Supplementary Information: Immunologic and epidemiologic drivers of norovirus transmission in daycare and school outbreaks

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S1 Supplementary Information

S2 Transmission Model for Daycare Centers and Schools

Transmission occurs either directly through person-to-person contact or indirectly through fomite-mediated pathways i.e., shedding and pickup of virus in shared environments. Individuals start as either susceptible S, partially immune P, or fully recovered R depending on acquired immunity and innate resistance status (Figure). Susceptible and partially immune individuals become infected according to the force of infection $\lambda(t)$, which is based on: (1) the number of symptomatic (I), and asymptomatic (A_1, A_2, and A_3) individuals; (2) the number of pathogens on fomites in the environment (F_1 and F_2); (3) the human to human and fomite to human transmission rates (β_{HH}; and β_{FH}); and (4) The asymptomatic transmission reduction factor (β_A) which reduces the efficiency of transmission compared with symptomatic individuals. Excluded individuals, X, do not contribute to transmission.

Force of Infection

$$\lambda(t) = [I + \beta_A(A_1 e^{-\sigma(\frac{1}{\phi})} + A_2 e^{-\sigma(\frac{1}{\phi}+\frac{1}{\rho})} + A_3 e^{-\sigma(\frac{1}{\phi}+\frac{1}{\rho}+\frac{1}{\rho})})]\beta_{HH} + (F_1 + F_2)\beta_{FH} \quad (1)$$

Once infected, individuals pass through an approximately gamma-distributed incubation period i.e. E_1, E_2, and E_3. It is gamma-distributed to represent the empirical distribution observed [1] in the literature. After they pass through the incubation period, they become symptomatic. After an individual is symptomatic, they pass through an approximately gamma-distributed asymptomatic period i.e., A_1, A_2, and A_3 that represents post-symptomatic shedding and exhibits a reduction in shedding by stage (e.g., individuals in

A_2 shed less than individual in A_1, see below for details). A proportion of infected individuals who originate in S do not become symptomatic and pass directly from E_3 to A_1. Individuals who start as partially immune can become infected, but do not become symptomatic and move directly to A_1.

A proportion of symptomatic individuals become excluded and move into the X compartment. After their symptoms resolve, they move to A_1 and return to the general population with the normal transmission and shedding rates for the A_1 compartment. Finally, all individuals who become infected eventually progress to the fully recovered state. All symptomatic and asymptomatic individuals (unless excluded) shed pathogen into the environment as follows:

$$\begin{aligned} Shedding &= \alpha_I I + \alpha_I \beta_A (A_1 e^{-\sigma(\frac{1}{\phi})} + A_2 e^{-\sigma(\frac{1}{\phi}+\frac{1}{\rho})} + A_3 e^{-\sigma(\frac{1}{\phi}+\frac{1}{\rho}+\frac{1}{\rho})}) \\ \dot{F}_1 &= Shedding - \xi F_1 \\ \dot{F}_2 &= \xi F_1 - \xi F_2 \end{aligned} \tag{2}$$

where α_I is the shedding rate for symptomatic individuals, and the reduction factors for shedding among asymptomatic individuals is β_A.

The amount of shedding is reduced exponentially as individuals progress across the approximately gamma-distributed asymptomatic period by σ for each state transition [2]. The symptomatic period, ϕ, and the recovery rate, ρ (i.e., from A_1 to A_2 etc.), account for the length of time that individuals shed at certain rates.

Viral concentration on fomites is tracked in the venue. Norovirus pathogen decay on fomites occurs in a biphasic pattern with an initial rapid rate of die-off followed by a period of slower die-off [3, 4]. Since we are simulating a single outbreak, waning immunity is ignored. See Appendix Section S4 for the full model equations, Table S1 for initial condition ranges, and Table for parameter ranges.

S3 Model Features

We incorporated different model features to examine mechanisms that can recreate the explosive outbreaks and low ARs characteristic of norovirus. We considered the following models (see Figure for reference):

- **Baseline Model**: In this scenario, we simulated a fully susceptible population, with no individual exclusion. All individuals started in the susceptible, S, compartment.

- **Immunity Model**: In this scenario, we simulated partial population immunity with no individual exclusion. Because there is strain-dependent variation in the amount of protection innate resistance provides [5], and due to the fact that there is not an established correlate of norovirus protection that would be able to quantify acquired partial immunity, we examined different proportions of immunity. We assumed that those with innate resistance could not become infected at all and started as fully immune (in the R compartment), while those with acquired immunity started as partially immune (in P). Individuals in P could become infected, but not diseased. Non-diseased individuals were assumed to not be detectable during norovirus outbreaks and therefore were not counted in the numerator of the attack rate. Twenty percent of the population started in the R compartment i.e., with innate resistance [5], and we varied the total number with acquired immunity (P). We chose to vary the percentage starting with acquired immunity, because again there is not a well established correlate of protection [6]. Finally, we calibrated the proportion of individuals with acquired immunity to the data by sweeping over a broad range of Latin Hypercube Sampled [7] values (Table).

- **Individual Exclusion Model**: In this scenario, we simulated a fully susceptible population (i.e., all individuals started in the S compartment) with individual exclusion.

During the simulation, a proportion of diseased individuals were removed from normal mixing and shedding, i.e., excluded. Excluded individuals do not contribute to transmission.

- **Combined Model**: In this scenario, we simulated partial population immunity, with individual exclusion.

Each of the above approaches were simulated stochastically. The stochastic simulation is a tau leaping version of the model [8] based on the Gillespie algorithm in which the stochastic model is approximate, but more efficient. The proportion of individuals across disease states is updated at each large predefined time step (the time interval is denoted τ). We then ran the model 10 times using different random number generator seeds for each parameter set and population size to account for stochastic variation (to confirm our choice for number of stochastic realizations see Appendix section S11).

S4 Model Equations

As noted above, the model was simulated stochastically, but the equivalent ordinary differential equations are:

Force of Infection

$$\begin{aligned} N_{inf} &= [I + \beta_A(A_1 e^{-\sigma(\frac{1}{\phi})} + A_2 e^{-\sigma(\frac{1}{\phi}+\frac{1}{\rho})} + A_3 e^{-\sigma(\frac{1}{\phi}+\frac{1}{\rho}+\frac{1}{\rho})})] \\ \lambda &= N_{inf}\beta_{HH} + (F_1 + F_2)\beta_{FH} \end{aligned} \tag{3}$$

Human Transmission Model

$$\begin{aligned} \dot{S} &= -\lambda S \\ \dot{E}_1 &= \lambda S - \mu E_1 \\ \dot{E}_2 &= \mu E_1 - \mu E_2 \\ \dot{E}_3 &= \mu E_2 - \theta\mu E_3 - (1-\theta)\mu E_3 \\ \dot{I} &= (1-\theta)\mu E_3 - \phi I - \upsilon I \\ \dot{X} &= \upsilon I - \frac{1}{\frac{1}{\phi} - \frac{1}{\upsilon} + \frac{1}{qTime}} X \\ \dot{A}_1 &= \phi I - \rho A_1 + \lambda P + \theta\mu E_3 + \frac{1}{\frac{1}{\phi} - \frac{1}{\upsilon} + \frac{1}{qTime}} X \\ \dot{A}_2 &= \rho A_1 - \rho A_2 \\ \dot{A}_3 &= \rho A_2 - \rho A_3 \\ \dot{P} &= -\lambda P \\ \dot{R} &= \rho A_3 \end{aligned} \tag{4}$$

$$
\begin{aligned}
Shedding &= \alpha_I I + \alpha_I \beta_A (A_1 e^{-\sigma(\frac{1}{\phi})} + A_2 e^{-\sigma(\frac{1}{\phi}+\frac{1}{\rho})} + A_3 e^{-\sigma(\frac{1}{\phi}+\frac{1}{\rho}+\frac{1}{\rho})}) \\
\dot{F}_1 &= Shedding - \xi F_1 \\
\dot{F}_2 &= \xi F_1 - \xi F_2
\end{aligned}
\tag{5}
$$

S5 Initial Conditions

In the baseline model, we start all individuals as Susceptible (S). In the immunity and combined models, 20% of individuals start as fully recovered (R) and some proportion of individuals start with partial immunity (P). This proportion is randomly sampled between 0 and 80%. Finally, 10 million pathogens start in the F_1 compartment to initiate the outbreak. However, this number was varied from 0 to 100 million in a sensitivity analysis. Another sensitivity analysis seeded the outbreak with a single infectious individual.

Table S1: Initial Condition Values and Uncertainty Ranges

State	Description	Value/Uncertainty Range[1]
S	Susceptible	Total population randomly sampled from NORS data – (Number Partially Immune + Number with innate resistance).
E_1 to E_3	Exposed	0 (people)
I	Symptomatic	0 (people) in main analysis and 1 person in the sensitivity analysis seeding with an infectious individual
A_1 to A_3	Asymptomatic	0 (people)
R	Recovered	0 (people) in the baseline scenario and 20% of individuals (representing innate resistance) in the immunity and combined models [5, 9]
P	Partially Immune	0 (people) in the baseline scenario and we vary the prevalence of acquired immunity from 0 to 80% in the immunity and combined scenarios (people) [5, 9, 10]
X	Excluded	0 (people)
F_1 and F_2	Contaminated Fomite Tracking Compartments	10 million pathogens on F_1 in the main analysis and we varied this from 0 pathogens to 100 million pathogens in the sensitivity analysis examining different initial seeding

[1] Initial conditions with ranges are calibrated to the data and ranges indicate bounds of a multivariate uniform distribution

S6 Calibration of Model Parameters

We calibrated each venue–specific model separately to its corresponding NORS data using sample-importance-resampling [11]. This approach allowed us to obtain an array parameter sets upon which, if the model is run, will recreate the NORS data distribution to the best ability of the model.

S6.1 Initial Sample:

We ran the model with 10,000 randomly sampled parameter and initial condition sets (collectively denoted 'parameter sets', and listed in Table) using Latin Hypercube Sampling [7]. The parameter ranges that we sampled from (i.e., our priors) indicated the bounds of a multivariate uniform distribution. Each parameter set was run in a school setting and separately, in a daycare setting. The only distinction between the model setup for schools and daycares was the starting population size (the sets of parameter values are the same), which is taken from the NORS outbreak data in the corresponding setting (Table S6). The NORS data includes separate attack rates (ARs) and populations for students and staff, but only one overall outbreak duration.

For a given venue–specific model, parameter sets were excluded from calibration if the outbreak was ongoing when the simulation ended (i.e., > 60 days, set according to the NORS data). We note that all the outbreaks in the NORS calibration dataset had ended by this point (the maximum duration was 40 days for daycare and 32 days for schools).

S6.2 Calculating the Likelihood:

We derived 2 kernel density estimates of the 3-dimensional probability distribution of student ARs, student population size, and outbreak durations: one for NORS, KDE_{NORS}, and one for the model results (generated from all model runs together), KDE_{Model}. The kernel density estimates were computed using the KS package in R which was designed for kernel smoothing of multidimensional data [12, 13]. We first used a fully informed prior by deriving the likelihood from the KDE_{NORS} directly. In other words, for a given model output generated by running the model on a single parameter set, we looked up how likely our model results (including AR, duration and population) were to appear in the NORS data using KDE_{NORS}. Next, because our predefined parameter ranges in the model represented our subjective best-guesses (i.e., our prior), we used KDE_{Model} (the model-derived kernel density estimate) to examine how weakening our prior (i.e., making it more uninformed) might affect results. Specifically, the likelihood estimate of a given parameter set was calculated by taking the NORS kernel density estimated value which corresponded to a given AR, population size, and outbreak duration from the model results and dividing that by the model kernel density estimate value i.e., we plugged our model outputs into both of these kernel density estimates, resulting in a fully uninformed prior. In other words, we looked up how likely our model results were to appear in the NORS data and divided by how likely our model results were in the entire pool of model results (wherein the shape of this pool of results is directly affected by our prior). By doing this, we effectively canceled the over-weighting of certain model results that occurred due to our parameter ranges. We subsequently investigated how results change when reducing the effect of the model kernel density estimate by using the following hill function:

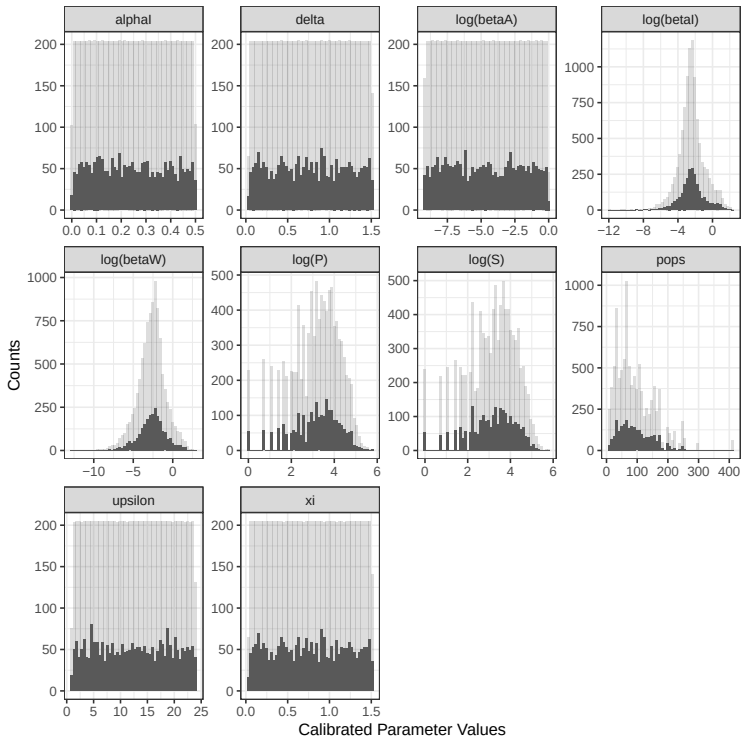
$$Likelihood = \frac{KDE_{NORS}[AR_{model}, Population_{model}, Duration_{model}]}{KDE_{Model}[AR_{model}, Population_{model}, Duration_{model}] + C} \tag{6}$$

where KDE represents the kernel density estimate, and [AR_{model}, $Population_{model}$, $Duration_{model}$] represents indices used to lookup the corresponding KDE_{NORS} value (i.e., to determine how likely our model results are to appear in the NORS data) and KDE_{model} value. C was the set to equal 0, 1, the 25^{th}, 50^{th}, 75^{th} percentiles of all KDE_{model} values to explore how weaker or stronger priors might affect calibration (i.e., as C increases, the prior or the effect of our predefined parameter ranges become stronger).

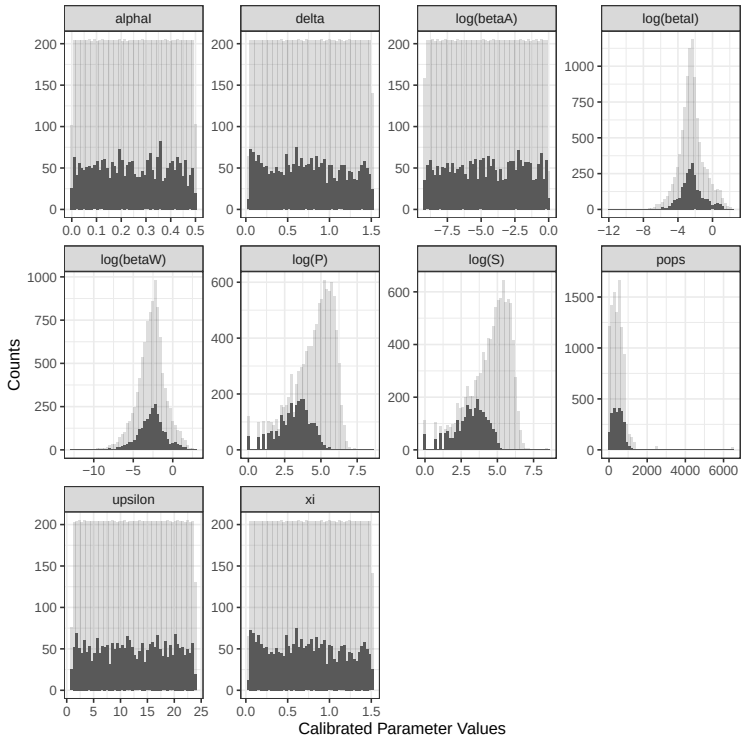
For each simulation, the AR was defined as the total number of symptomatic individuals divided by the total population and the outbreak duration was defined as the number of days from the first symptomatic incident case to the last symptomatic incident case.

S6.3 Deriving our posterior

Finally, we resampled parameter sets 2,500 times with replacement using the likelihoods as weights to obtain a final array of parameter sets that, if used as inputs for the model, could most closely recreate the NORS data distribution. The final distributions of parameter values represent our posterior values (Figure S1).



(a) Daycare



(b) School

Figure S1: Parameter ranges from initial sampled parameter values (our priors) in light grey overlaid on the posterior distributions in dark grey of parameter values among re-sampled parameter sets. Some parameters and initial conditions were log transformed (indicated as such) to more clearly display their distributions.

S6.4 Calibration and Selecting the Strength of our Prior

We initially calibrated using with a fully informed prior i.e., we looked up model outputs in KDE_{NORS} only (and did not divide by KDE_{Model}). We found that although the models were generally able to recreate the distribution of the NORS data, the large majority of parameter sets yielded model results in specific regions of the NORS data distribution. Therefore, the majority of resampled parameter sets were taken from these regions and resulted in results (specifically outbreak durations) that were not consistent with the NORS data. See Appendix Section S7.1 for attack rates, durations, and Kullback-Leibler divergence from the fully informed prior analysis. The fact that model results were over-represented in specific regions was likely due to our pre-selected parameter ranges i.e., our prior, therefore we explored whether making the prior weaker (i.e., plugging model outputs into KDE_{Model} and calculating likelihoods with the hill function see Appendix Table S7.1 for results) might improve calibration.

S7 Selecting the Strength of our Prior Results

We initially calibrated each model scenario to the NORS data without accounting for the distribution of model results. In other words, likelihoods were calculated based on how well the model results match the NORS data only. We next examined how weakening the prior might improve model calibration to NORS data.

Below are Kullback-Leibler divergence values for different values of C in the likelihood hill function (see Equation 6).

Table S2: Venue-specific Kullback-Leibler divergence for All Models for different priors: Median (95% CI) [Mean]

Model	Daycare	School
Fully Uninformed Prior		
Baseline	3.32	5.95
Immunity	0.57	0.32
Individual Exclusion	0.24	2.5
Combined	0.11	0.26
C is set to 25^{th} percentiles of all model kernel density estimate values		
Baseline	3.29	5.83
Immunity	0.47	0.36
Individual Exclusion	0.22	2.41
Combined	0.15	0.29
C is set to 50^{th} percentiles of all model kernel density estimate values		
Baseline	3.29	5.84
Immunity	0.48	0.32
Individual Exclusion	0.38	2.56
Combined	0.18	0.34
C is set to 75^{th} percentiles of all model kernel density estimate values		
Baseline	3.1	5.89
Immunity	0.67	0.47
Individual Exclusion	0.33	2.52
Combined	0.27	0.44
Fully informed Prior		
Baseline	8.9	8.55
Immunity	4.97	2.98
Individual Exclusion	2.13	3.33
Combined	2.45	1.39

S7.1 Results from Fully Informed Prior Analysis

Below are the attack rates, durations, and Kullback-Leibler divergence from the fully informed prior analysis.

Table S3: Venue-specific Attack Rates for All Models (fully informed prior): Median (95% CI) [Mean]

Model	Daycare	School
Baseline	65.5% (0%, 76.3%) [60.8%]	64.6% (0%, 73.3%) [58.5%]
Immunity	22% (1.1%, 50%) [23%]	16.7% (1.8%, 53.6%) [20.4%]
Individual Exclusion	42.9% (1.5%, 73.7%) [39.7%]	10% (0.1%, 70.8%) [25.9%]
Combined	19.2% (1.4%, 50%) [21.2%]	12.1% (0.3%, 51.9%) [16.2%]
NORS	21.5% (4.5%, 69.2%) [25.3%]	15.3% (4.6%, 68.4%) [20.4%]

Table S4: Venue-specific Outbreak Durations for All Models (fully informed prior): Median (95% CI) [Mean]

Model	Daycare	School
Baseline	4 days (0, 14) [4.8]	5 days (0, 10) [4.7]
Immunity	4 days (1, 14) [4.8]	5 days (1, 15) [6]
Individual Exclusion	7 days (1, 26.5) [8.9]	7 days (1, 28) [9.1]
Combined	5 days (1, 22) [6.9]	5 days (1, 23) [7.4]
NORS	13 days (2, 40) [14.6]	8 days (1, 32) [10.8]

Table S5: Venue-specific Kullback-Leibler divergence for All Models (fully informed prior): Median (95% CI) [Mean]

Model	Daycare	School
Baseline	8.9	8.55
Immunity	4.97	2.98
Individual Exclusion	2.13	3.33
Combined	2.45	1.39

Although the initial Latin Hypercube sampled simulations of the combined model were able to recreate almost the entire joint distribution of ARs and durations observed in the NORS data, a large proportion of the these simulations had very short outbreak durations (and these short duration simulations were weighted highly in the sample-importance-resampling as they are also common in NORS). This skewed the calibrated distributions of durations in the combined model toward the shorter-duration end of the NORS data, so that the median model-generated durations were lower than those in NORS. Therefore, for

a model to be able to calibrate well, it is required to both (1) recreate the joint distribution of attack rates and durations in the NORS data, and (2) evenly distribute model runs across the distribution. This led us to examine how weaker priors accounting for the distribution of model results might improve the calibration. We found that the model scenarios consistently performed the approximately same relative to each other (e.g., the combined model always performed better than the baseline model) regardless of which prior we used (see Appendix Table S7.1). We ultimately chose to present results from a fully uninformed prior (see Equation 6 with C=0) because this yielded the best overall fit both graphically and with respect to Kullback-Leibler divergence.

S8 NORS Calibration Data

We calibrated our models to the NORS data below. In total, there were 165 daycare outbreaks and 397 school outbreaks.

Table S6: Calibration Data from NORS

Metric	Median (5^{th} to 95^{th} percentiles) [Mean]
Population sizes of daycare venue	80 people (7, 410) [94.7]
Population sizes of school venue	420 people (6, 6486) [447.3]
Attack rate within daycare venue	21.5% (4.5%, 69.2%) [25.3%]
Attack rate within school venues	15.3% (4.6%, 68.4%) [20.4%]
Outbreak duration within daycare venue	13 days (2, 40) [14.6]
Outbreak duration within school venues	8 days (1, 32) [10.8]

S9 Attack Rates vs. Outbreak Duration Stratified by NORS Population Sizes

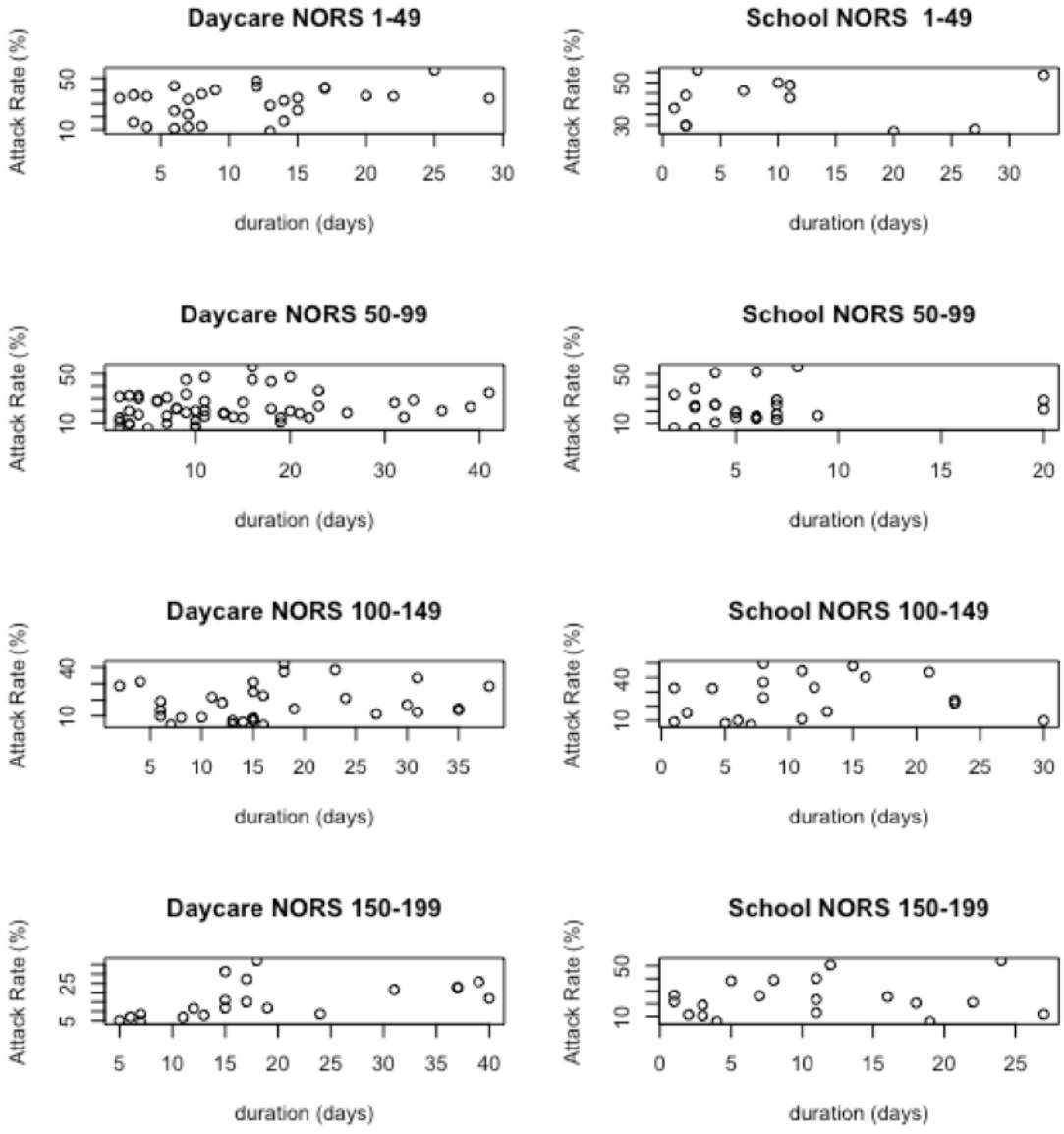


Figure S2: NORS data: Attack rates vs. outbreak duration stratified by exposed population size.

S10 Results from Calibration for Each Model with NORS Data

Below are pairwise scatter plots examining joint distributions of attack rate (%), outbreak durations (days), and population sizes (people). The NORS data is in the upper left corner and all models are displayed with individual points colored by the log of the number of Times Calibrated. Points in white were not resampled.

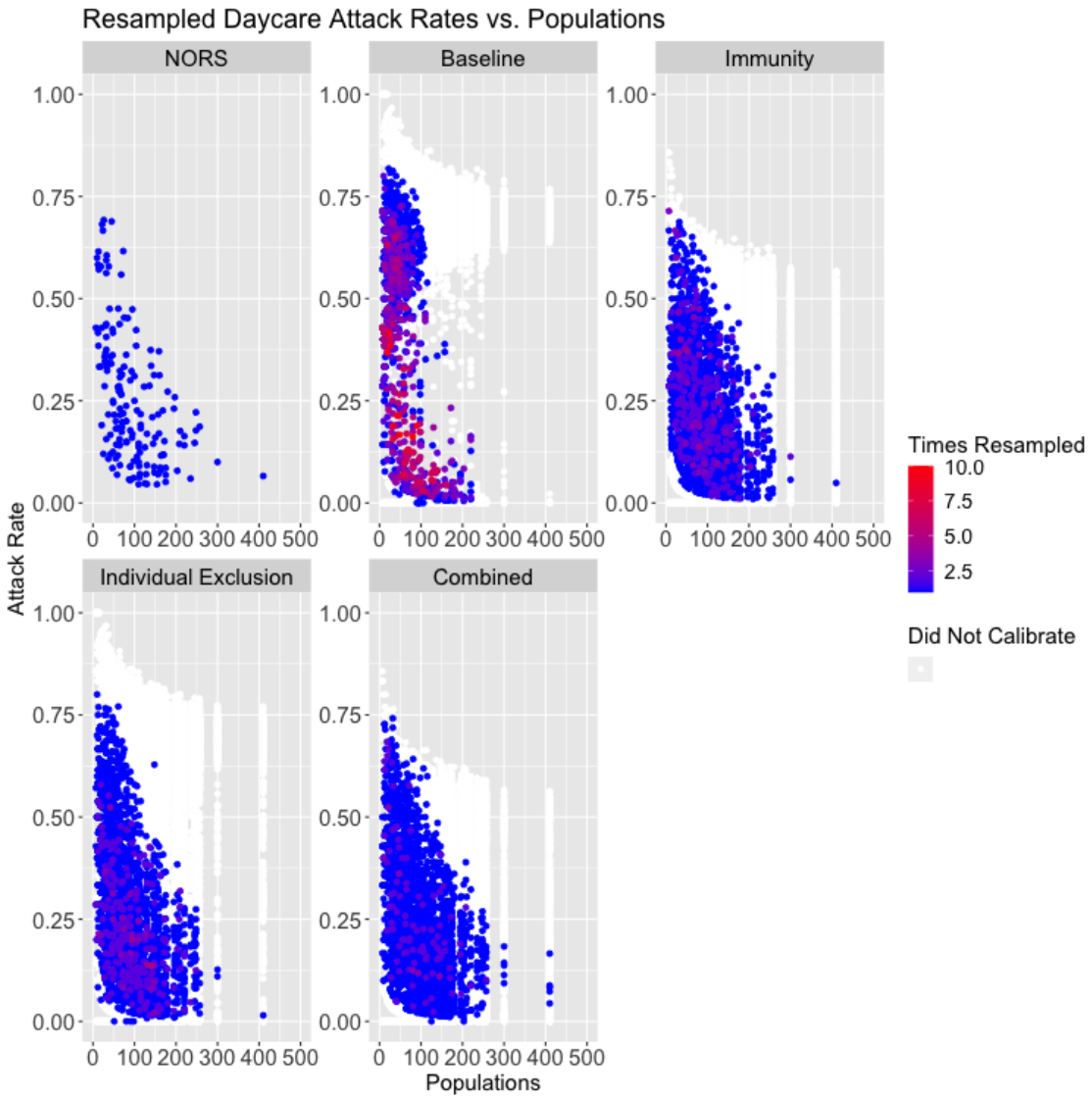


Figure S3: Attack rate vs. population in daycares for the NORS data (top left), with all remaining panels showing results from resampled parameter and initial conditions by model scenario. Points correspond to individual parameter sets and are colored by the amount of times they were resampled.

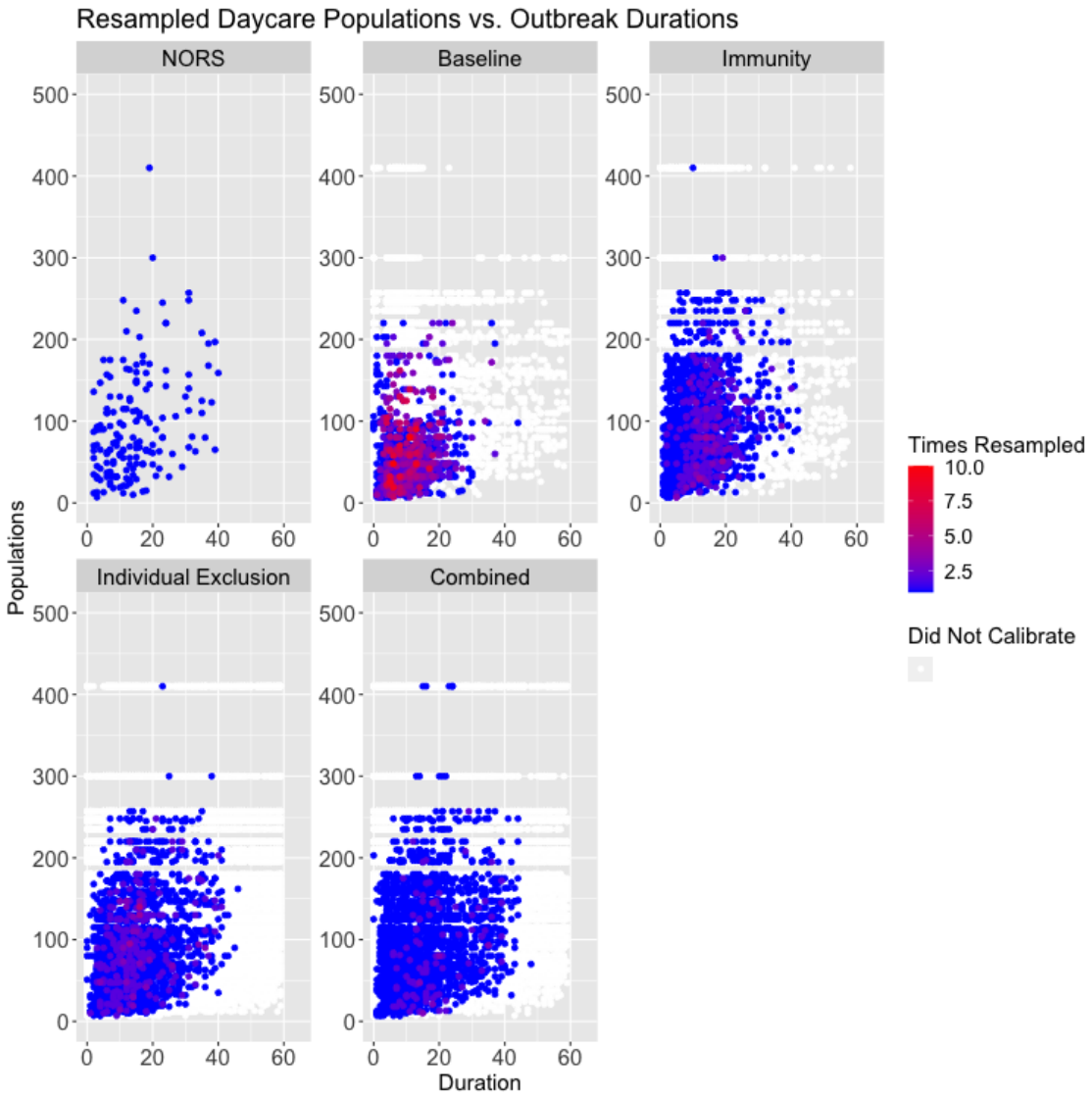


Figure S4: Population vs. outbreak duration in daycares for the NORS data (top left), with all remaining panels showing results from resampled parameter and initial conditions by model scenario. Points correspond to individual parameter sets and are colored by the amount of times they were resampled.

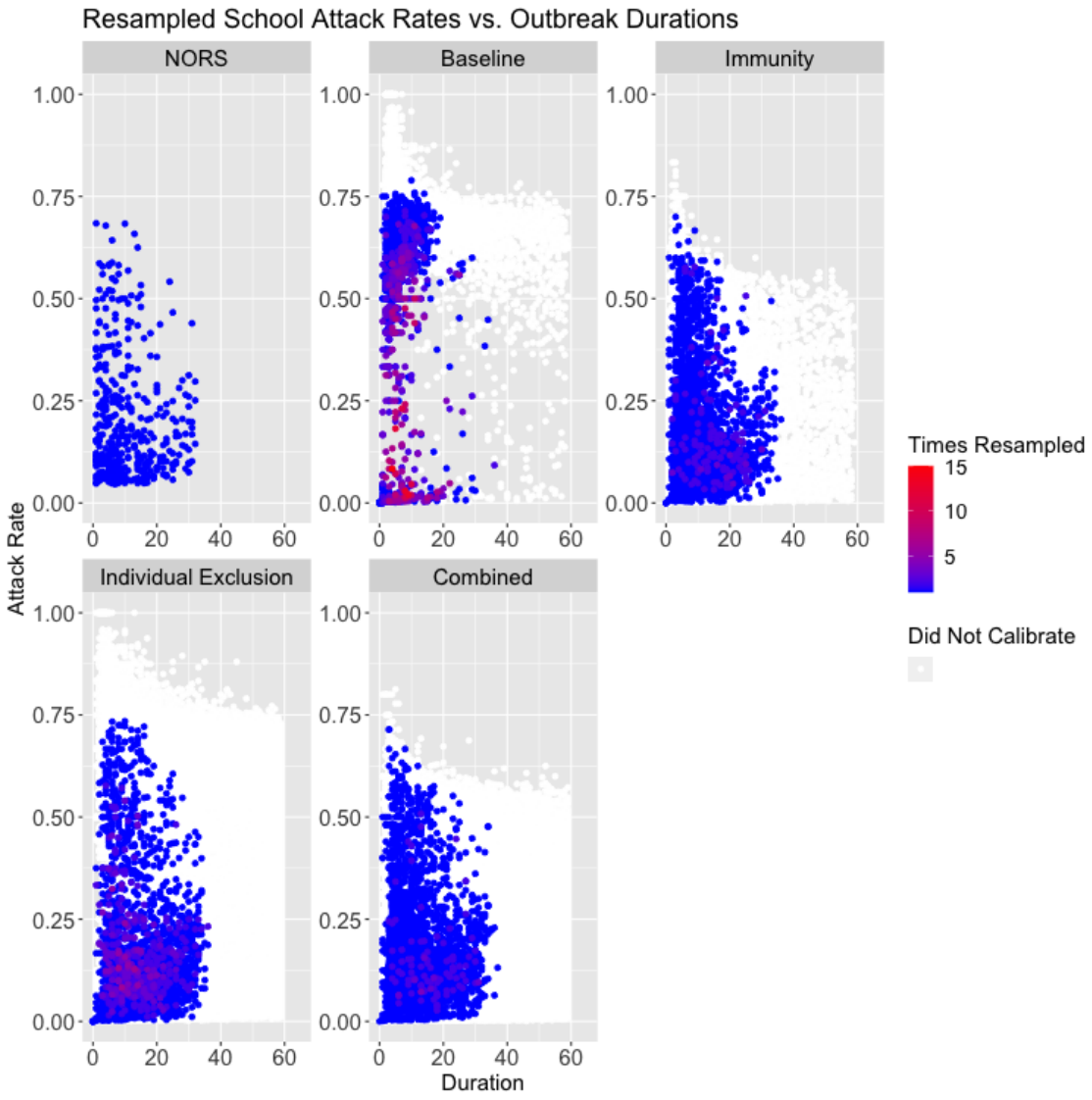


Figure S5: Attack rate vs. outbreak duration in schools for the NORS data (top left), with all remaining panels showing results from resampled parameter and initial conditions by model scenario. Points correspond to individual parameter sets and are colored by the amount of times they were resampled.

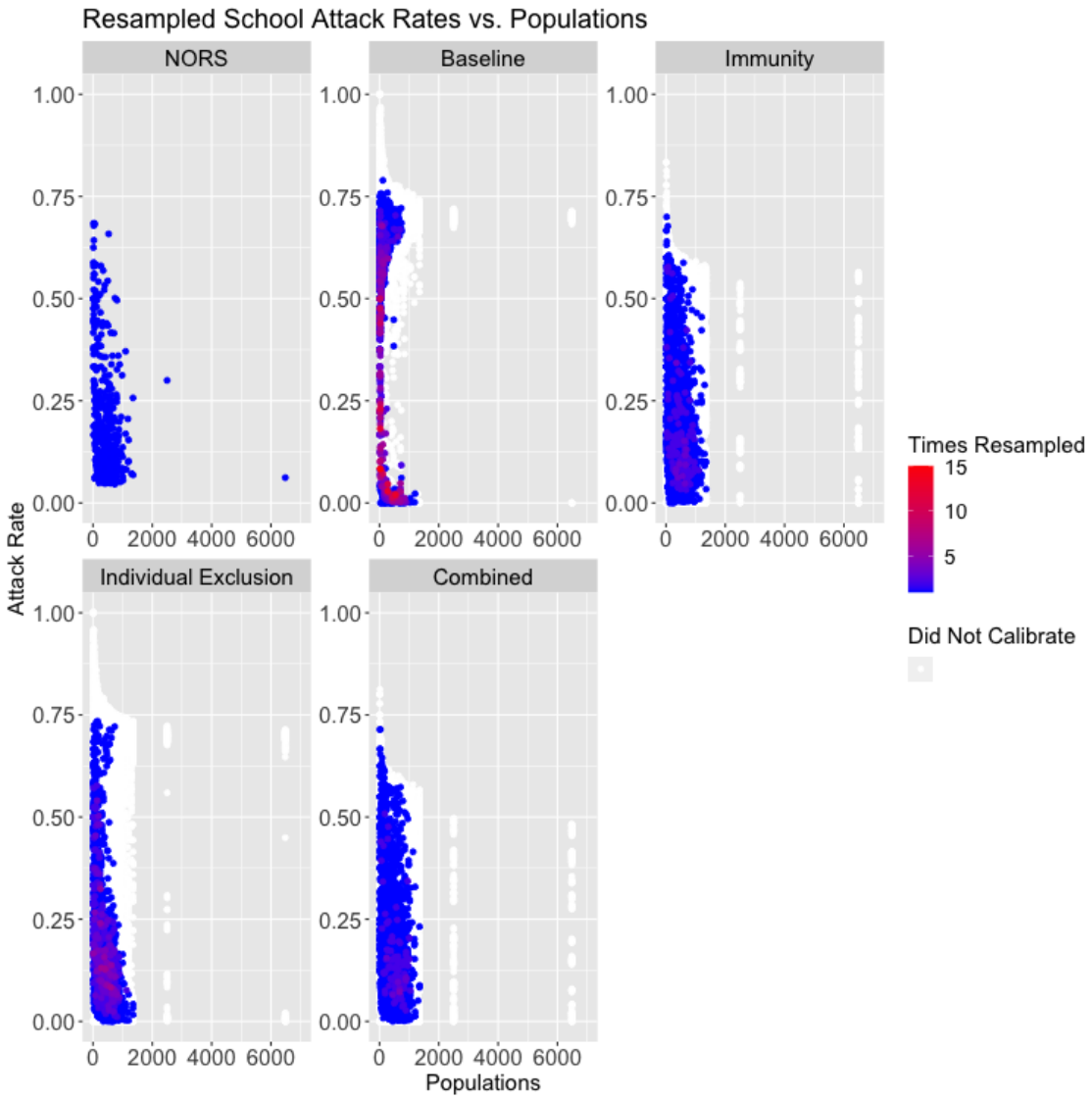


Figure S6: Attack rate vs. population in schools for the NORS data (top left), with all remaining panels showing results from resampled parameter and initial conditions by model scenario. Points correspond to individual parameter sets and are colored by the amount of times they were resampled.

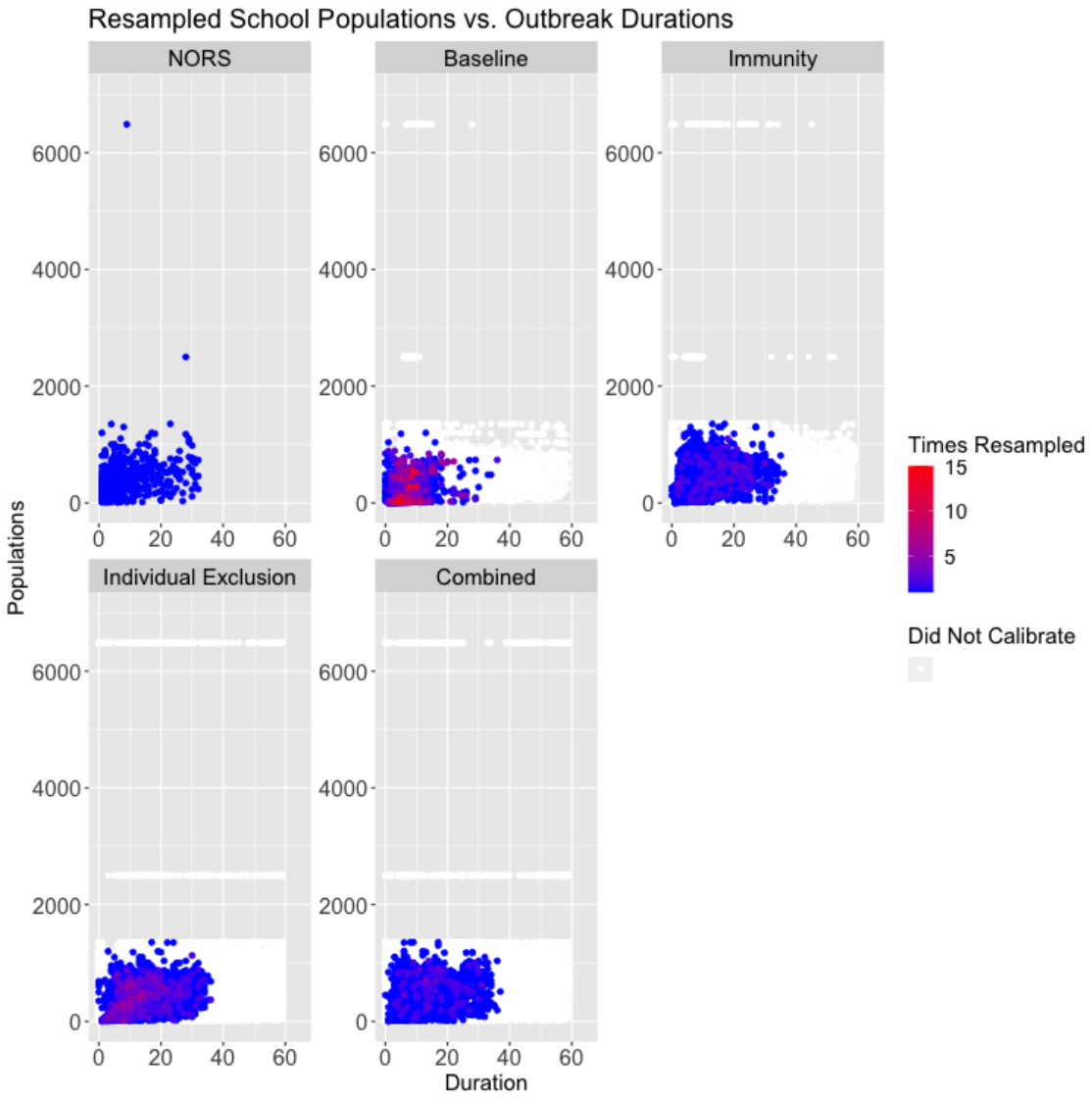


Figure S7: Population vs. outbreak duration in schools for the NORS data (top left), with all remaining panels showing results from resampled parameter and initial conditions by model scenario. Points correspond to individual parameter sets and are colored by the amount of times they were resampled.

Next, to facilitate ease of comparison between the model and data we present here the model output displayed as a 2 dimensional density plot (i.e., among resampled parameter sets) overlaid on the NORS data points

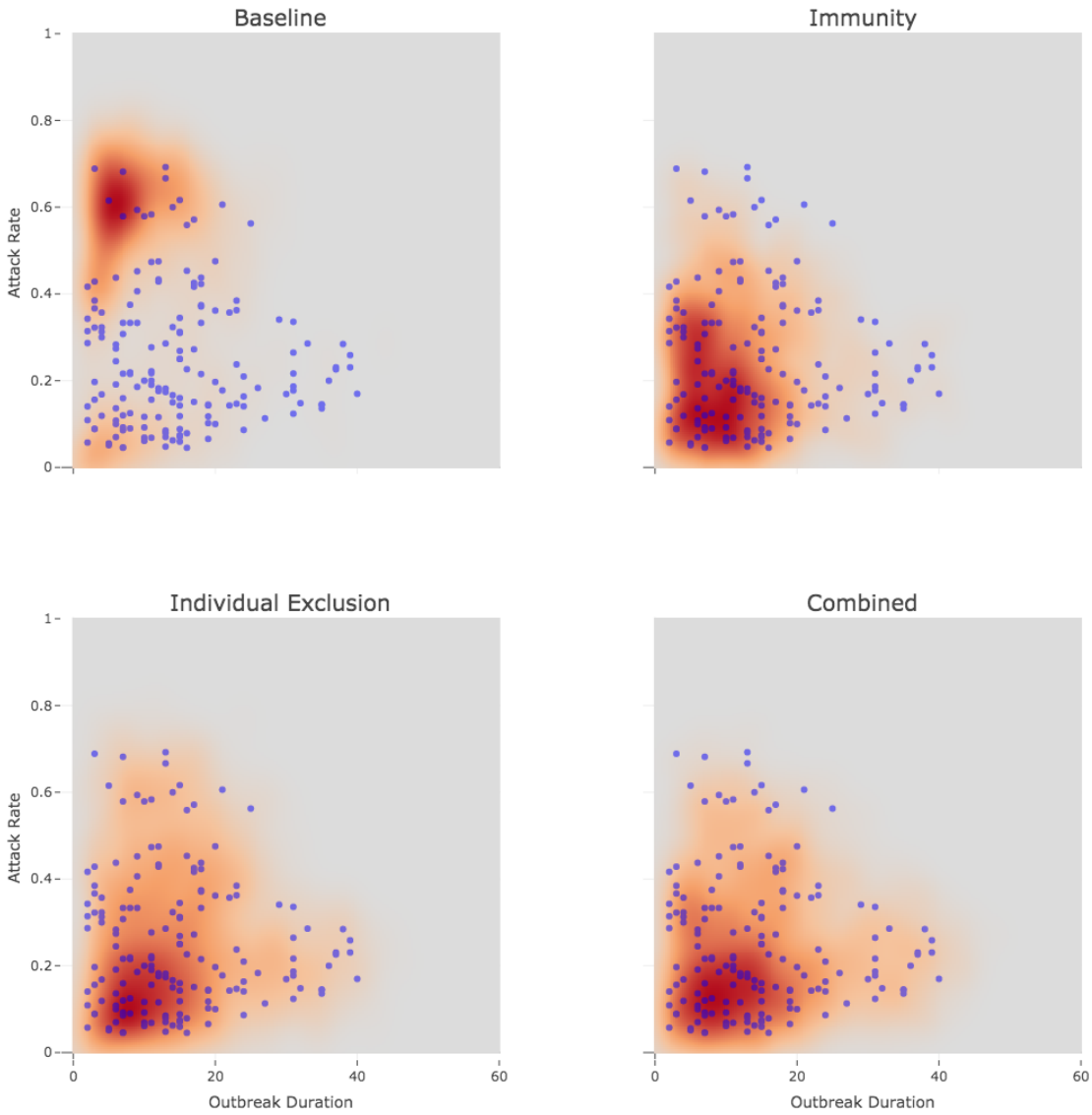


Figure S8: Attack rates vs. outbreak duration in daycares for all models. Density corresponds to model outputs from resampled parameter sets and points correspond to NORS data.

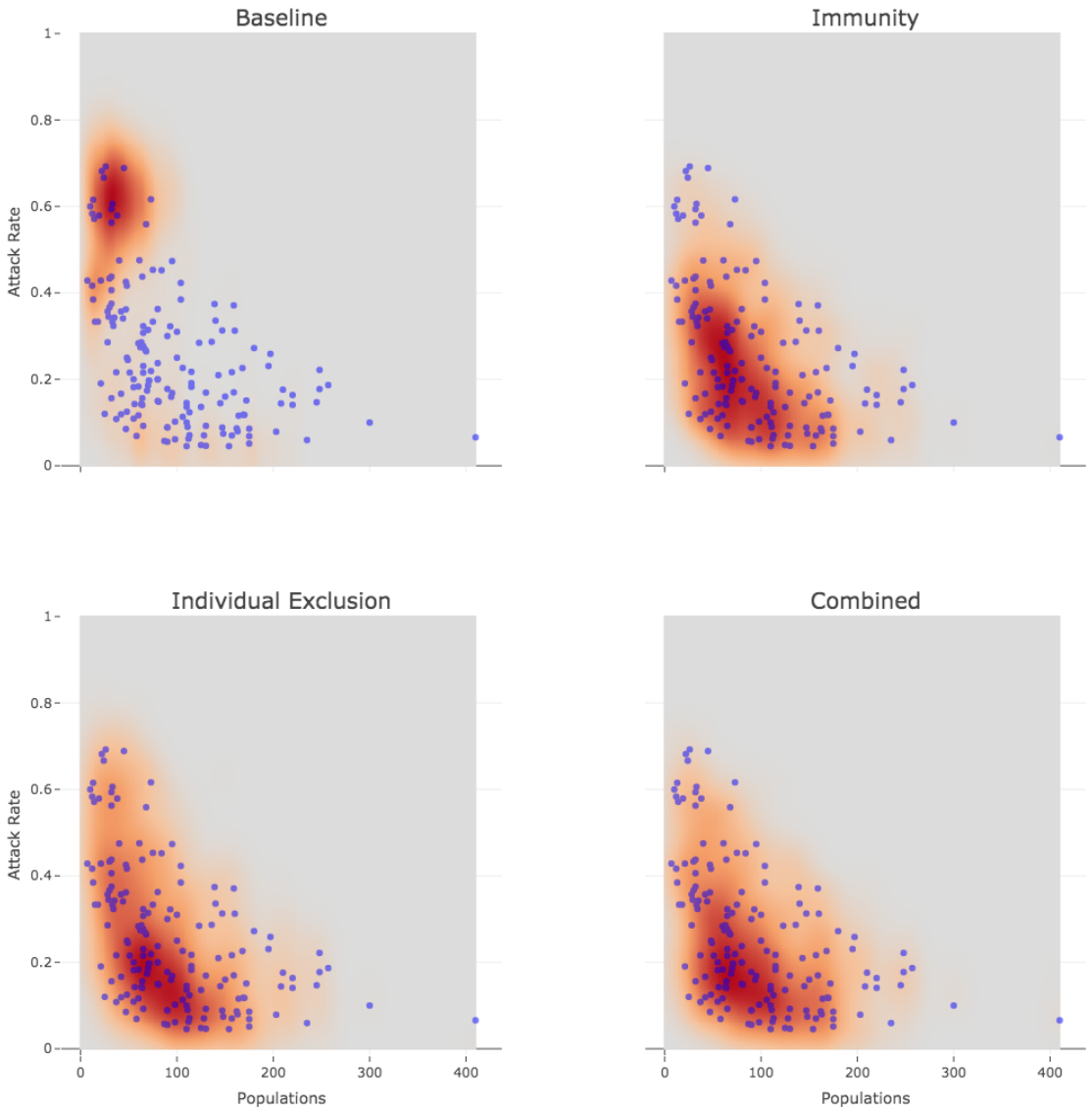


Figure S9: Attack rates vs. populations in daycares for all models. Density corresponds to model outputs from resampled parameter sets and points correspond to NORS data.

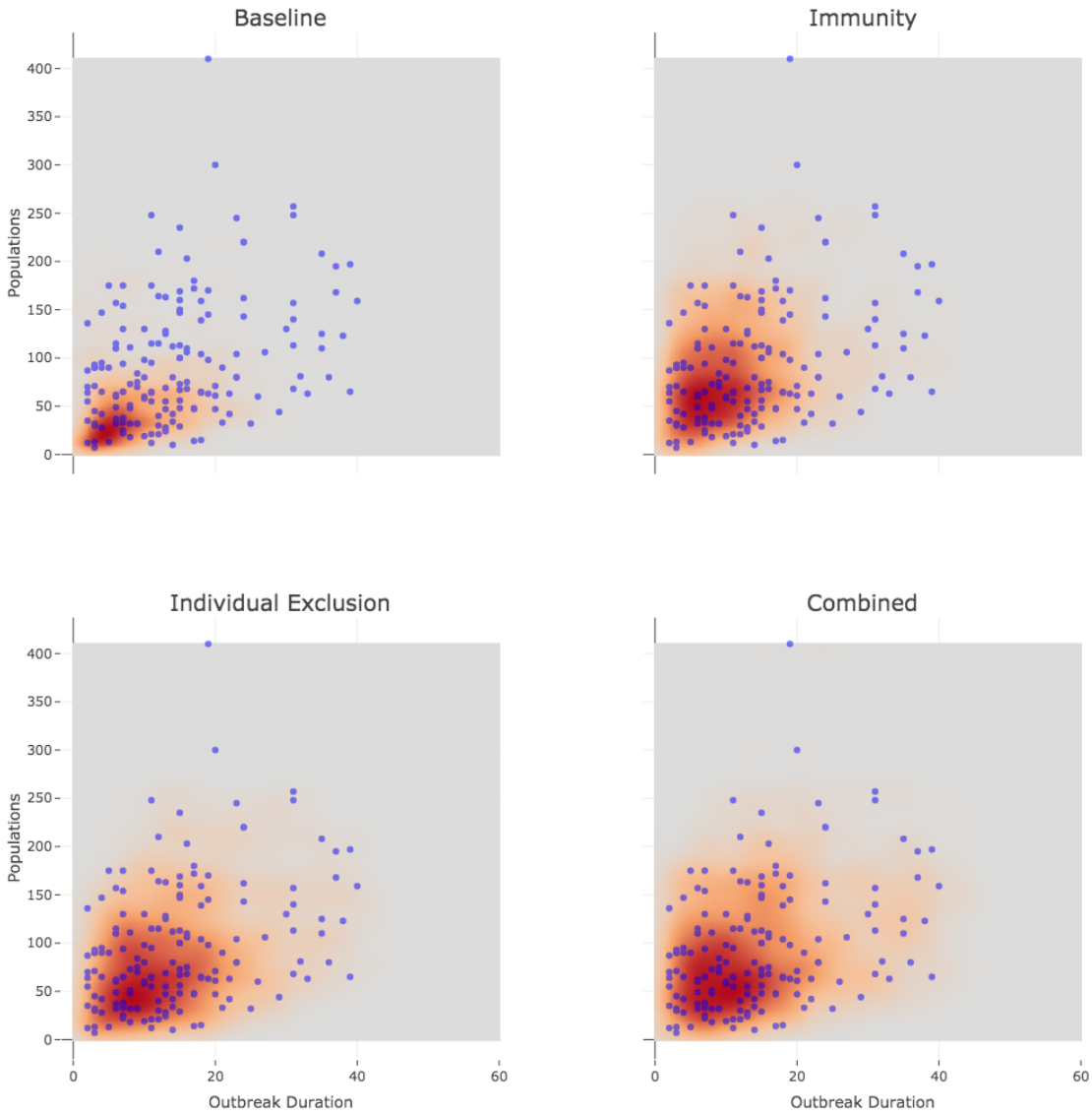


Figure S10: Populations vs. outbreak durations in daycares for all models. Density corresponds to model outputs from resampled parameter sets and points correspond to NORS data.

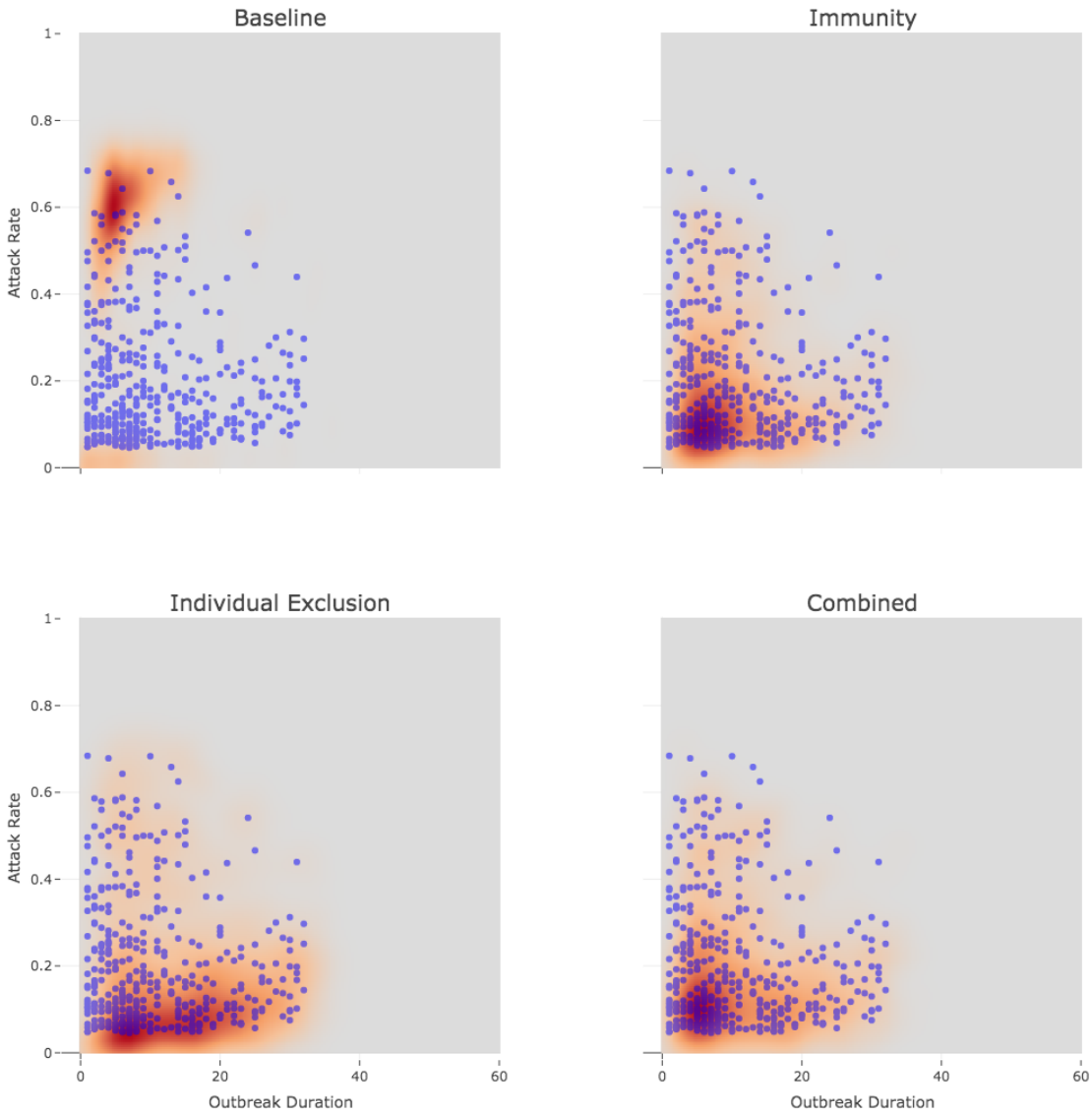


Figure S11: Attack rates vs. outbreak duration in schools for all models. Density corresponds to model outputs from resampled parameter sets and points correspond to NORS data.

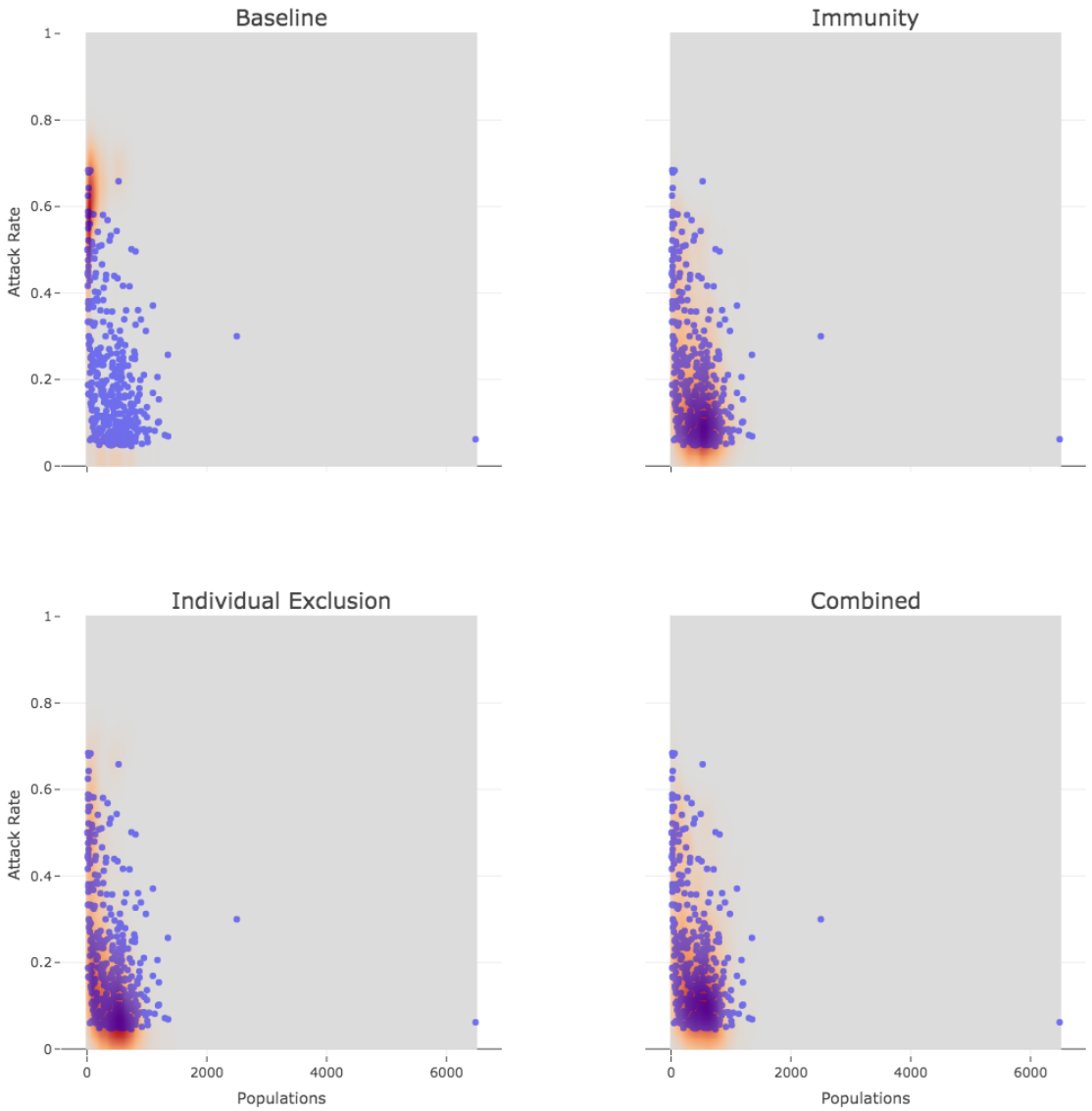


Figure S12: Attack rates vs. populations in schools for all models. Density corresponds to model outputs from resampled parameter sets and points correspond to NORS data.

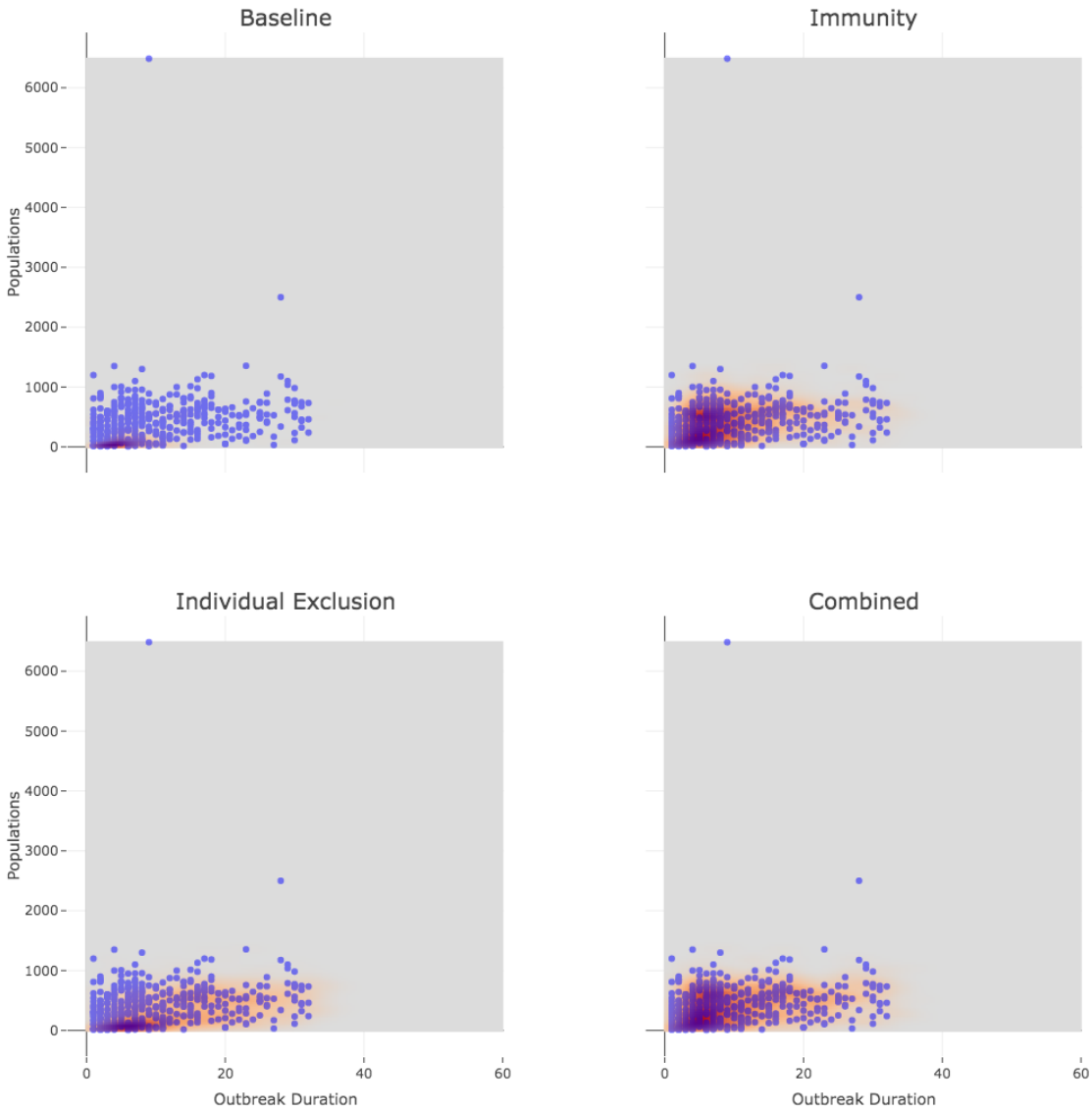


Figure S13: Populations vs. outbreak durations in schools for all models. Density corresponds to model outputs from resampled parameter sets and points correspond to NORS data.

S11 Sensitivity Analyses: Stochastic Runs

To confirm our choice of 10 stochastic runs for each parameter set, we compared model results among resampled parameter sets when running the combined model with 10, 50 and 100 stochastic realizations.

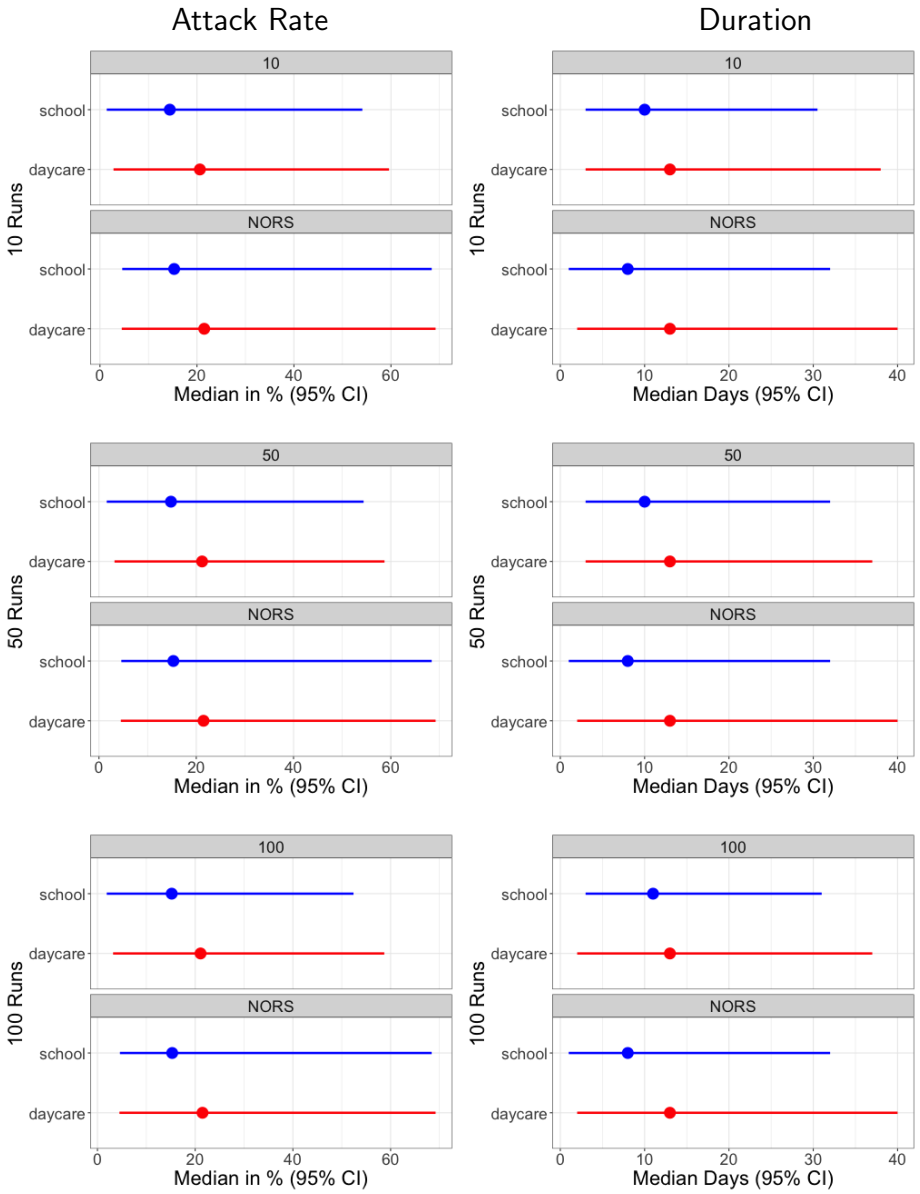


Figure S14: ARs (left column) and durations (right column) for the combined model run with 10, 50 and 100 random seeds for each parameter set.

Overall, we observed minimal differences between total numbers of stochastic realizations. This confirmed that our choice of 10 stochastic runs for each parameter set was sufficient.

S12 Sensitivity Analyses: Initial Conditions

We conducted sensitivity analyses to ensure that our model results were robust to key simplifying assumptions. To assess whether the outbreak durations were affected by the choice of initial conditions in different compartments, we conducted two sensitivity analyses. First, we ran the model varying the number of pathogens starting in the environment from 0 to 100 million and second, we seeded the model with a single infectious individual.

S12.1 Sensitivity Analysis Results:

According to the Kullback-Leibler divergence, all sensitivity analyses performed fairly well and were relatively close to the original combined model. See Table for Kullback-Leibler divergence values of the main analyses.

Below are attack rates and durations from seeding scenario the sensitivity analyses.

Table S7: Venue-specific Attack Rates for Sensitivity Analyses: Median (95% CI) [Mean]

Model	Daycare	School
Seeding: Varying Pathogens in Environment	20.8% (3.1%, 55.6%) [23.2%]	14.3% (1.9%, 52.3%) [18.4%]
Seeding: Diseased Individual	22.2% (3.1%, 58.1%) [24.9%]	15.1% (1.2%, 53.1%) [19.1%]
NORS	21.5% (4.5%, 69.2%) [25.3%]	15.3% (4.6%, 68.4%) [20.4%]

Table S8: Venue-specific Outbreak Durations for Sensitivity Analyses: Median (95% CI) [Mean]

Model	Daycare	School
Seeding: Varying Pathogens in Environment	13 days (2, 36) [14]	10 days (3, 30) [12]
Seeding: Diseased Individual	12 days (2, 36) [13.6]	9 days (3, 30) [11.2]
NORS	13 days (2, 40) [14.6]	8 days (1, 32) [10.8]

S13 Staff and Students Model

We added staff into the model, to understand whether or not they can affect how norovirus is spread within venues.

S13.1 Students and Staff Model for Daycare and School

In the staff and student model, there is a staff age group and a student age group. To derive the human-to-human transmission rates, we assume that the younger age group (i.e., the students) transmit at higher rates than the older age group (i.e., the staff) due to both contact rates [14] and susceptibility decreasing with age (e.g. represented by levels of norovirus antibody titers [15]). Specifically, the human-to-human transmission matrix is derived by taking the β_{HH} from the students only model and setting that to the student to student transmission rate. Next, we assume that the inter-age transmission rates (i.e., staff to student and student to staff transmission are equal) and calculate that by multiplying the student to student transmission rate by a randomly sampled reduction factor between [0,1]. Finally, the staff-to-staff transmission rate is calculated by multiplying the inter-age transmission rate by a randomly sampled reduction factor between [0,1] (this factor is also used to derive the fomite-to-staff transmission rate).

Next, for fomite-to-human transmission there are two rates, one for students and one for staff. The fomite-to-student transmission rate is calculated in the same way as the student only model i.e., β_{HH} multiplied by a randomly sampled parameter between [0, 2]. The fomite-to-staff transmission rate is derived by multiplying the fomite-to-student rate by the same factor used to derive the staff-to-staff transmission rate (mentioned above) between

[0,1]. Overall, the force of infection for the staff and students model is as follows:

$$\begin{aligned}
\lambda(t)_{tot} &= [I + \beta_A(A_1 e^{-\sigma(\frac{1}{\phi})} + A_2 e^{-\sigma(\frac{1}{\phi}+\frac{1}{\rho})} + A_3 e^{-\sigma(\frac{1}{\phi}+\frac{1}{\rho}+\frac{1}{\rho})})]\beta_{HH} \\
\lambda(t)_1 &= \lambda(t-1)_1 + (F_1 + F_2)\beta_{Wk} \\
\lambda(t)_2 &= \lambda(t-1)_2 + (F_1 + F_2)\beta_{Wa}
\end{aligned} \tag{7}$$

where $\lambda(t)_{tot}$ is the total force of infection (and is a vector representing the student force of infection as the first element and the staff force of infection as the second element. Thus the human-to-human transmission rate (β_{HH}) is a 2 by 2 matrix. $\lambda(t)_1$ and $\lambda(t)_2$ are added to the force of infection for students and staff, respectively. Finally, β_{Wk} and β_{Wa} are the fomite-to-human transmission rates for students and staff, respectively.

Finally, with respect to shedding, staff and students shed into a single shared environment. Thus, the shedding and fomite tracking equations are as follows:

$$\begin{aligned}
Shedding &= \alpha_I I + \alpha_I \beta_A(A_1 e^{-\sigma(\frac{1}{\phi})} + A_2 e^{-\sigma(\frac{1}{\phi}+\frac{1}{\rho})} + A_3 e^{-\sigma(\frac{1}{\phi}+\frac{1}{\rho}+\frac{1}{\rho})}) \\
\dot{F}_1 &= \sum Shedding - \xi F_1 \\
\dot{F}_2 &= \xi F_1 - \xi F_2
\end{aligned} \tag{8}$$

where the sum of shedding across both age groups is added to the F_1 compartment because there is a single environmental compartment in each venue.

For the immunity and combined models we assumed that staff had higher rates of partial immunity than children [15]. All other model equations are the same as the student only model, we just vectorized the equations to keep track of student and staff compartments separately. see Appendix Section S4 for details.

S13.2 Students and Staff Model Likelihood Calculation

To derive an overall likelihood for a given venue, we took the NORS kernel density estimate values which corresponded to a given AR and population size for students from the model and divided by the model kernel density estimate values which corresponded to a given AR and population size for students from the model. We multiplied this by the corresponding staff value (i.e., NORS kernel density estimate divided by model kernel density estimate), and finally, multiplied by the NORS kernel density estimate value divided by the model kernel density estimate value which corresponded to a given outbreak duration and total venue population from the model. More details can be found in Section . We did not calculate a full 5-dimensional kernel density estimate due to computational limitations. Therefore, a key limitation in our approach for this sensitivity analysis is that we are assuming independence between different kernel density estimates (e.g., the student joint distribution of ARs and population size is assumed to be independent of the staff distribution).

We calibrated the student and staff model to 137 daycare and 240 school outbreaks.

S13.3 Students and Staff Model Results

The distributions of attack rates and durations as well as the Kullback-Leibler divergence revealed that combined model calibrated best to the NORS data.

Table S9: Kullback-Leibler Divergence Metrics for the Students and Staff Model

Model	Daycare Students	Daycare Staff	Daycare Outbreak Duration	School Students	School Staff	School Outbreak Duration
Baseline	15.84	17.06	9.76	15.43	14.84	1.39
Immunity	0.23	1.07	0.37	0.35	1.13	0.24
Individual Exclusion	0.62	2.44	0.76	4.43	3.91	2.21
Combined	0.41	0.48	0.15	0.12	0.39	0.16

Table S10: Venue-specific Attack Rates for Students and Staff Model: Median (95% CI) [Mean]

Model	Daycare Students	Daycare Staff	School Students	School Staff
Baseline	44.3% (2.4%, 44.3%) [33.5%]	40% (0%, 40%) [33.3%]	1.1% (1.1%, 2.1%) [1.3%]	6.7% (0%, 6.7%) [6.2%]
Immunity	24.6% (4.4%, 60.3%) [26.7%]	16.7% (0%, 57.1%) [19.7%]	9.7% (1.8%, 44%) [12.6%]	4.9% (0%, 25%) [6.3%]
Individual Exclusion	17.2% (4%, 43.7%) [19.2%]	18.8% (3.8%, 36.4%) [18.4%]	8.2% (1%, 22.8%) [8.9%]	13.3% (1.6%, 31.4%) [14.3%]
Combined	29.8% (7.2%, 63.1%) [31.4%]	20% (0%, 61.5%) [22.9%]	13.5% (2.8%, 51.4%) [17.4%]	7% (0%, 42.1%) [9.7%]
NORS	21.6% (4.8%, 69.2%) [25.3%]	21.4% (0%, 75%) [24.8%]	14.1% (4.8%, 71.3%) [18.8%]	6.5% (0%, 56.7%) [11.6%]

Table S11: Venue-specific Outbreak Durations for Students and Staff Model: Median (95% CI) [Mean]

Model	Daycare	School
Baseline	17 days (2, 17) [14.5]	2 days (2, 2) [2]
Immunity	13 days (3, 34) [13.8]	13 days (3, 32) [14.5]
Individual Exclusion	21 days (3, 43) [22.8]	18 days (3, 33) [18.4]
Combined	15 days (4, 40) [17.4]	13 days (3, 33) [14.7]
NORS	14 days (2, 40) [15.5]	11 days (2, 33) [12.9]

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