Supplementary Materials for

Quantitatively assessing early detection strategies for mitigating COVID-19 and future pandemics

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The PDF file includes:

Materials and Methods

Description of model predicting cases at detection.

Our branching process-based model predicts the cumulative number of cases at the time of detection for a given detection system and outbreak. It follows the approach of branching process simulation models used previously to model the spread of COVID-19 (*46*, *47*) and other infectious diseases (*48*), but with the main added step of simulating each infected person's chance of being detected by the detection system. The values for parameters for detection systems can be found in table S2. The values for epidemiological parameters for outbreaks (R0, serial interval, dispersion, hospitalization rate, and time to hospitalization) can be found in Fig. 2 and table S3. As in previous models (*48*), we assume the offspring distribution (the number of secondary cases infected by each primary case) is negative binomial with mean R0.

In hospital monitoring, hospitals would test for high-priority pathogen families (e.g. coronaviruses) in patients presenting with severe infectious symptoms in hospital emergency departments (*18*). Similarly, in wastewater monitoring, governments would test for pathogens in city wastewater treatment plants daily, and monitor for high and increasing levels of high-priority pathogen families (*20*). In air travel monitoring, governments would test airplane sewage (*21*) or bridge air on incoming international flights for the same pathogens. The parameters of these systems are shown in table S2.

Our model also accounts for different delays involved in different detection systems. For example, if the 500th case of a COVID-19-like outbreak triggers the detection threshold in both the hospital and wastewater monitoring systems, because of the significant delay from infection to hospitalization compared to the delay from infection to fecal shedding, the wastewater system would catch the outbreak earlier.

In systems that test individuals (hospital and air travel individual monitoring), the threshold is measured in an absolute *number* of cases. In systems that test wastewater (community and air travel wastewater monitoring), the threshold or sensitivity is measured in prevalence (cases as a *percentage* of the population) (*49*, *56*, *57*). To predict the number of cases and time to detection, we need to convert this percentage back to a number of cases, so the wastewater detection time depends on the catchment population size.

To estimate wastewater sensitivity measured in prevalence, we used data from (*49*). (*49*) conducted PCR testing for SARS-CoV-2 1687 longitudinal wastewater samples from 353 sampling locations in 40 US states in early 2020, and synced these with publicly reported local daily new COVID-19 case counts. This enables us to estimate a distribution of the wastewater sensitivity: the lowest case count required to trigger positive detection in wastewater. Of the 353 sampling locations, 47 had both SARS-CoV-2-positive and negative samples such that local case counts on days of positive samples were all higher than those on days of negative samples. We thus knew each sampling location's sensitivity is between the maximum of case counts on negative sample days and the minimum of case counts on positive sample days. We took the midpoint of this maximum and minimum as the location's sensitivity; this gave us 47 local sensitivities. We fitted this to a log-normal distribution with a median of 2.5 daily new cases per 100,000 people. As expected, this distribution is similarly shaped but slightly left-shifted of the distribution of raw case counts reported in Figure 2b of (*49*) (median 3.7 per 100,000), because the latter distribution is an upper bound of the former.

To use this distribution in our model, in each simulation run, we first randomly drew a wastewater sensitivity from this distribution, and then we needed to convert this *reported incidence i* to the *true (reported and unreported) number* of cases shedding fecally into public wastewater systems up to the time of wastewater detection. We converted as follows. Let day T be the day on which the incidence *i* is reported. First we assumed the wastewater SARS-CoV-2 level on day T is proportional to the number of COVID-19 cases who are fecally shedding on day T, which we estimate as the number of fecal shedders infected 2 days before, given the dominant peak in fecal shedding on day 2 of infection (*56*). We infer the number of fecal shedders infected on day T-2 from the incidence as follows. To account for underreporting, we first estimate a true daily incidence of 5.7 x i with symptom onset on day T, based on estimates of the ratio of true to reported COVID-19 cases in the United States in early 2020 (*50*). (This study's abstract reports true cases are 5-50x reported ones, but this refers to the early March 1-April 4, 2020, period. We calculated the factor of 5.7 from the study's data when we use the fuller March 1-May 16 period, which overlaps better with the February-June 2020 period in (*49*) and reflects less underreporting as the pandemic developed and testing capacity increased. We calculated this underreporting factor as an average of state-level underreporting factors, weighted by frequency of each state among the wastewater samples in (*49*).) Finally, we multiply by (a) the fraction of cases who shed fecally (0.5 (*58*)) and (b) the fraction of people connected to central sewage (0.8 in the US (*59*), which is the area from which the (*49*) threshold is derived). This gives us the one-time prevalence of cases *p* who contribute to the wastewater SARS-CoV-2 level on day T. For a given catchment with population *c*, this one-time number of cases is *cp*, and we estimate the cumulative number of fecal shedders up to this time as $\sum_{t=T}^{0} \frac{cp}{R_0^{t/7}} \approx \int_{t=0}^{T} R_0^{t/7}$, where $T = \log_{R_0^{t/7}}(cp)$ is the number of days for the daily exponential outbreak incidence curve to grow from 1 to *cp* cases.

To check this estimate, we identified studies that compared wastewater and hospital COVID-19 trends (*19*, *49*). (*19*) found that trends in wastewater SARS-CoV-2 values led trends in hospital admissions by 1-4 days in New Haven (catchment size 2e+05). We estimate that wastewater detection would lead hospital detection of COVID-19 in New Haven by -0.8 to 3 weeks (90% CI). This is consistent with the 1-4d lead estimate from (*19*). Similarly, (*49*) found that trends in wastewater led those in clinical data by 4 days in Massachusetts (catchment size 2,300,000). Their clinical data are dated by date of reporting rather than sample gathering; assuming that hospital admissions are 5 days ahead of tests by date of reporting (*19*), then wastewater is 5d-4d=1 day behind hospital admissions. We estimate that wastewater detection would lead hospital detection of COVID-19 in Massachusetts by -4 to -0.09 weeks (90% CI). This is consistent with the 1-day lag estimate from (*49*).

<u>Validation of model in US states.</u>

We gathered two sources of data for each state: dates of COVID-19 detection and COVID-19 case counts in early 2020. For the former, we searched media reports and US state public health press releases to determine the dates of the first COVID-19 case reported in each US state. Sources for each state's detection date are listed in table S4. We were able to identify such dates for all 50 states.

For the latter, we used literature estimates of true (tested and untested) COVID-19 case counts, which incorporate COVID-19 mortality data to deal with variation in testing capacity among states (*50*). We received a time series of weekly symptomatic COVID-19 case estimates for March 1-May 10, 2020 and divided by a symptomatic rate of 0.55 to get an estimate of total (symptomatic and asymptomatic) cases (*43*). We specifically used estimates from the adjusted mMAP (mortality maximum a posteriori) method because (*50*) had mMAP estimates for all 50 states, whereas other methods from the same study were missing estimates for various states. We fit an exponential curve of case counts in each state to extrapolate cases back to January 2020. In the data we received, all states had case data for all weeks in March 1-May 10, 2020.

We used our model to predict the weeks until detection in each US state (y-axis in Fig. S7). Because most US states detected their first case by travel (table S4), we modeled a travel-based detection system similarly to how we modeled the aforementioned detection systems. We simulated a growing stream of imported travel cases ($R0^i$ cases for the *i*-th generation and global R0 = 2.5), and as for the other detection systems, we simulated infection and detection steps for each generation, except that we only allowed travel-associated cases to be detected. We assumed that the state COVID-19 outbreaks had the same values for all epidemiological parameters except for R0, which we allowed to vary by state to account for state-specific conditions. We obtained state-specific R0 values from (*60*). The values for shared parameters were obtained from literature (table S3). We used a detection delay of 12 days (5-day incubation period (*43*) plus 7-day test and reporting turnaround in early 2020 in the US (*61*)) because many first cases were detected following symptoms. The only parameter we were unable to precisely estimate from literature was the probability of a travel case being detected. We noted that this rate was at most the COVID-19 symptomatic rate (0.55 (*43*)) and at least the hospitalization rate (0.03 (*43*)): in the highest-detecting scenario, every symptomatic case would volunteer to be tested; in the lowest-detecting scenario, only hospitalized travel cases would get flagged for testing. So we chose a rate of 0.1, near the two rates' geometric mean. The predicted detection time for each state (the y-value reported in Fig. S7) was the mean of 100 simulations.

We compared these predictions to ground truth estimates in each state (x-axis in Fig. S7). These ground truth estimates were calculated by summing the aforementioned weekly case counts from the first week of January 2020 until the date of detection in that state (Fig. S8).

<u>Comparison of COVID-19 detection times in the actual pandemic versus with proposed early detection systems.</u>

We used our model to examine whether the early detection systems could have detected COVID-19 earlier than in the actual pandemic. To do this, we used two data sources: (1) literature estimates of total (tested and untested) COVID-19 case counts in late 2019 and early 2020 (*51*) and (2) simulation output from our model. We then used (1) to calculate the cumulative number of cases when COVID-19 was actually detected, and compared this to results from (2).

For (1), we chose to use estimates from (*51*), which quantifies both the time of SARS-CoV-2 introduction into humans and the time series of cases following said introduction. These estimates are based on phylodynamic rooting methods applied to SARS-CoV-2 sequence data, combined with epidemic simulations and accounting for epidemiological data on the first known cases of COVID-19. These estimates improve upon previous attempts to time SARS-CoV-2's introduction into humans, which are solely based on phylodynamic rooting methods to quantify the time to the most recent common ancestor of SARS-CoV-2 sequences (*62*).

As instructed by (*51*), we downloaded "BEAST.primary.IH.Dec10_16.linB.Dec15_25.linA.cumulativeInfections.timedGEMF_combined.stats.pickle" from GitHub (*63*) to obtain the distribution of daily case counts. Conditioning on the fact that there were at least six COVID-19-related hospitalizations by 2019-12-29 (*64*), we narrowed the distribution to those epidemic simulations with the top 25 percent of hospitalizations and case counts. We simulated 100 draws from this distribution, and then took the number of cases on 2019-12-29 in each simulation to get 100 values for the distribution of cumulative cases at detection in the actual pandemic ("Actual pandemic" boxplot in Fig. 1B). We chose 2019-12-29 as the date that COVID-19 was detected in the actual pandemic, because this was the date of the first report of an outbreak of pneumonia cases to health authorities in Wuhan (*65*).

For (2), we ran our model for COVID-19 (see table S3 for the epidemiological parameters used) and all three detection systems (100 simulations for each system). For each detection system, this gave us the estimated number of cases until detection of COVID-19 if that system had been in place at the start of the pandemic. We assumed the system was present in the community in which COVID-19 originated. We compared each system to the actual pandemic, and determined that detection could have occurred earlier with the system if there was a statistically significant difference in cases until detection between the actual pandemic and the simulated world with the system (Fig. 1B). Statistical significance was assessed by a 1-sided t-test in which the alternative hypothesis was that the detection system performed better.

We could empirically test our model predictions for the cases until wastewater detection by using literature-estimated total COVID-19 cases in Massachusetts (*50*) and Massachusetts wastewater SARS-CoV-2 data (*52*) in early 2020. We aimed to use these to estimate the cases until COVID-19 wastewater detection in Massachusetts in early 2020, but because Massachusetts wastewater sampling for COVID-19 started only after the Massachusetts outbreak was underway, wastewater samples were positive for SARS-CoV-2 on the first day of testing, so this first day of testing was later than when wastewater detection could have caught SARS-CoV-2 if wastewater detection had been in place in advance. Thus we could only calculate an upper bound on the true cases until detection. We downloaded the wastewater time series from the Massachusetts Water Resources Authority (MWRA) website and synced it with the COVID-19 case count time series (Fig. S9). We multiplied the Massachusetts statewide cases by 0.33 (equal to 2,300,000/6,900,000) because the MWRA data covers 2,300,000 people, out of 6,900,000 people in Massachusetts in 2020. We then summed these case counts up to the date of apparent wastewater detection to get an upper bound for cases at detection, and checked whether our model prediction was consistent with this bound.

<u>Model-simulated cases required to trigger COVID-19 detection versus mathematical approximations.</u>

We compared the model simulations of cases until detection with our derived mathematical formula, Equation (1) (Fig. S10). The points in Fig. S10 are the same as in Fig. 2A. The dashed lines are generated by plugging values into Equation (1) for each detection system: we plugged in the detection threshold, detection probability, outbreak R0, and detection delay (measured in number of generations, i.e. serial intervals) for d, p_{test}, R0, and g, respectively.

<u>Comparison of detection systems for different infectious diseases.</u>

We applied our model to several outbreaks of recent interest: COVID-19, monkeypox (2022), polio (2013-2014), Ebola (2013-2016) and flu (2009 pandemic) (Fig. 2A). Because of the lack of data on the number of cases at the time of detection in previous outbreaks (except for the COVID-19 data used in Fig. 1B), we used our model to estimate status quo detection times for the outbreaks. Because many recent outbreaks have been detected in healthcare settings (*54*, *64*, *66*, *67*), we assumed status quo detection was similar to hospital monitoring, except with a lower detection probability per case (p_{test}) to reflect that symptomatic cases are less likely to be tested for a panel of diseases without the proposed systematic, proactive testing scheme. The per-case detection probability for status quo was set to 0.67 times that of hospital monitoring to match our modeled status quo detection times for COVID-19 with those estimated independently by (*51*) (Fig. 1B).

Supplementary Text

<u>Earliness of lockdown versus lockdown success for 85 countries' first 2020 COVID-19 lockdowns.</u>

To test the importance of early response, we asked whether countries that started COVID-19 lockdown earlier were better able to achieve low case counts post-lockdown (Fig. S1). We gathered (1) country lockdown dates from media reports (table S1), and combined these with (2) country-level COVID-19 confirmed case counts (*68*) to estimate the infectious number of cases in each country at the time of lockdown. We gathered complete data for 85 countries and only analyzed these countries. In 2020, countries which instituted lockdown before 1,000 infectious cases were much more likely to contain COVID-19 initially, and this earliness of lockdown was more predictive of lockdown success than lockdown duration (Fig. S1). A lockdown was deemed successful if the average number of daily cases in the 7 days following lockdown is fewer than 10 cases. Of the 85 countries, 68 started lockdown before 1,000 infectious cases. 38% (26/68) of these countries with earlier lockdowns contained COVID-19 initially, compared to 0% (0/17) of countries with later lockdowns (a statistically significant difference at p = 0.0057). This is robust across many thresholds and definitions of lockdown success (Fig. S4) and caseload-based definitions of lockdown earliness (Fig. S5). Earliness of lockdown (measured by caseload) was also more predictive of lockdown success than geographical location (Fig. S2) and earliness measured by the raw lockdown start date (Fig. S3).

This analysis has limitations. First, we do not account for significant variation among countries in the extent of COVID-19 testing, the number of imported cases (approximated by the amount of travel), demographics and age structure, country size and density, and other factors; all of these can affect measurements of lockdown success. Countries which did not test extensively may be recorded as having low cases post-lockdown and as having started lockdown early, which could partially explain the observed association between lockdown earliness and success. However, this does not seem to explain most of the relationship: countries like Thailand and New Zealand, which tested extensively per capita (*69*), were among the countries with early, successful lockdowns. Second, we cannot definitively distinguish correlation from causation: the association between earlier lockdown and fewer cases post-lockdown may be because countries which were willing to implement lockdown earlier were also more willing to implement and comply with more stringent lockdowns. Nevertheless, the observed association between lockdown earliness and success is consistent with the hypothesis that lockdown earliness improves chances of success.

We used (1) and (2) to calculate (a) the infectious number of cases in each country at the time of lockdown (as a measure of the earliness of lockdown) and (b) the number of cases in each country following lockdown (as a measure of the lockdown's success). For (1), we only analyzed countries' first lockdowns and required these lockdowns to start before 2021-01-01 and last longer than 7 days. When a country had regional lockdowns which differed from the national lockdown, we used the start and end dates of the national lockdown. If the country had no national lockdown and only regional lockdowns, we used the dates of the regional lockdown with the median start date.

For (a), we used overall case counts to estimate the *infectious* cases at the lockdown start date by assuming (i) a 5-day infectious period (*43*) and therefore (ii) that the infectious cases on day T are 1/5 * (cases on day T-4) + 2/5 * (cases on day T-3) + … + 5/5 * (cases on day T). We also performed a sensitivity analysis using the raw case count average at the start of lockdown instead of the infectious case count (Fig. S5). For (b), we calculated the average daily new cases for the 7 days after the lockdown was lifted, and we considered a lockdown successful if this average was fewer than a threshold of 10 cases. We performed a sensitivity analysis for thresholds of 3, 10, 30 and 100 cases (Fig. S4).

To calculate statistical significance of the different lockdown success rates between countries with earlier and later lockdowns, we used the 2-sample test for equality of proportions implemented in R's prop.test.

Validation of model in US states.

In validating our model in US state data, we were able to predict US state detection times with a mean absolute error of 0.97 weeks (Fig. S7). We achieved this with a relatively simple validation setup: R0 was the only parameter we allowed to vary among states, which did not allow the model to account for differing state testing turnaround and capacity or inter-state variation in growth rate of imported cases. Gathering those data and accounting for those could improve the model's accuracy. (Other inter-state variables like differing age structures and demographics, as well as lockdown policies and pandemic-induced mobility changes, should be accounted for in the state-specific R0's.)

Derivation for mathematical approximation of cases until detection

As an intuitive summary of the derivation, we break down the number of cases until detection into two variables: (i) the cases that occur until the infection of the "threshold case" (the final case needed to trigger detection), and (ii) the cases that occur afterwards during the delay between the threshold case's infection and detection. In the formula, d/p_{test} corresponds to (i), and each of those $(R_0 - 1)/R_0 * d/p_{test}$ cases in the last generation spawns an outbreak process proportional to $\sum_{n=1}^{g} R_0^n$ cases, corresponding to (ii).

Full derivation: Assume the outbreak starts in a community covered by the detection system. We want the mean and variance of the cumulative number of cases C which have occurred by the time the detection system is triggered. The outbreak occurs in generations, where the index case is generation 0 and each generation of cases creates the next generation of cases. We can express C as follows:

$$C = T + \sum_{n=1}^{g} C_n$$

where T is the number of cases infected until the threshold case is infected, C_i is the number of infectious cases in the i-th generation after the threshold case is infected, and g is the number of generations which occur in the delay between the threshold case's infection and detection. Note first that

$$T \sim NBinom(d, p_{test})$$

where d is the detection threshold (the number of cases which need to be detected to constitute an outbreak) and p_{test} is the probability any particular case is tested. For example, in the hospital system, $p_{test} = hosp\_rate$.

For the mean of C, we will need:

$$\mathbb{E}[C_n] = \mathbb{E}\big[\mathbb{E}[C_n|T]\big] \approx \mathbb{E}\left[\frac{R_0 - 1}{R_0} T R_0^n\right] = (R_0 - 1)(R_0^{n-1}) \frac{d}{p_{test}}$$

The first expansion of $\mathbb{E}[C_n]$ derives from two facts: (a) C_n is the sum of approximately $\frac{R_0-1}{R_0}T$ independent and identically distributed branching processes, so that the mean of C_n is $\frac{R_0-1}{R_0}T$ times the mean of one branching process. (b) From branching process mathematics, the mean of Z_n, the number of entities in the n-th generation of a branching process, is $\mathbb{E}[O]^n$ (*70*), where O is the offspring distribution (the distribution of the number of secondary cases infected by each primary case). In this study, O is negative binomial with mean R_0 and dispersion 0.01 (*48*). Thus

$$\mathbb{E}[C] = \mathbb{E}[T] + \sum_{n=1}^{g} \mathbb{E}\,[C_n] \approx \frac{d}{p_{test}}\left(1 + (R_0 - 1)\sum_{n=1}^{g} R_0^{n-1}\right) = \frac{d \times R_0^g}{p_{test}}$$

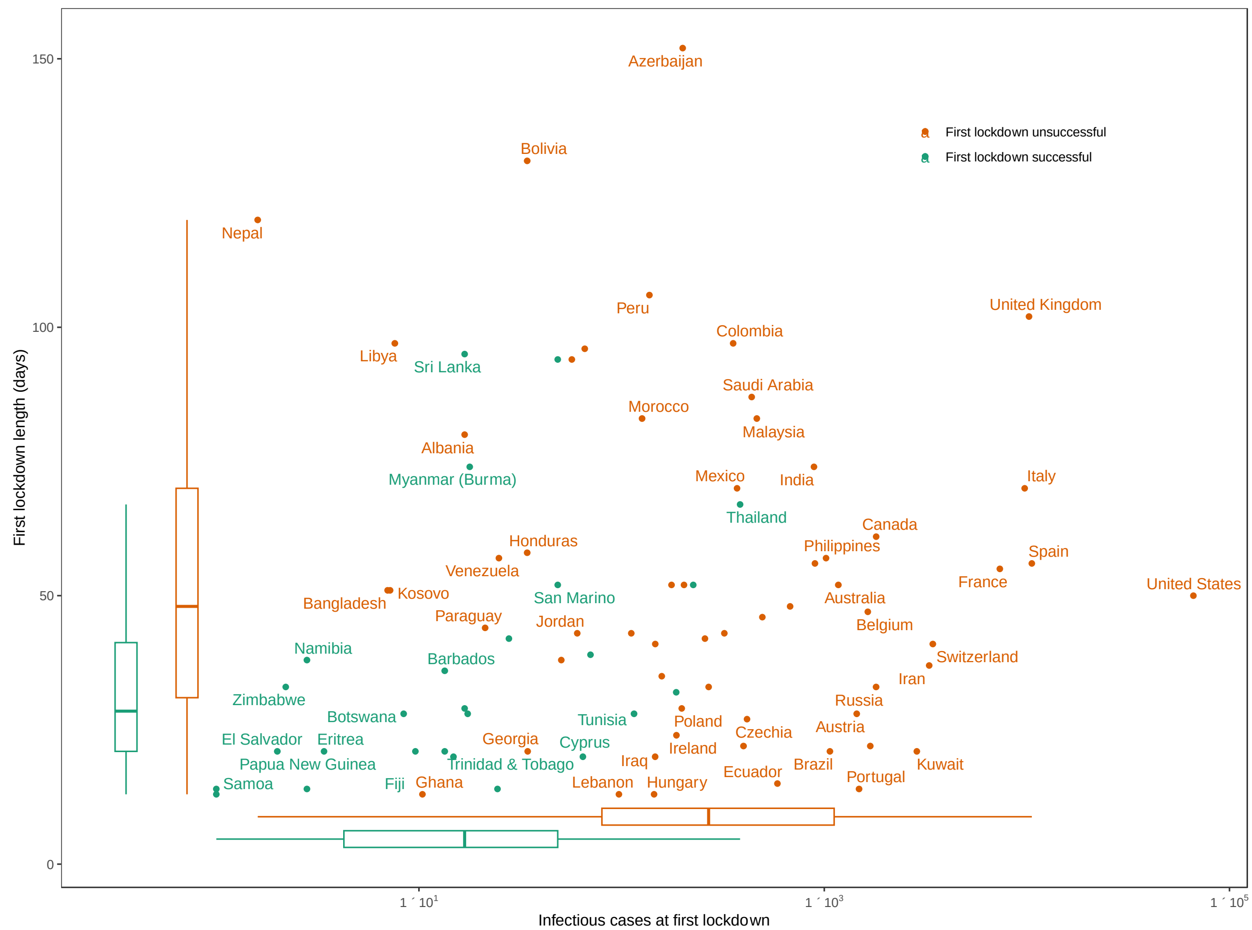


Fig. S1. Earliness of lockdown (x-axis) versus lockdown length in days (y-axis) and lockdown success for 85 countries' first 2020 COVID-19 lockdowns (first lockdown unsuccessful (orange) and first lockdown successful (teal)). Earliness is measured by the number of infectious cases at the start of lockdown. A lockdown is successful if the average number of daily cases following lockdown is less than 10 for 7 days. Boxplots on the axes show marginal distributions and the separation of successful and unsuccessful lockdowns by lockdown earliness and length.

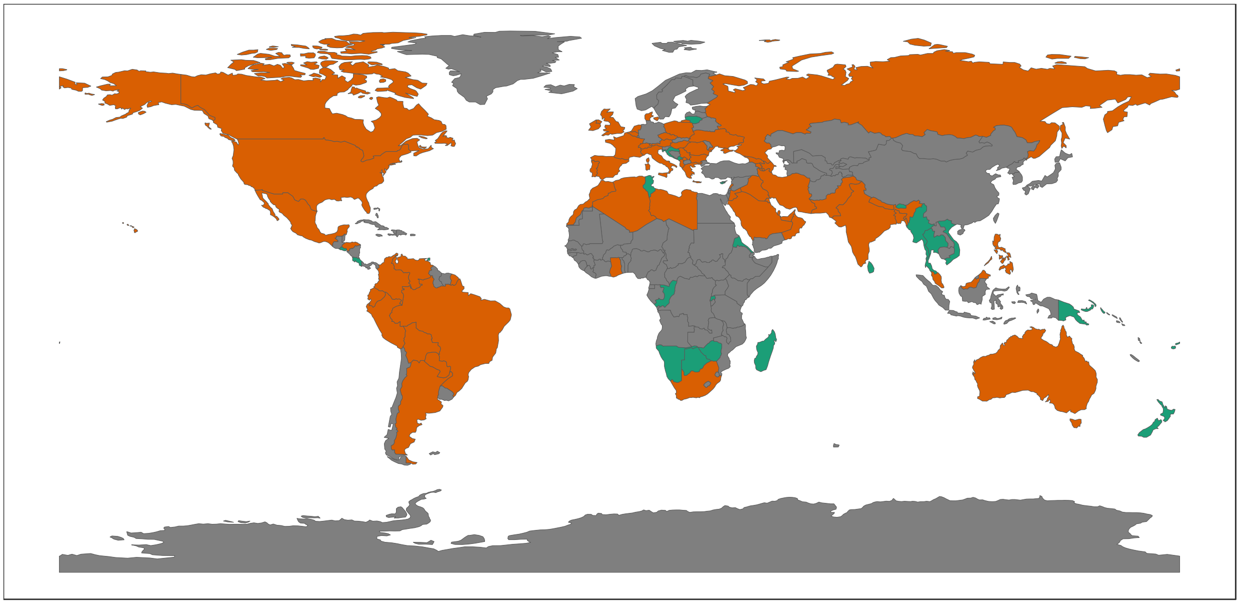


Fig. S2. Countries colored by whether their first lockdowns successfully contained COVID-19 initially.

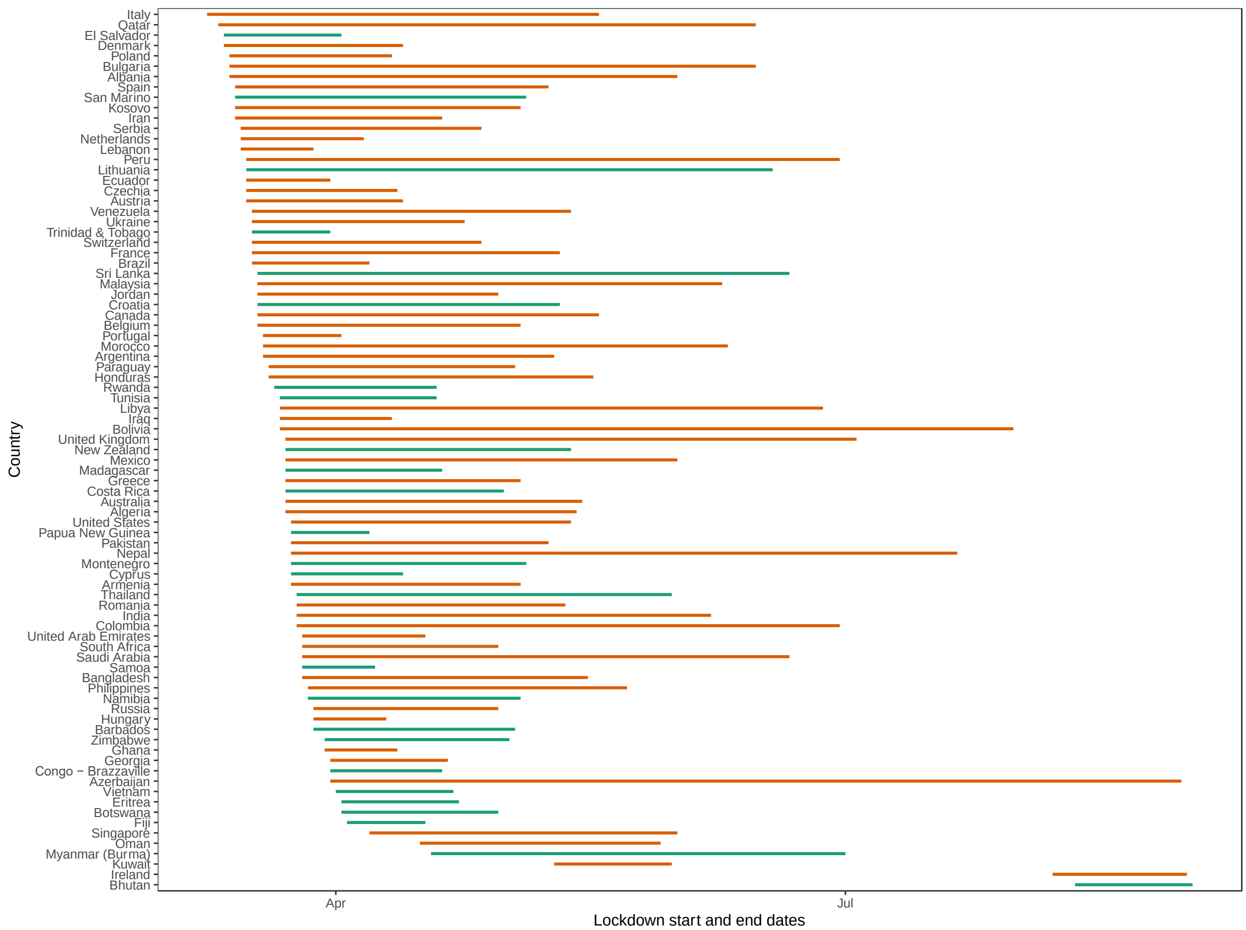


Fig. S3. Durations and start and end dates of lockdowns in various countries.

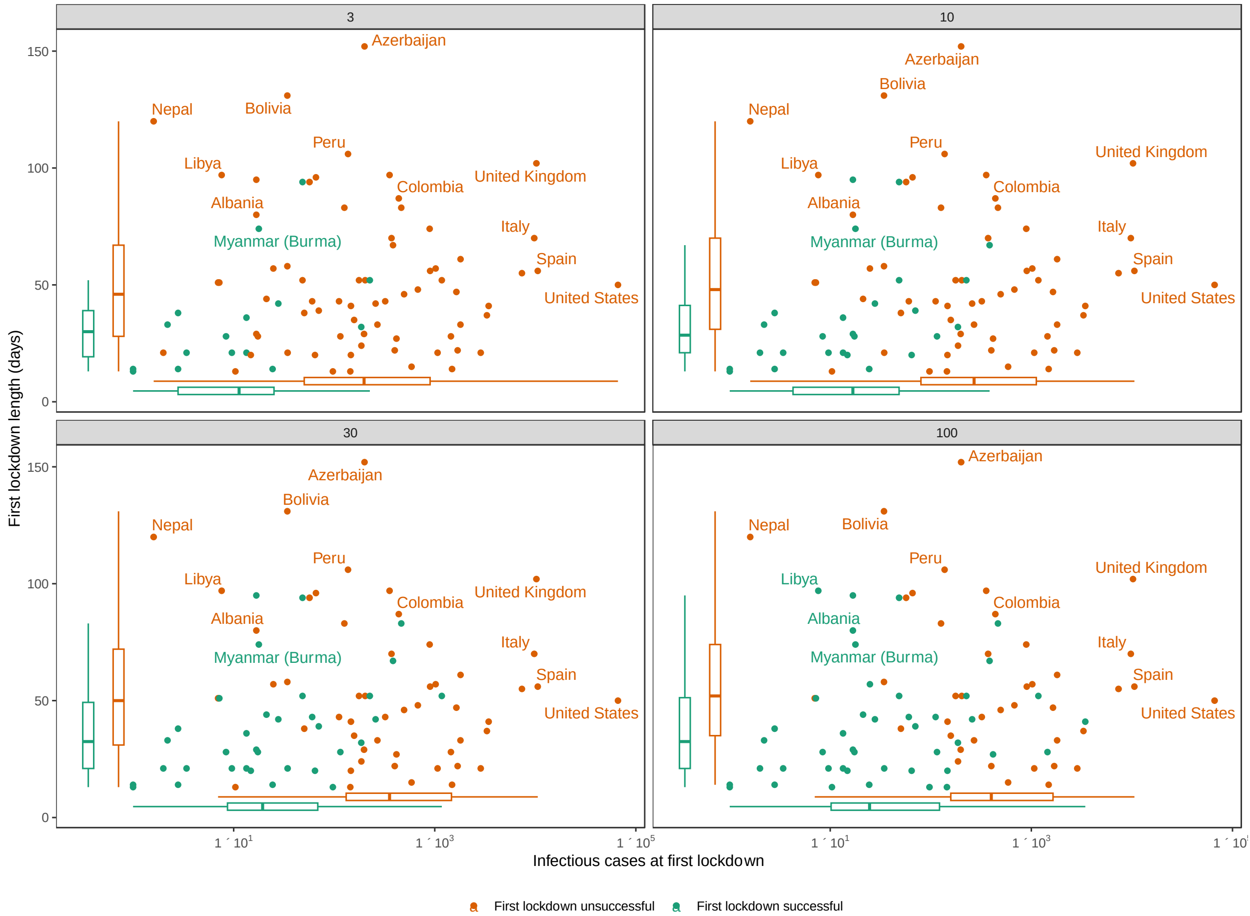


Fig. S4. Earliness of lockdown (x-axis) versus lockdown length in days (y-axis) and lockdown success (first lockdown unsuccessful (orange) and first lockdown successful (teal)), analogous to fig. S1, for 4 different thresholds of lockdown success (thresholds shown in gray labels). A lockdown is successful if the average number of daily cases following lockdown is less than the threshold for 7 days.

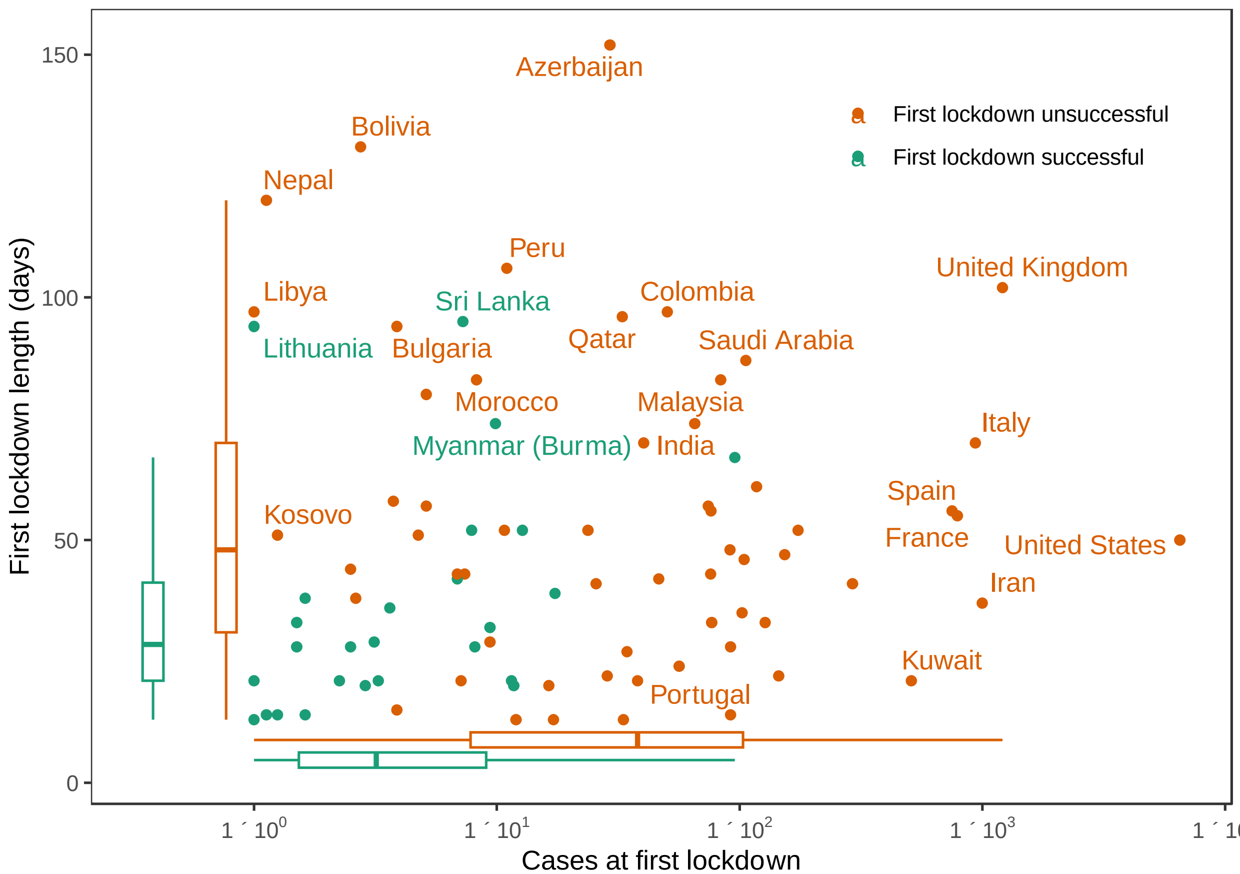


Fig. S5. Earliness of lockdown (x-axis) versus lockdown length in days (y-axis) and lockdown success (first lockdown unsuccessful (orange) and first lockdown successful (teal)), analogous to fig. S1, except that earliness of lockdown is measured here in terms of all cases (rather than infectious cases) at lockdown.

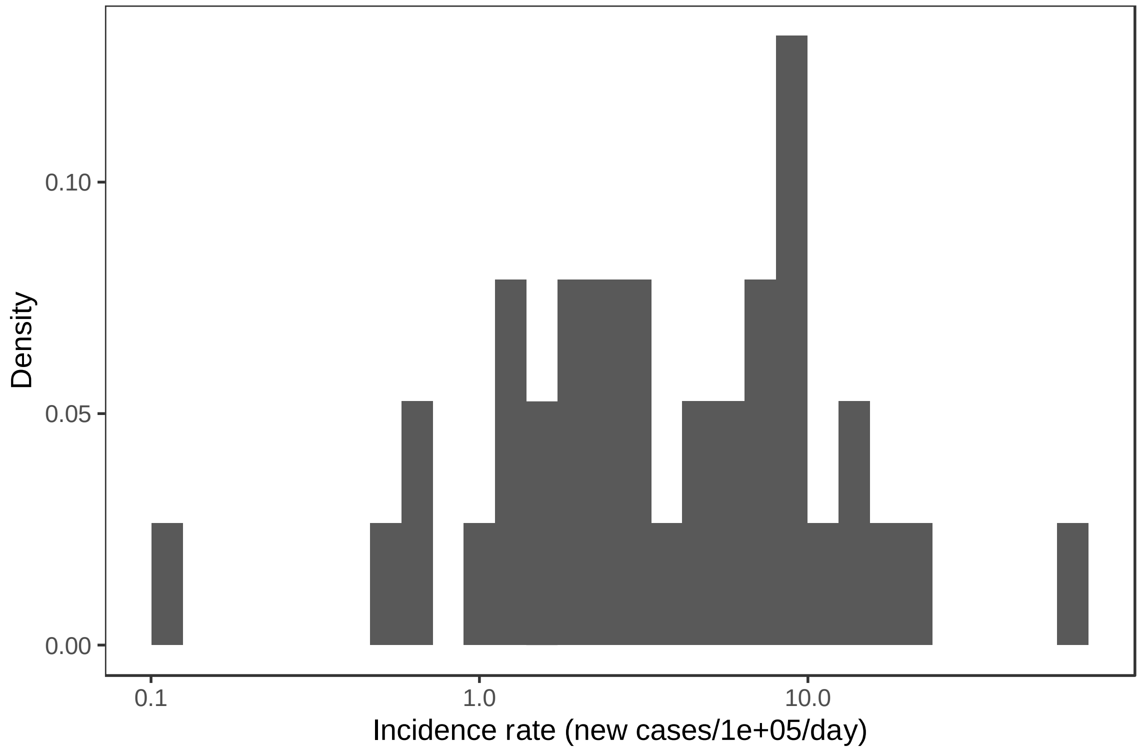


Fig. S6. Distribution of wastewater sensitivity estimated from reported COVID-19 incidences and wastewater sample data from 47 sampling locations from (*49*).

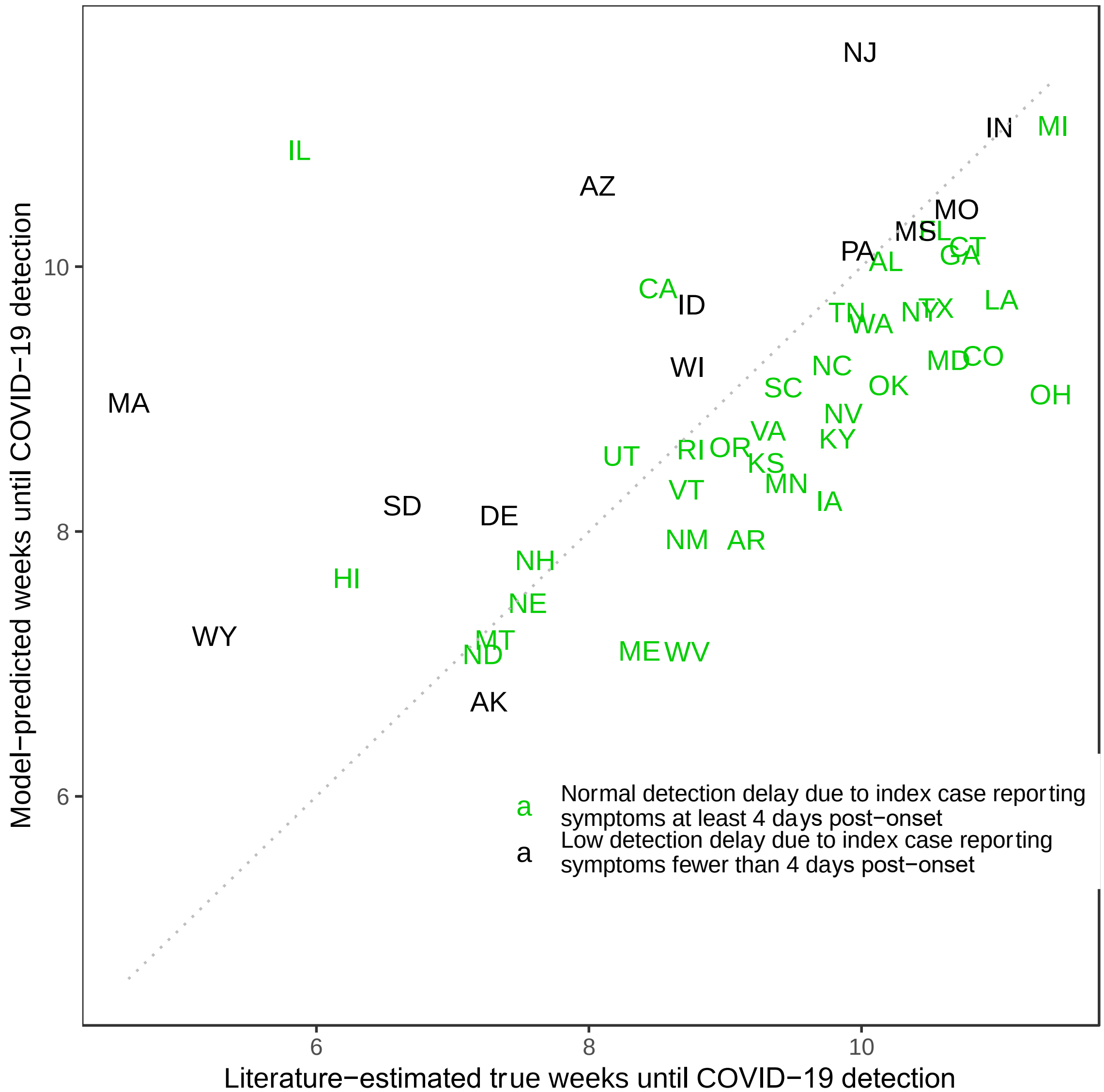
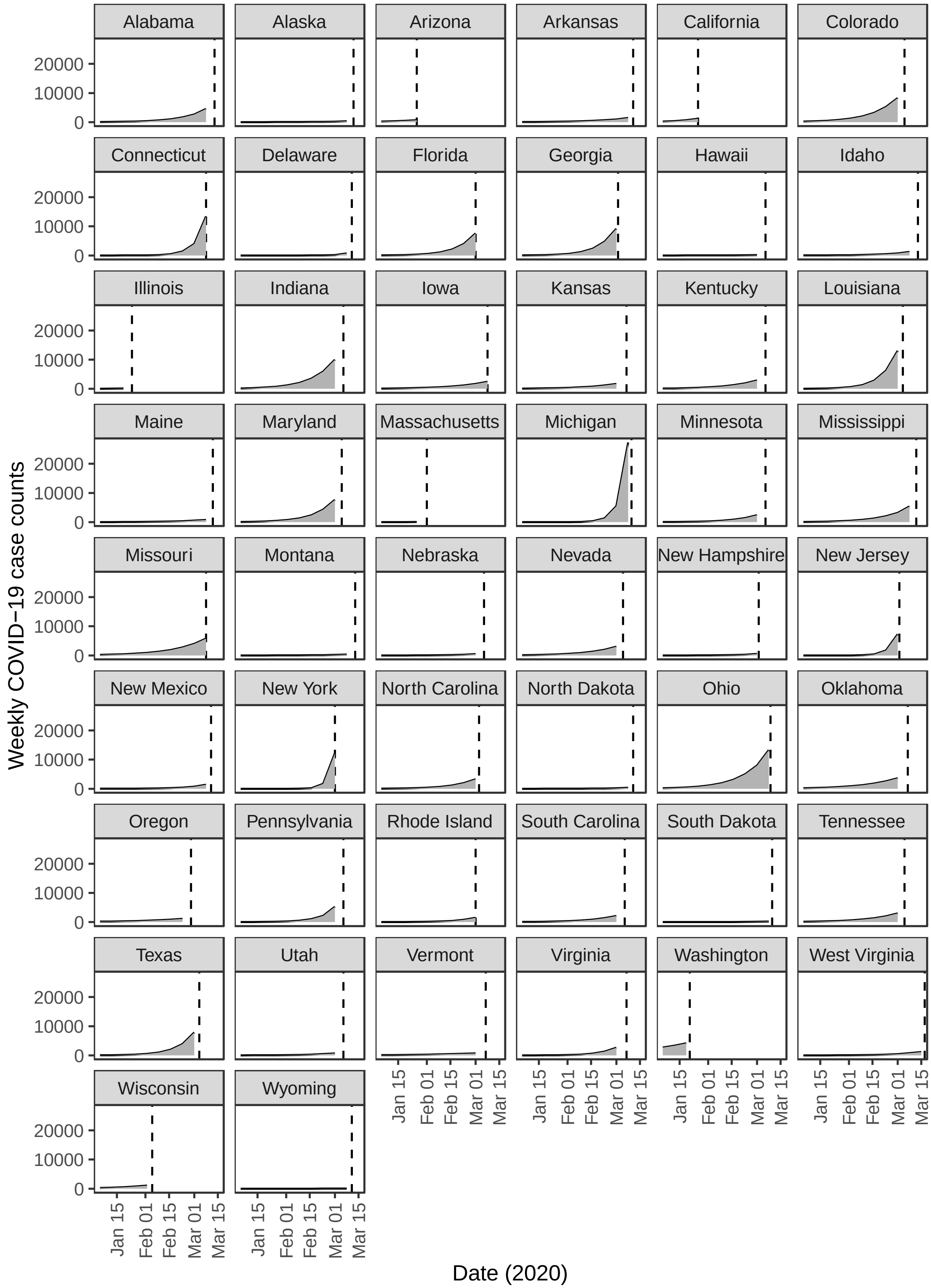


Fig. S7. Actual versus predicted COVID-19 weeks required to trigger each US state's detection of its first 2020 COVID-19 outbreak (by monitoring symptomatic travel-associated cases).


Alabama
Alaska
Arizona
Arkansas
California
Colorado
Connecticut
Delaware
Florida
Georgia
Hawaii
Idaho
Illinois
Indiana
Iowa
Kansas
Kentucky
Louisiana
Maine
Maryland
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Montana
Nebraska
Nevada
New Hampshire
New Jersey
New Mexico
New York
North Carolina
North Dakota
Ohio
Oklahoma
Oregon
Pennsylvania
Rhode Island
South Carolina
South Dakota
Tennessee
Texas
Utah
Vermont
Virginia
Washington
West Virginia
Wisconsin
Wyoming
20000
10000
0
Weekly COVID−19 case counts
Jan 15
Feb 01
Feb 15
Mar 01
Mar 15
Date (2020)

Fig. S8. COVID-19 cases leading up to COVID-19 detection in 50 US states, which are used as the x-axis in fig. S7. Y-values here are literature estimates of total (tested plus untested) cases (*50*). We extrapolated these cases based on exponential fit back to January 1, 2020. Dashed lines mark the date of the first detected case in the state, and the shaded areas under the curve denote the cumulative number of cases until detection.

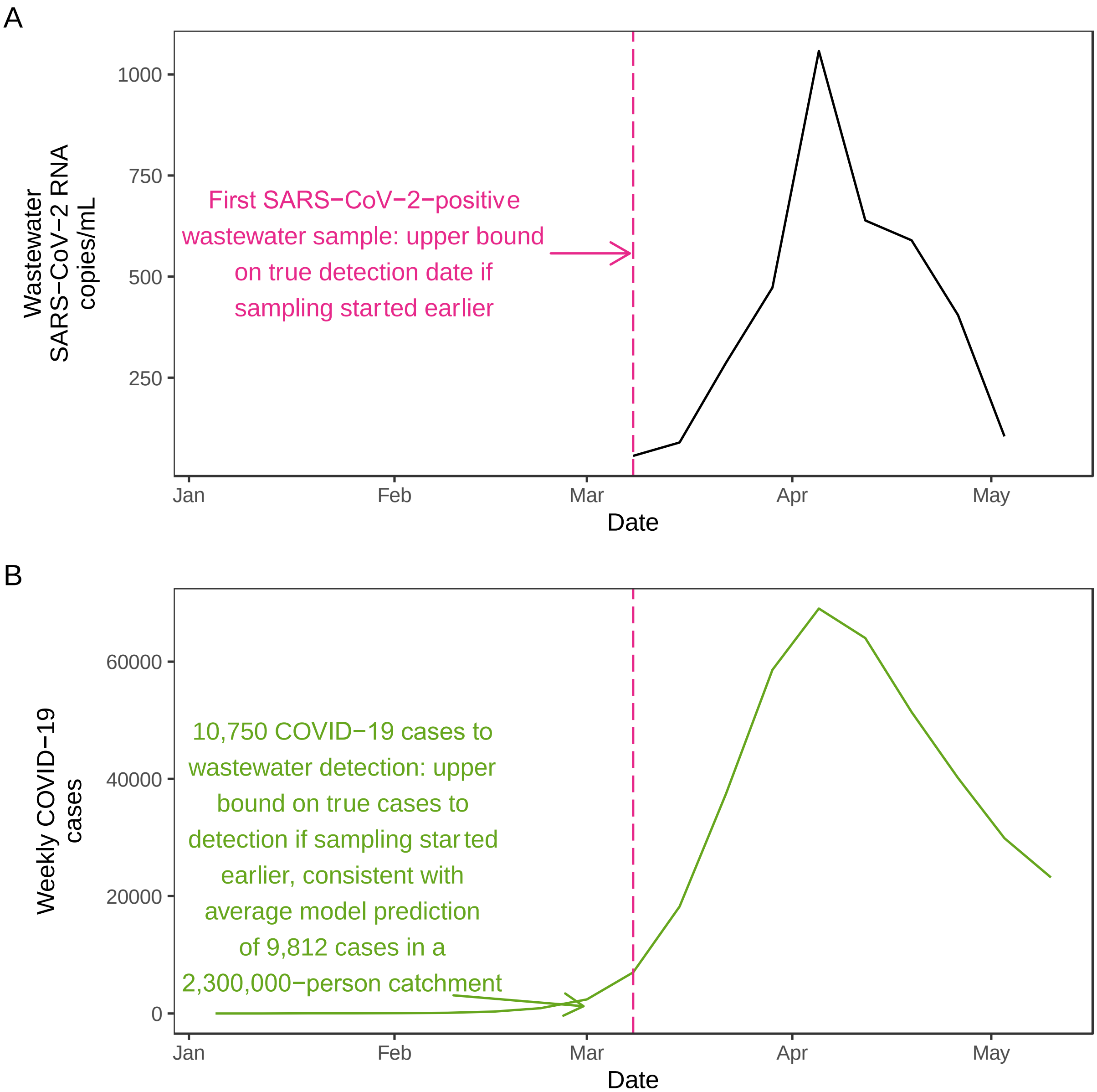

Fig. S9. Number of COVID-19 cases in Massachusetts before wastewater detection in 2020. (**A**) 7-day averages of SARS-CoV-2 RNA copies/mL in wastewater from the Deer Island Treatment Plant (combined Southern and Northern plants), the Massachusetts Water Resources Authority (MWRA) plant treating wastewater from 3.1 million people in the Boston metropolitan area in the United States (based on (*52*)). (**B**) Weekly non-cumulative COVID-19 case counts in the MWRA-covered communities (based on literature estimates of total tested and untested cases in (*50*)).

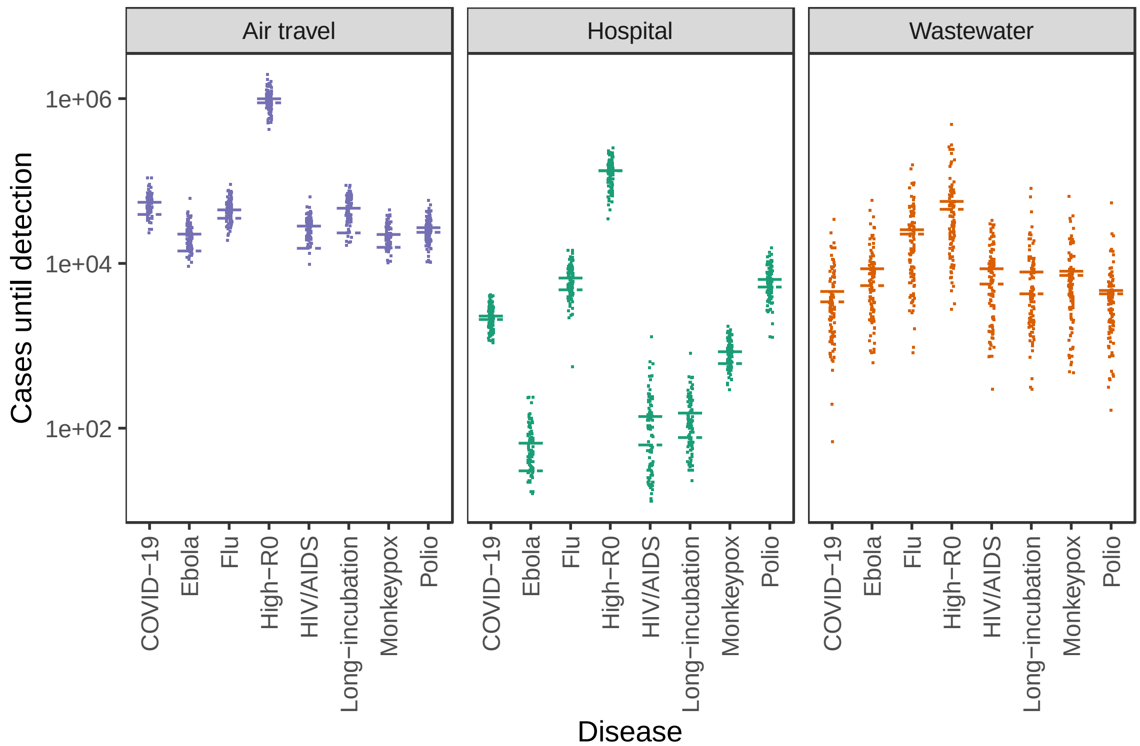

Fig. S10. Comparison of simulation model of cases until detection versus mathematical approximation (hospital (teal), wastewater (orange) and air travel (purple)) in a 650,000-person catchment. Solid lines are the means of simulated case counts; dashed lines are the approximated means based on the derived formula for cases at detection.

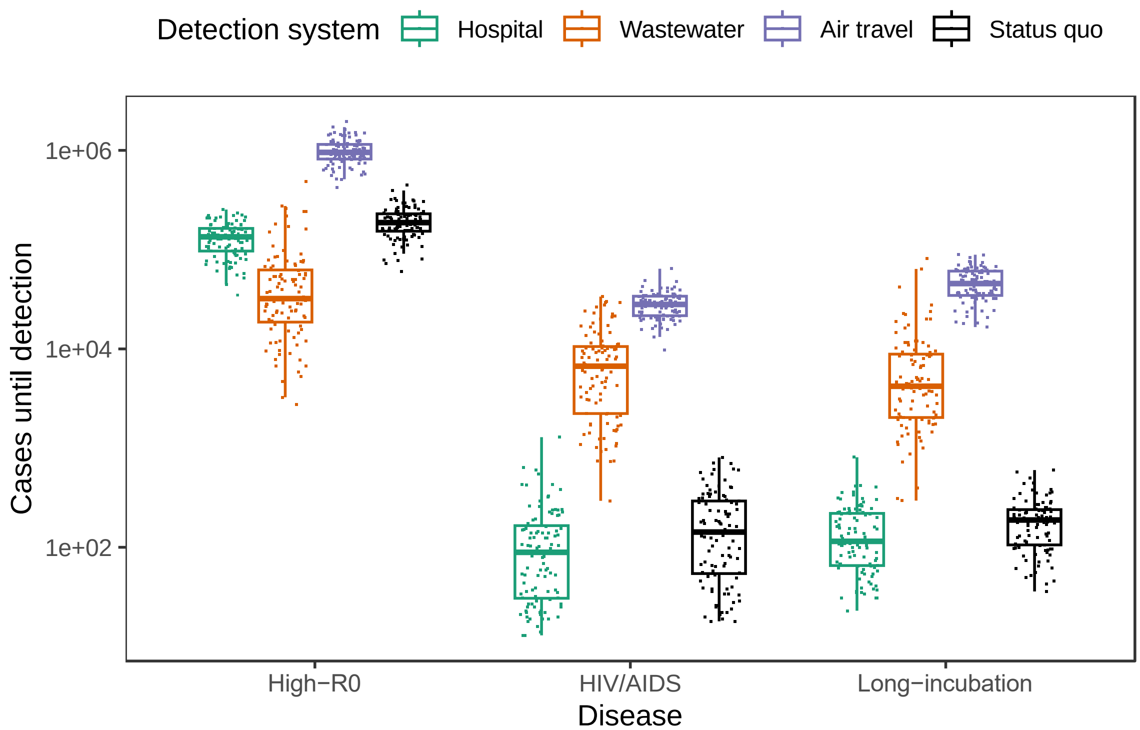

Fig. S11. Earliness of detection for detection systems in cases for additional infectious diseases in a 650,000-person catchment, akin to Fig. 2A (hospital (teal), wastewater (orange), air travel (purple) and status quo (black)).

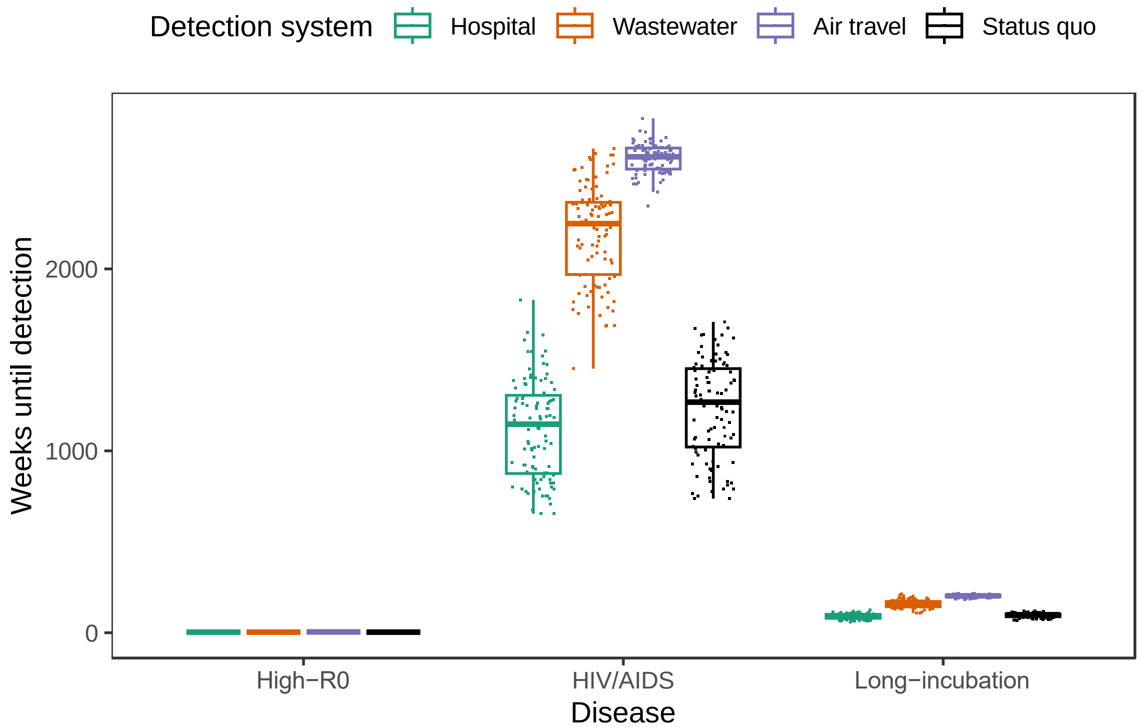

Fig. S12. Earliness of detection for detection systems in weeks for additional infectious diseases in a 650,000-person catchment, akin to Fig. 2A (hospital (teal), wastewater (orange), air travel (purple) and status quo (black)).

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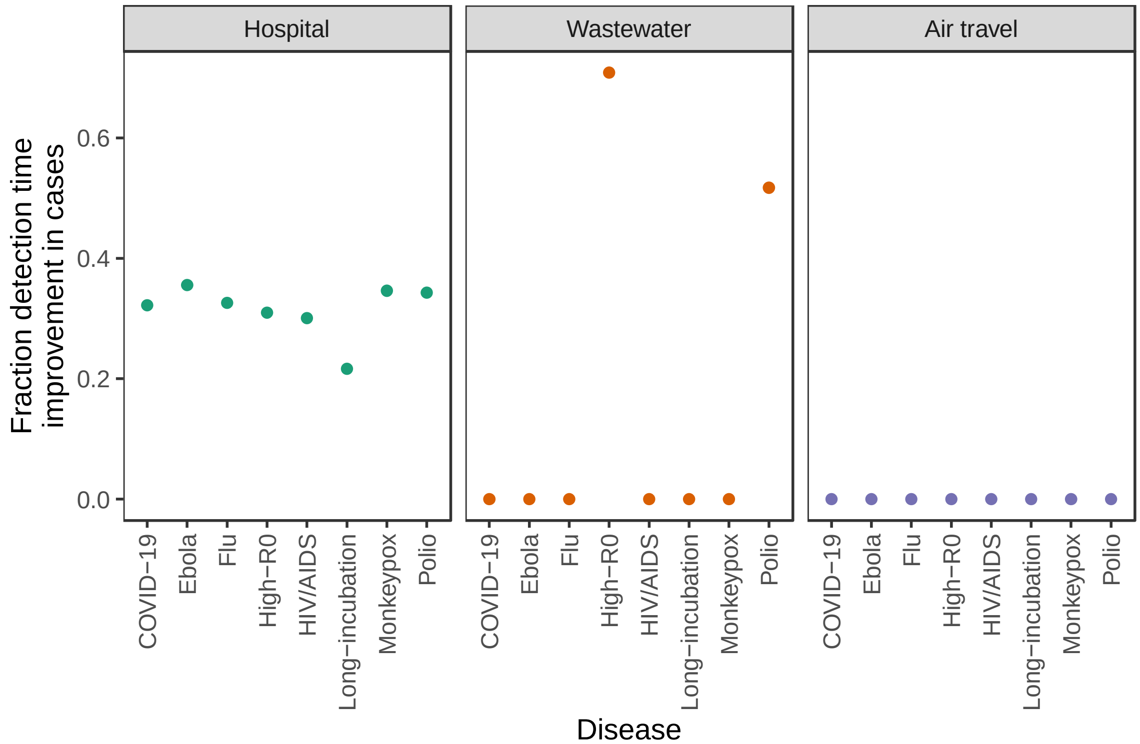


Fig. S13. Percent improvement in detection times in cases of the proposed systems over status quo detection for multiple outbreaks (air travel (purple), hospital (teal) and wastewater (orange)). Improvements are calculated for each detection system and outbreak by dividing the system's mean detection time in cases into from the mean status quo detection time for that outbreak in Fig. 2A.

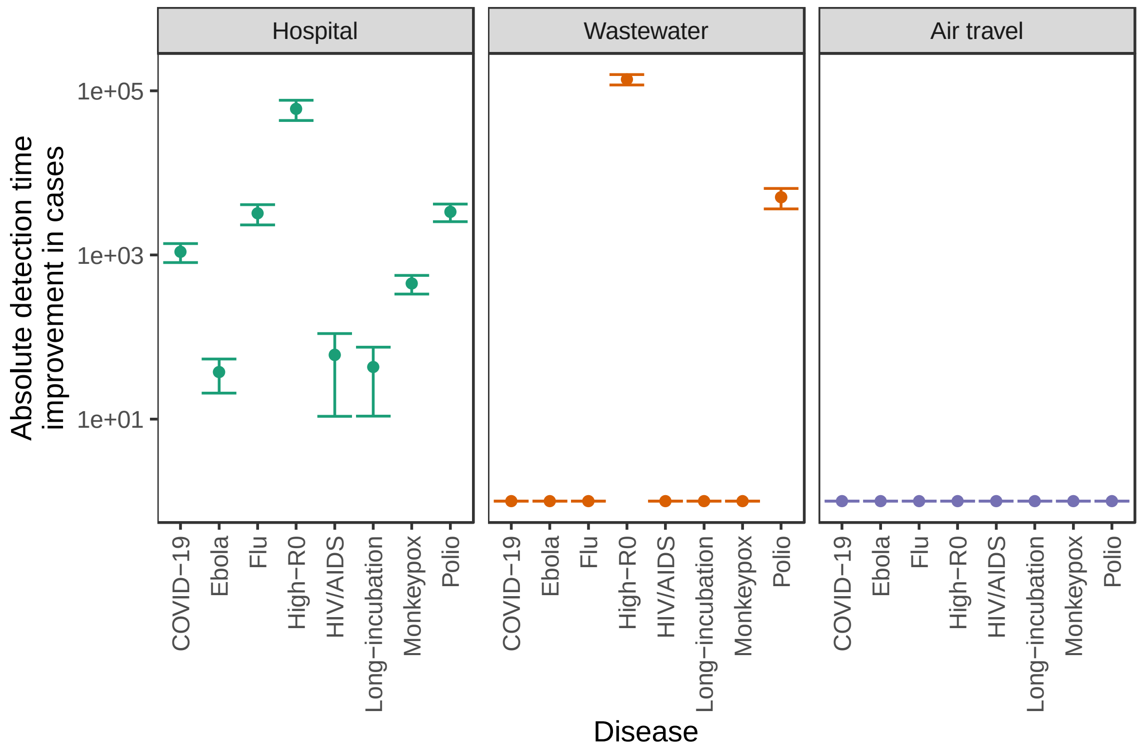


Fig. S14. Absolute improvement in detection times in cases of the proposed systems over status quo detection for multiple outbreaks (air travel (purple), hospital (teal) and wastewater (orange)). Improvements are calculated for each detection system and outbreak by subtracting the system's mean detection time in cases from from the mean status quo detection time for that outbreak in Fig. 2A.

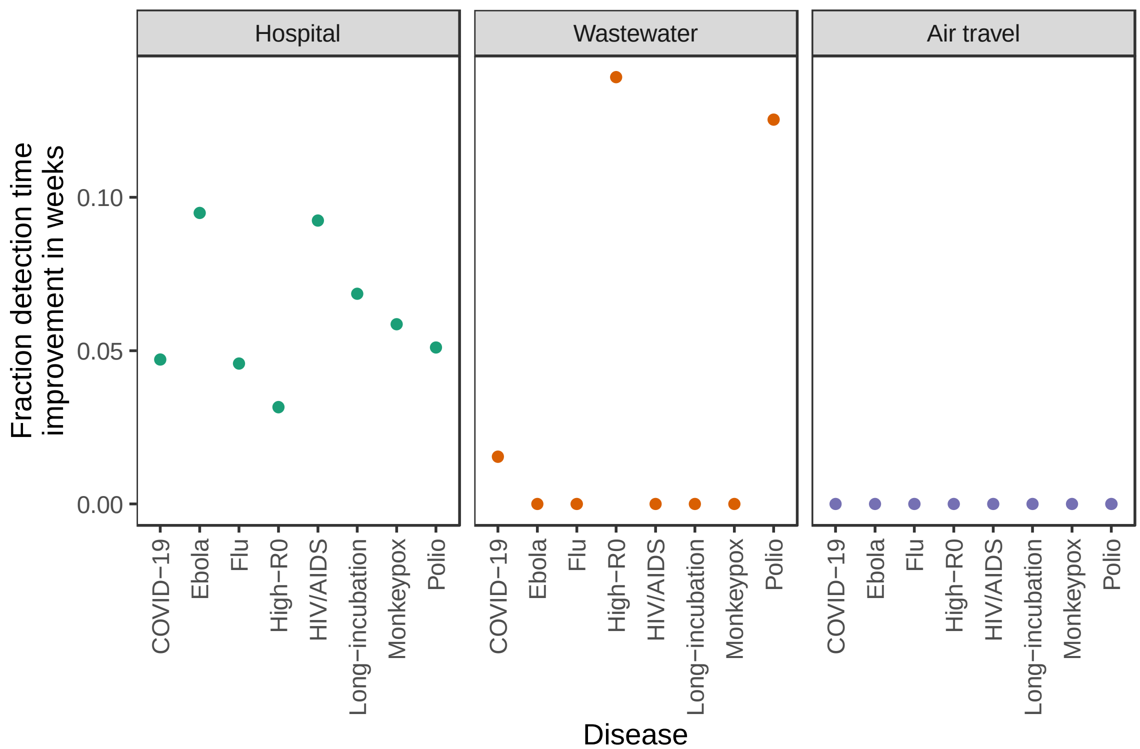


Fig. S15. Percent improvement in detection times in weeks of the proposed systems over status quo detection for multiple outbreaks (air travel (purple), hospital (teal) and wastewater (orange)). Improvements are calculated for each detection system and outbreak by dividing the system's mean detection time in weeks into from the mean status quo detection time for that outbreak in Fig. 2A.

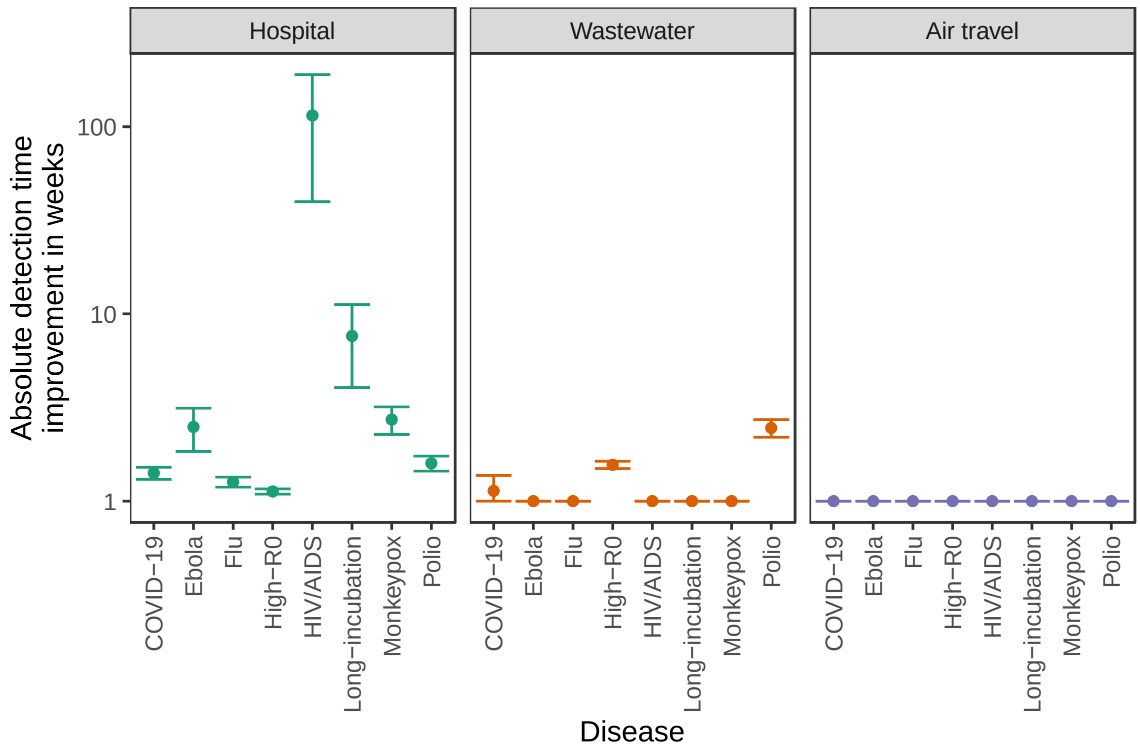
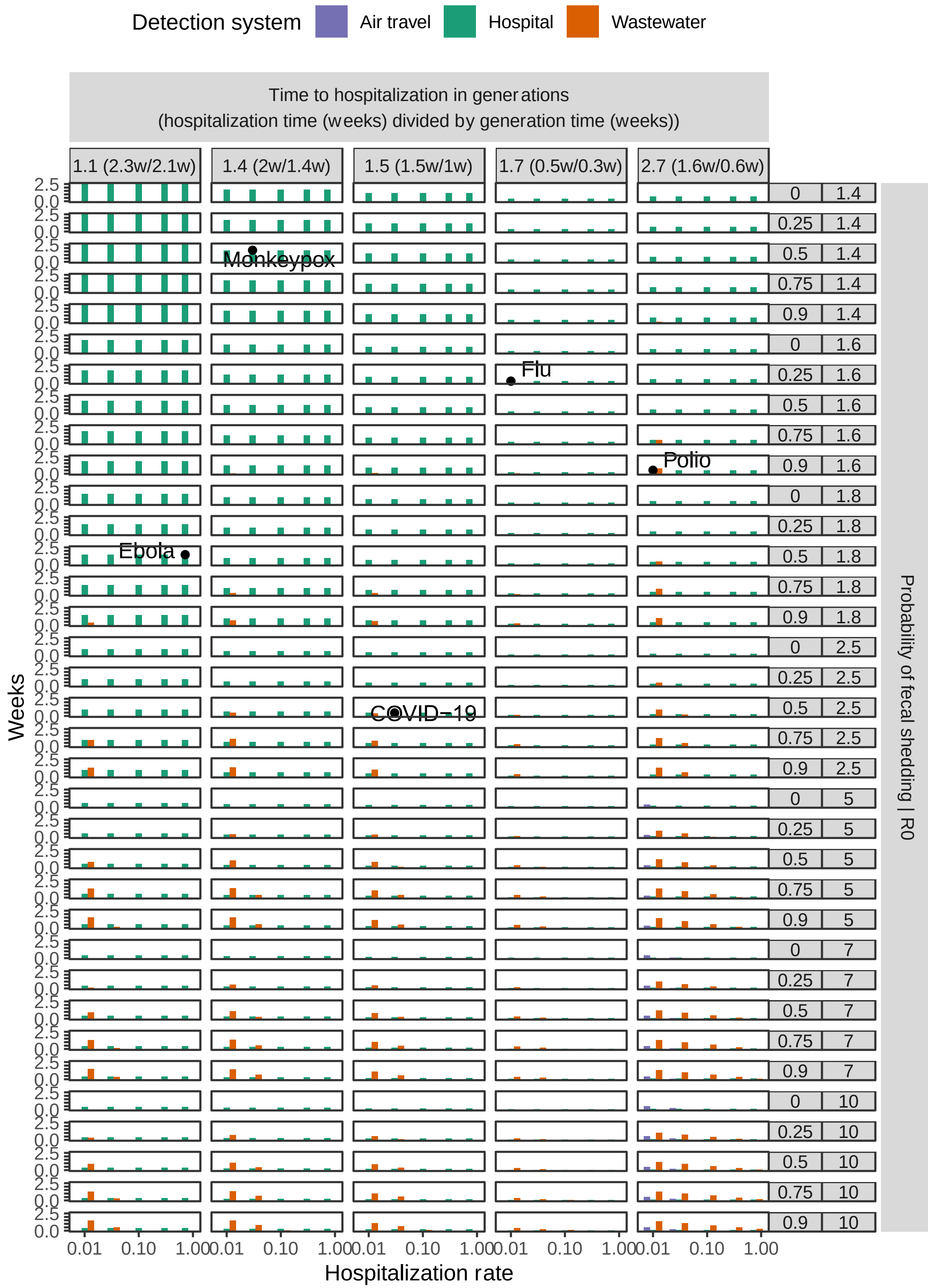


Fig. S16. Absolute improvement in detection times in weeks of the proposed systems over status quo detection for multiple outbreaks (air travel (purple), hospital (teal) and wastewater (orange)). Improvements are calculated for each detection system and outbreak by subtracting the system's mean detection time in weeks from from the mean status quo detection time for that outbreak in Fig. 2A.



Detection system
Air travel
Hospital
Wastewater
Time to hospitalization in generations
(hospitalization time (weeks) divided by generation time (weeks))
1.1 (2.3w/2.1w)
1.4 (2w/1.4w)
1.5 (1.5w/1w)
1.7 (0.5w/0.3w)
2.7 (1.6w/0.6w)
Monkeypox
Flu
Polio
Ebola
COVID−19
Weeks
Hospitalization rate
Probability of fecal shedding | R0

Fig. S17. Average weeks gained over status quo detection by the proposed detection systems across the epidemiological space of possible diseases. This is similar to Fig. 3.

Table S1. Dates of first COVID-19 lockdowns implemented by 85 countries in 2020. Dates are sourced from media reports.

Country/Region	First lockdown start date	First lockdown end date	First lockdown length (days)
Albania	2020-03-13	2020-06-01	80
Algeria	2020-03-23	2020-05-14	52
Argentina	2020-03-19	2020-05-10	52
Armenia	2020-03-24	2020-05-04	41
Australia	2020-03-23	2020-05-15	52
Austria	2020-03-16	2020-04-13	28
Azerbaijan	2020-03-31	2020-08-30	152
Bangladesh	2020-03-26	2020-05-16	51
Barbados	2020-03-28	2020-05-03	36
Belgium	2020-03-18	2020-05-04	47
Bhutan	2020-08-11	2020-09-01	21
Bolivia	2020-03-22	2020-07-31	131
Botswana	2020-04-02	2020-04-30	28
Brazil	2020-03-17	2020-04-07	21
Bulgaria	2020-03-13	2020-06-15	94
Canada	2020-03-18	2020-05-18	61
Colombia	2020-03-25	2020-06-30	97
Congo - Brazzaville	2020-03-31	2020-04-20	20
Costa Rica	2020-03-23	2020-05-01	39
Croatia	2020-03-18	2020-05-11	32
Cyprus	2020-03-24	2020-04-13	20
Czechia	2020-03-16	2020-04-12	27
Denmark	2020-03-12	2020-04-13	33
Ecuador	2020-03-16	2020-03-31	15
El Salvador	2020-03-12	2020-04-02	21
Eritrea	2020-04-02	2020-04-23	21
Fiji	2020-04-03	2020-04-17	14
France	2020-03-17	2020-05-11	55
Georgia	2020-03-31	2020-04-21	21
Ghana	2020-03-30	2020-04-12	13
Greece	2020-03-23	2020-05-04	42
Honduras	2020-03-20	2020-05-17	58
Hungary	2020-03-28	2020-04-10	13
India	2020-03-25	2020-06-07	74
Iran	2020-03-14	2020-04-20	37
Iraq	2020-03-22	2020-04-11	20
Ireland	2020-08-07	2020-08-31	24
Italy	2020-03-09	2020-05-18	70
Jordan	2020-03-18	2020-04-30	43

Country/Region	First lockdown start date	First lockdown end date	First lockdown length (days)
Kosovo	2020-03-14	2020-05-04	51
Kuwait	2020-05-10	2020-05-31	21
Lebanon	2020-03-15	2020-03-28	13
Libya	2020-03-22	2020-06-27	97
Lithuania	2020-03-16	2020-06-18	94
Madagascar	2020-03-23	2020-04-20	28
Malaysia	2020-03-18	2020-06-09	83
Mexico	2020-03-23	2020-06-01	70
Montenegro	2020-03-24	2020-05-05	42
Morocco	2020-03-19	2020-06-10	83
Myanmar (Burma)	2020-04-18	2020-07-01	74
Namibia	2020-03-27	2020-05-04	38
Nepal	2020-03-24	2020-07-21	120
Netherlands	2020-03-15	2020-04-06	22
New Zealand	2020-03-23	2020-05-13	52
Oman	2020-04-16	2020-05-29	43
Pakistan	2020-03-24	2020-05-09	46
Papua New Guinea	2020-03-24	2020-04-07	14
Paraguay	2020-03-20	2020-05-03	44
Peru	2020-03-16	2020-06-30	106
Philippines	2020-03-27	2020-05-23	57
Poland	2020-03-13	2020-04-11	29
Portugal	2020-03-19	2020-04-02	14
Qatar	2020-03-11	2020-06-15	96
Romania	2020-03-25	2020-05-12	48
Russia	2020-03-28	2020-04-30	33
Rwanda	2020-03-21	2020-04-19	29
Samoa	2020-03-26	2020-04-08	13
San Marino	2020-03-14	2020-05-05	52
Saudi Arabia	2020-03-26	2020-06-21	87
Serbia	2020-03-15	2020-04-27	43
Singapore	2020-04-07	2020-06-01	56
South Africa	2020-03-26	2020-04-30	35
Spain	2020-03-14	2020-05-09	56
Sri Lanka	2020-03-18	2020-06-21	95
Switzerland	2020-03-17	2020-04-27	41
Thailand	2020-03-25	2020-05-31	67
Trinidad & Tobago	2020-03-17	2020-03-31	14
Tunisia	2020-03-22	2020-04-19	28
Ukraine	2020-03-17	2020-04-24	38
United Arab Emirates	2020-03-26	2020-04-17	22

Country/Region	First lockdown start date	First lockdown end date	First lockdown length (days)
United Kingdom	2020-03-23	2020-07-03	102
United States	2020-03-24	2020-05-13	50
Venezuela	2020-03-17	2020-05-13	57
Vietnam	2020-04-01	2020-04-22	21
Zimbabwe	2020-03-30	2020-05-02	33

Table S2. Threshold, delay, and probability for 3 proposed early detection systems.

Detection system	Detection probability	Detection threshold	Detection delay
Hospital [1]	outbreak hospitalization rate	10	(outbreak time to hospitalization (weeks) + logistical detection delay)/outbreak serial interval (weeks)
Wastewater [2]	fraction of people connected to central sewage * outbreak probability of fecal shedding	adjusted draw from (*49*) (median 2.5e-5) * community catchment population (non-cumulative)	(outbreak time to fecal shedding (weeks) + logistical detection delay)/outbreak serial interval (weeks)
Air travel [3]	weekly probability of international travel * symptomatic rate	10	(outbreak serial interval (weeks) + logistical detection delay)/outbreak serial interval (weeks)

[1] Detection threshold: The government or hospital implementing the system chooses the detection threshold they consider to be sufficient. For COVID-19, Wuhan hospitals were willing to report the "extraordinary" situation to local health authorities after seven known cases (*64*). During the 2002-2004 SARS-CoV-1 outbreak, hospital officials became alarmed after one patient and eight doctors and nurses became sick (*66*). Thus we choose a detection threshold of ten.

[2] See Materials and methods for details on setting the detection threshold. Detection delay: (*58*, *71*). Detection probability: Fecal shedding tends to constitute more of the human pathogen nucleic acid in wastewater than urine, saliva, or other specimens, due to higher rates of shedding and higher pathogen loads in feces (*58*, *72*). The fraction of people connected to central sewage in Wuhan is estimated at 80% based on a 2016 Asian Development Bank appraisal stating that Wuhan aimed to treat this fraction of wastewater in 2010 (*73*); this fraction is similar to the fraction of US households connected to public sewers (83%) (*59*).

[3] Detection threshold: reasoning is similar to hospital monitoring reasoning for detection threshold.

Table S3. Epidemiological parameters of outbreaks studied.

Outbreak	Hospitalization rate	R0	Serial interval (weeks)	Time to hospitalization (weeks)	Probability of fecal shedding	Dispersion
COVID-19 [1]	0.03	2.5	1.0	1.5	0.50	0.7
Monkeypox (2022) [2]	0.03	1.4	1.4	2.0	0.50	0.1
Polio (2013-2014) [3]	0.01	1.6	0.6	1.6	0.90	0.1
Ebola (2013-2016) [4]	0.72	1.8	2.1	2.3	0.50	0.1
Flu (2009 pandemic) [5]	0.01	1.6	0.3	0.5	0.25	0.1
High-R0 (hypothetical)	0.03	20.0	1.0	1.5	0.50	0.1
HIV/AIDS (1980s-) [6]	1.00	2.5	234.0	468.0	0.37	0.1
Long-incubation (hypothetical) [7]	0.50	3.0	20.8	25.0	0.50	0.1

[1] (*43*, *58*, *74*, *75*).

[2] (*44*, *76*). Due to the lack of *infection* hospitalization rates at this time, we infer the infection hospitalization rate to be 0.03 by halving the estimated *case* hospitalization rates of 0.06-0.07 for the 2022 monkeypox outbreak (*77*, *78*). We choose half because a majority of monkeypox infections are symptomatic (*79*) and some fraction of those will seek medical care and get tested. Time to hospitalization is estimated by adding the incubation period of 7 days to the median time from symptom onset to hospitalization (7 days) (*80*). We and others are unable to find estimates of monkeypox fecal shedding rates (*81*), but it has been detectable in wastewater during the 2022 monkeypox outbreak (*82*), so we assign a value of 0.5, in line with SARS-CoV-2 and flu, but on the higher end because monkeypox causes symptoms more broadly than in just the respiratory system.

[3] Due to lack of data and estimates of R0 for polio in 2022, we use an R0 of 1.6 from the Israel 2013-2014 wild poliovirus type 1 outbreak (*55*) to represent a polio outbreak in a population with sanitation systems and high levels of vaccination coverage (*83*, *84*). Hospitalization rate is inferred from the fact that less than or near 1% of polio infections result in flaccid paralysis (*85*). Serial interval is estimated as the latent period plus one half of the infectious period (*86*): in the Israel outbreak, this was estimated as $1/\sigma + 1/2 * 1/\gamma = 4 + 1/2 * 1/0.93 \approx 4.5$ days (Table 2 in (*55*)). Hospitalization time is inferred from the several-day period of minor illness, symptom-free period of 1-3 days, and then onset of paralysis within 2-3 days (*85*). Probability of fecal shedding was inferred from literature estimates in enteroviruses (*87*) and in vaccinated children (*88*).

[4] (*89*, *90*). The time to hospitalization is estimated as the sum of the incubation period (9-12 days (*91*)) and the time from symptom onset to hospital admission (5.7 days (*92*)). We and others are unable to find precise estimates of Ebola fecal shedding rates, but Ebola has commonly been detected in stool when measured (*72*), so we assign a value of 0.5, in line with SARS-CoV-2 and

flu, but on the higher end because Ebola causes symptoms more broadly than in just the respiratory system.

[5] (*93*, *94*). The hospitalization rate was estimated by multiplying the symptomatic hospitalization rate of 0.0144 (the proportion of symptomatic cases requiring hospitalization) (*95*) by the symptomatic rate of 0.8 (the proportion of all cases who were symptomatic) (*96*). The hospitalization time was estimated as the sum of the incubation period (1.4 days (*97*)) and the time from symptom onset to hospital admission (2 days (*98*)).

[6] (*99–102*). Probability of fecal shedding is calculated using estimates that 60% of HIV-positive patients show gastrointestinal symptoms (*103*) and 5/9 and 1/10 of HIV-positive patients showing and not showing gastrointestinal symptoms, respectively, test positive in fecal samples for HIV nucleic acid (*104*).

[7] These parameters are very loosely inspired by the parameters for long-incubation diseases like tuberculosis (assuming cases are untreated) (*105–107*). Time to active disease is used as a proxy for time to hospitalization. The serial interval is estimated by taking estimates from the antibiotic era and subtracting 12 months to account for 12 months of antibiotics treatment, and this is consistent with the observed pre-antibiotic era incubation period of at least 1-1.5 months (assuming transmission starts approximately when symptoms appear), because the serial interval is the latent period plus half the infectious period. Reproductive number is selected from the higher end of (*107*) because most of the studies in that review are from the antibiotic era.

Table S4. Date of first reported COVID-19 case in each of 50 US states. Dates are sourced from media reports and state public health agency press releases. An index case is considered to be caught unusually early if caught earlier than 4 days after symptom onset.

Location	Postal code	First case date	Index case caught unusually early
Washington [1]	WA	2020-01-21	FALSE
Illinois [2]	IL	2020-01-24	FALSE
Arizona [3]	AZ	2020-01-26	TRUE
California [4]	CA	2020-01-26	FALSE
Massachusetts [5]	MA	2020-02-01	TRUE
Wisconsin [6]	WI	2020-02-05	TRUE
Oregon [7]	OR	2020-02-28	FALSE
New York [8]	NY	2020-03-01	FALSE
Florida [9]	FL	2020-03-01	FALSE
Rhode Island [10]	RI	2020-03-01	FALSE
Georgia [11]	GA	2020-03-02	FALSE
New Hampshire [12]	NH	2020-03-02	FALSE
New Jersey [13]	NJ	2020-03-02	TRUE
North Carolina [14]	NC	2020-03-03	FALSE
Louisiana [15]	LA	2020-03-04	FALSE
Texas [16]	TX	2020-03-04	FALSE
Maryland [17]	MD	2020-03-05	FALSE
Colorado [18]	CO	2020-03-05	FALSE
Tennessee [19]	TN	2020-03-05	FALSE
Nevada [20]	NV	2020-03-05	FALSE
Hawaii [21]	HI	2020-03-06	FALSE
Minnesota [22]	MN	2020-03-06	FALSE
Utah [23]	UT	2020-03-06	FALSE
Nebraska [24]	NE	2020-03-06	FALSE
Indiana [25]	IN	2020-03-06	TRUE
Pennsylvania [26]	PA	2020-03-06	TRUE
Kentucky [27]	KY	2020-03-06	FALSE
South Carolina [28]	SC	2020-03-06	FALSE
Virginia [29]	VA	2020-03-07	FALSE
Oklahoma [30]	OK	2020-03-07	FALSE
Kansas [31]	KS	2020-03-07	FALSE
Vermont [32]	VT	2020-03-07	FALSE
Iowa [33]	IA	2020-03-08	FALSE
Missouri [34]	MO	2020-03-08	TRUE
Connecticut [35]	CT	2020-03-08	FALSE
Ohio [36]	OH	2020-03-09	FALSE
Michigan [37]	MI	2020-03-10	FALSE
South Dakota [38]	SD	2020-03-10	TRUE

Location	Postal code	First case date	Index case caught unusually early
New Mexico [39]	NM	2020-03-11	FALSE
North Dakota [40]	ND	2020-03-11	FALSE
Arkansas [41]	AR	2020-03-11	FALSE
Delaware [42]	DE	2020-03-11	TRUE
Wyoming [43]	WY	2020-03-11	TRUE
Maine [44]	ME	2020-03-12	FALSE
Alaska [45]	AK	2020-03-12	TRUE
Mississippi [46]	MS	2020-03-12	TRUE
Idaho [47]	ID	2020-03-13	TRUE
Alabama [48]	AL	2020-03-13	FALSE
Montana [49]	MT	2020-03-13	FALSE
West Virginia [50]	WV	2020-03-17	FALSE

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