June 25 and July 31–October 10, 2022, the proportion of monkeypox vaccine recipients increased from 15 to 23% among Hispanic and from 6 to 13% among Black population [56]. In addition, although vaccines are more recently available, behavioral

modification within high-risk groups appears to be driving declines in cases. Continuing these behaviors (e.g., limiting one-time sexual encounters) is crucial in slowing the transmission of monkeypox [5, 42, 57]. Based on the early evidence from Europe, the World Health Organization (WHO) is quite optimistic that the current outbreak of monkeypox can be contained with the improvement in vaccine supply chains in addition to early detection of the cases and educational interventions which lead to behavioral modifications in the high-risk groups [58]. Moreover, recent research indicates that the majority of monkeypox cases resulting in severe disease or death have been among MSM with compromised immune systems (e.g., due to untreated HIV infection). Specifically, increased burden has been noted among Black populations, and those experiencing mental health challenges or housing insecurities, reflecting the existing inequities in access to resources diagnosis, treatment, and prevention of monkeypox [59].

Our study is not exempt from limitations. First, our analysis relied on weekly time series data of lab-confirmed monkeypox cases from two sources, which display irregular daily reporting patterns [24, 25]. These sources use different approaches in compiling data and

Bleichrodt *et al. BMC Medicine*   (2023) 21:19

Page 17 of 20

Table 2 Predicted cumulative number of newly forecasted monkeypox cases and 95% PIs for the top-ranked model

Week		Brazil	Canada	England	France	Germany	Spain	US (OWID)	U.S. (CDC)	World
07-28-2022	Median	8463.7	742.3	773.9	872.4	591.2	1391.2	4838.8	3972.2	20,957.3
	LB	6067.5	622.3	322.9	245.6	234.1	0.0	2038.2	1482.7	14,263.4
	UB	11,783.6	887.6	1384.3	2322.0	972.4	5137.4	17,645.5	14,737.1	32,121.5
08-04-2022	Median	1187.2	385.9	660.3	522.6	458.7	966.3	33,042.3	31,740.8	34,936.8
	LB	651.6	215.0	224.7	62.0	167.6	0.0	21,005.3	20,265.5	24,148.0
	UB	2841.9	621.8	1157.7	1316.6	767.2	3435.6	55,553.7	52,503.6	42,706.4
08-11-2022	Median	2685.3	254.5	434.9	286.1	420.3	1237.7	6058.4	4301.5	22,930.0
	LB	1477.3	143.3	79.0	0.0	162.3	0.0	2242.7	3118.5	15,153.2
	UB	5348.1	385.7	848.3	924.7	696.3	3754.3	20,689.6	5592.6	32,717.9
08-18-2022	Median	1631.6	231.2	251.2	152.8	354.1	1158.6	6247.6	4539.4	18,643.0
	LB	711.3	120.6	32.6	0.0	114.4	0.0	1816.2	3226.2	12,818.4
	UB	3662.6	352.7	515.4	677.8	593.4	3503.7	15,853.4	6067.3	25,447.7
08-25-2022	Median	2312.1	185.7	147.6	609.1	277.7	806.8	3420.0	3756.9	15,412.5
	LB	1288.4	97.3	11.7	0.0	57.8	0.0	610.6	2218.4	9456.3
	UB	3903.2	277.4	340.1	2517.0	506.4	2753.8	7594.1	5342.4	22,458.5
09-01-2022	Median	1593.3	111.7	130.1	503.9	147.1	755.3	3824.4	3175.9	12,899.5
	LB	768.7	8.0	9.9	0.0	0.0	0.0	571.0	1697.9	7794.2
	UB	2599.4	240.7	281.3	2252.0	410.0	2166.7	8101.4	4689.0	18,540.1
09-08-2022	Median	1723.7	75.6	108.4	438.6	56.7	271.0	2978.7	2542.4	9097.0
	LB	866.6	1.9	0.0	0.0	0.0	0.0	223.6	959.6	5279.6
	UB	2648.9	180.9	267.2	1998.6	158.0	933.0	6706.9	4176.0	13,323.9
09-15-2022	Median	2401.9	66.0	74.0	346.6	51.6	143.9	3826.9	2526.1	11,764.0
	LB	844.3	0.0	0.0	0.0	0.0	0.0	690.5	999.5	5704.9
	UB	4116.9	415.6	733.7	1836.3	303.1	739.6	7379.2	4086.6	18,545.3
09-22-2022	Median	2144.9	41.7	79.9	357.9	12.8	143.3	2958.6	2011.8	10,205.4
	LB	875.0	0.0	0.0	0.0	0.0	0.0	265.3	768.4	4305.2
	UB	3452.4	354.2	734.6	1882.9	236.1	663.5	6078.7	3299.8	16,332.0
09-29-2022	Median	1534.7	29.5	45.0	115.6	7.7	32.3	3365.1	1395.1	8853.4
	LB	320.1	0.0	0.0	0.0	0.0	0.0	326.2	377.7	3312.8
	UB	2898.0	223.8	701.1	1432.3	215.9	437.5	6758.5	2469.3	14,514.1
10-06-2022	Median	1117.8	13.6	20.0	32.7	4.3	66.1	1017.4	931.4	5297.9
	LB	129.8	0.0	0.0	0.0	0.0	0.0	0.0	330.9	244.2
	UB	2240.8	129.0	574.3	1229.4	131.4	335.6	5154.0	1551.8	11,508.3
10-13-2022	Median	878.9	14.2	2.7	10.3	1.5	43.0	1806.3	910.1	6231.5
	LB	25.0	0.0	0.0	0.0	0.0	0.0	0.0	245.3	487.8
	UB	1951.5	90.4	342.8	1088.0	125.7	315.6	5544.5	1603.5	12,468.0

Predicted cumulative number of newly reported monkeypox cases and 95% PIs for each 4-week ahead forecasts for the weeks of 7-28-2022 through 10-13-2022 based on a weekly cases using a 10-week calibration period for the top-ranked sub-epidemic model

addressing data issues, which affect the characterization of the epidemic curve. For example, the CDC data uses cases with reporting data that includes either the positive laboratory test report date, CDC call center reporting date, or case data entry date into CDC's emergency response common operating platform [24]. The OWID team uses laboratory-confirmed case data reported to the World Health Organization via WHO Member States [25, 60]. In addition, the data used for forecasting could also be underestimated due to delays between the date of testing and the date of reporting. Also, the weekly data used in our real-time forecasts has exhibited revisions that retrospectively adjusted the time series. Hence, significant increases or decreases may be observed in reported cases for the same date between forecasting periods. Indeed, the CDC acknowledged the presence of data adjustments within their posted data [61]. Similar issues have been noted in COVID-19 forecasting studies since ground truth data adjustments occurred during the pandemic [20]. Nevertheless, in the case of our study and

the COVID-19 forecasting study, forecasts are being conducted in real time using ground truth data. Therefore, each weekly forecast is generated using the latest time series available on each prediction date whereas forecasts were scored using the most up-to-date data at the time of the study (week of October 13th, 2022). Because we are dealing with limited epidemic data in this study, we often examined forecasts derived from the second-ranked sub-epidemic model even when it yielded substantially diminished statistical support relative to the top-ranked model. The models employed in this study are semi-mechanistic in that they give insight into the nature of the process that generated the epidemic trends in terms of the aggregation of sub-epidemic trajectories. However, the models are not intended to quantify the effects of different factors, such as behavior change and vaccination, on the declining trend. Finally, it should be noted that our short-term forecasts are based on the inherent assumption that current behavior practices will not change substantially, at least over short time horizons. Further, our models are not sensitive to long-term forecasting episodic risk behaviors that are seasonal or event specific (e.g., LGBTQ Pride festivals). For example, a previous study has reported episodic risk behaviors among MSM, such as condomless anal sex with new male sex partners while vacationing [62].

In future work, we plan to systematically assess the forecasting performance of the models against other competing models, such as the Autoregressive Integrated Moving Average (ARIMA), which has been broadly applied to forecast time series of epidemics and various other phenomena such as the weather and the stock market [19, 63, 64]. During the COVID-19, this sub-epidemic modeling framework demonstrated reliable forecasting performance in 10- to 30-day ahead forecasts of daily deaths, outperforming ARIMA models in weekly short-term forecasts covering the U.S. trajectory of the COVID-19 pandemic from the early phase of spring 2020 to the Omicron-dominated wave [19].

Conclusions

In summary, real-time forecasting during epidemic emergencies offers actionable information that governments can use to anticipate healthcare needs and strategize the intensity and configuration of public health interventions. Our study provides and assesses near-real time short-term forecasts of monkeypox cases globally and for seven countries that have reported a higher number of cases for a large part of the epidemic. Our models continue to predict a slowdown in the incidence of monkeypox both at the global and country levels. Overall,

our models have demonstrated utility in providing short-term forecasts, capturing the growth rate slowdown and peak timing with reasonable accuracy. Our findings likely reflect the impact of increased immunity and behavioral modification among high-risk populations.

Abbreviations

ARIMA	Autoregressive Integrated Moving Average model
CDC	The Centers for Disease Control and Prevention
LGBTQ	Lesbian, Gay, Bisexual, Transgender, and Queer/Questioning
MAE	Mean absolute error
mpox	Monkeypox
MSE	Mean square error
MSM	Men who have sex with men
OWID	Our World in Data
PI	Prediction interval
STI	Sexual transmitted illness
WHO	World Health Organization
WIS	Weighted Interval Score

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-022-02725-2.

Additional file 1: Supplementary figures. Additional figures related to the dissemination and evaluation of models used to produce the forecasts included within the study.

Additional file 2: Supplementary Tables. Additional tables related to the dissemination and evaluation of models used to produce the forecasts included within the study.

Authors' contributions
A.B., S.D., and G.C. analyzed the data. A.B. and G.C. retrieved and managed data; A.B., S.D., R.L., K.M., L.C., and G.C. wrote the first draft of the manuscript. All authors contributed to writing and revising subsequent versions of the manuscript. All authors read and approved the final manuscript.

Availability of data and materials
The datasets analyzed during the current study include the U.S. Monkeypox Case Trends Reported to CDC data [https://www.cdc.gov/poxvirus/monkeypox/response/2022/mpx-trends.html] and data available from the Our World in Health Monkeypox GitHub repository [https://github.com/owid/monkeypox]. The forecast generated during the current study are available in the Monkeypox short-term Forecasts, USA GitHub repository [https://github.com/gchowell/monkeypox-usa] and the Monkeypox Forecasting Center website [https://publichealth.gsu.edu/research/monkeypox-forecasting-center/].

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Bleichrodt *et al. BMC Medicine*   (2023) 21:19

Page 19 of 20

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Bleichrodt *et al. BMC Medicine*   (2023) 21:19

Page 20 of 20

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