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Comparing approaches for modelling indirect contact transmission of infectious diseases

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Abstract

Mathematical models describing indirect contact transmission are an important component of infectious disease mitigation and risk assessment. A model that tracks microorganisms between compartments by coupled ordinary differential equations or a Markov chain is benchmarked against a mechanistic interpretation of physical transfer of microorganisms from surfaces to fingers and subsequently to a susceptible person's facial mucosal membranes. The primary objective was to compare these models in their estimates of doses and changes in microorganism concentrations on hands and fomites over time. The abilities of the models to capture the impact of episodic events, such as hand hygiene, and of contact patterns were also explored. For both models, greater doses were estimated for the asymmetrical scenarios in which a more contaminated fomite was touched more often. Differing representations of hand hygiene in the Markov model did not notably impact estimated doses but affected pathogen concentration dynamics on hands. When using the Markov model, losses due to hand hygiene should be handled as separate events as opposed to time-averaging expected losses. The discrete event model demonstrated the effect of hand-to-mouth contact timing on dose. Understanding how model design influences estimated doses is important for advancing models as reliable risk assessment tools.

Keywords: indirect contact, infectious disease modelling, virus, exposure

Introduction

Protecting environmental and occupational health in the built environment is an increasingly important topic, and the COVID-19 pandemic has highlighted that these concerns extend to infectious diseases. One of the exposure pathways of concern for many infectious diseases is “indirect contact” or “fomite” exposure. In this pathway, individuals touch surfaces contaminated with pathogens, usually with their hands, and transfer the pathogen between subsequently touched surfaces. For pathogens, this pathway is of particular concern in environments with immunocompromised individuals such as healthcare facilities (1–4), but the pathway is also relevant for exposures to pesticides and chemicals (5–7).

Due to the complexity of human behaviour, the fate and transport of contaminants via the indirect contact route is commonly described using mathematical modelling. Such exposure modelling has long been a tool for relating data about environmental microbial contaminated to estimated exposures, doses, and risks within the quantitative microbial risk assessment (QMRA) research framework (8). One benefit to the application of exposure modelling within QMRA is the ability to address a range of scenarios and account for variability and uncertainty in environmental conditions and human behaviours that may drive the exposure magnitude (8). This provides value in not only assessing risk under a variety of conditions but also to compare engineering, behavioural, and administrative interventions for reducing exposure or risk; guide environmental microbial cleanliness standards for achieving specific risk thresholds; and gain insights regarding exposure determinants.

Two modelling approaches that have commonly been used for indirect contact exposure include: 1) compartment models in which discrete Markov chains (or ordinary differential equations) which are used to describe the movement of microbes between compartments over time, and 2) discrete event models in which sequential human behaviours and other events result in the transfer of microbes between hands, surfaces, and facial mucosal membranes. The discrete Markov chain model approach typically utilizes time-averaged rate constants to

describe microbial fate and transport, and has been recently used to estimate contributions of multiple SARS-CoV-2 exposure pathways to COVID-19 transmission (9). The discrete event approach originates from a fomite-mediated rotavirus model (10) and has recently been used to compare exposures for different types of healthcare worker behaviour sequences during various types of patient care (11) and to estimate SARS-CoV-2 exposures and COVID-19 risks for entire shifts of subsequent patient interactions and doffing events (12).

While both modelling approaches have been used to estimate microbial exposures for specific scenarios, the approaches conceptualize the exposure process differently, and one approach may be more suitable over the other for a given exposure scenario or research question. For example, a strength of the discrete Markov chain approach is its flexibility in addressing the fate and transport of virus among myriad compartments with a time-averaged approach, lending itself to simultaneous analysis of exposure through multiple media and routes (9). Because compartment models typically represent time-averaged transport processes using rate constants, special consideration must be given to represent acute changes in concentrations, such as during hand hygiene events. Treating losses from these acute events as time-averaged loss over the simulation could result in overestimates of dose. For scenarios in which event sequences may be important, such as the timing of hand hygiene or a hand-to-facial mucosal membrane contact following a contact with a highly contaminated surface, it is unknown how this approach may influence estimated exposures for such behaviours in comparison to an event-driven modelling strategy.

The discrete event modelling strategy has been used to explore questions related to the timing of hand hygiene, surface disinfection, and errors in personal protective equipment doffing. The timing of events can be represented as random variables that describe the frequency and sequence of events. This allows for the generation of many sequences of behaviours to investigate how these sequences affect exposure and subsequent risks (12,13).

In some cases where sequence data are lacking, events may only be informed by the frequency at which they are expected to occur with no regard to the sequence (14–16).

Given that both exposure models are used to address questions of microbial exposure in similar scenarios, yet have different underlying conceptual frameworks, the objective of this study is to compare the performance of the compartmental model simulated via Markov chain and the discrete event model to provide insight as to when one modelling method should be preferred over the other. To facilitate comparison, a simple contact exposure case study was used: a single individual contacting two fomites contaminated with microorganisms with their hand, contacting their facial mucous membranes and performing hand hygiene. Using this case study, the models are compared with respect to 1.) ability to capture the impact of episodic events, such as hand hygiene, on dose and 2.) ability to capture the impact of contact patterns on dose.

Methods

Model Scenarios

The case study that the models explored involved a single individual contacting two fomites contaminated with microorganisms with their hand, contacting their facial mucous membranes and performing hand hygiene. The model outcomes were the cumulative dose to the facial mucous membranes, and the change in microorganism concentrations on fomites over time. The case study was modelled using two methods – a discrete event model and a compartment model simulated by discrete time Markov chain (Markov model). Four scenarios were developed for each modelling method based on contact frequency and contact pattern. Two contact frequency conditions were explored: a) “symmetrical,” which we define as one in which contact frequencies with the fomites were equal over time and b) ”asymmetrical” contact frequencies, which we define as fomite A receiving more contact, and is the more contaminated fomite, as compared to fomite B.

To evaluate these different approaches, we have developed two symmetrical and two asymmetrical contact frequency approaches for both the discrete event and Markov modelling methods for exposure estimation (Table 1). Discrete event models 1 and 2 related to the symmetrical contact frequency approach. Discrete event model 1 involved alternating fomite A and fomite B contacts with a hand hygiene event every 4 contacts, where discrete event model 2 involved four sequential fomite A contacts followed by a hand hygiene event and four sequential fomite B contacts (Table 1).

Two Markov model approaches were explored for symmetrical fomite contact scenarios, where Markov model 1 separated losses due to hand hygiene from other loss moments, by using a separate transition probability matrix during a hand hygiene event, followed by a return to the other transition probability matrix during non-hand-hygiene events (Table 1). Markov model 2 incorporated loss from the hands due to hand hygiene with loss due to inactivation per timestep as an ongoing process, without a specific hand hygiene event (Table 1).

For asymmetrical contact scenarios, discrete event model 3 involved 3 rounds of repeated contacts with fomite A, followed by a hand hygiene event, and repeated contacts with fomite B (Table 1). Discrete event model 4 involved the following contact sequence between hand hygiene events: 3 contacts with fomite A and one contact with fomite B (Table 1). Markov model 3 was similar to Markov model 1, except that the assumption of greater contact frequency with fomite A increased the rate constant describing movement from hands to fomite A and decreased the rate describing movement from hands to fomite B (Table 1). Markov model 4 was similar to that of Markov model 1, except that transition probabilities between hands and fomite A were greater than those between hands and fomite B (Table 1).

For hand-to-mouth contacts, discrete event models involved randomly sampling moments for hand-to-mouth contacts (excluding the first event so that at least one hand had touched a contaminated surface). These events did not overwrite hand-to-fomite contacts. Rather, the fomite contact events were adjusted to include an interruption of the fomite contact

pattern with the hand-to-mouth contact, meaning hand hygiene events were sometimes offset by 1 minute from those in the Markov models. The Markov models accounted for transfer of microbes to the mouth per timestep, where the rate of transfer was either constant for the whole simulation or only occurring during time steps that did not involve hand hygiene events.

Model Descriptions

In the Markov model, microbial transfer between compartments (states) was described through first order rate constants (9,17). These rates were informed by fomite contact frequencies, microbial transfer efficiency, and fractions of the hand used for contacts (Table 1).

The rate of transfer from hand-to-fomites ($\lambda_{hands \rightarrow fomite}$) was calculated by,

$$\lambda_{hands \rightarrow fomite} = \frac{1}{2} S_h TE_{hf} H_f \quad (1)$$

where S_h is the fraction of the hand surface area of a single hand used for the contact, TE_{hs} is the hand-to-surface transfer efficiency, and H_f is the frequency of hand-to-fomite contacts. The rate accounts for the fact that only half of the available virus on the hands can transfer (single hand contact) as in the prior work (18). The calculation for the rate of transfer from hands to the mouth ($\lambda_{hands \rightarrow mouth}$) was similar,

$$\lambda_{hands \rightarrow mouth} = \frac{1}{2} S_m TE_{hm} H_m \quad (2)$$

where S_m is the fraction of the hand surface area of a single hand used for the hand-to-mouth contact, TE_{hm} is hand-to-mouth transfer efficiency, H_m is the frequency of hand-to-mouth contacts, and the one-half accounts for the fact that only half of the available virus on the hands can transfer (single hand contact). The rate of transfer from fomite-to-hands ($\lambda_{fomite \rightarrow hands}$) was calculated,

$$\lambda_{fomite \rightarrow hands} = \frac{A_h}{A_f} S_h TE_{fh} H_f \quad (3)$$

where A_h is total hand surface area for a single hand, A_f is fomite surface area, TE_{fh} is fomite-to-hand transfer efficiency, and other variables are as previously defined. These rates were then used to tabulate the one-step transition probability matrix (9).

For Markov models 2 and 4, a single transitional probability matrix per model was developed involving all activities, including hand hygiene ($\mathbf{P_3}$ for Markov model 2 and $\mathbf{P_5}$ for Markov model 4) (Table 1). For Markov models 1 and 3, two one-step transition probability matrices were developed: $\mathbf{P_1}$ and $\mathbf{P_4}$ involved all activities other than hand hygiene, and $\mathbf{P_H}$ represented the event of hand hygiene (Table 1). Examples of the probability matrices can be found in supplemental materials (Figures S1-S4). For Markov models 1 and 3, it was assumed hand hygiene events would occur over a minute so that the same $\log_{10}$ reduction would be achieved for a single hand hygiene event as in the discrete event models, which means $\mathbf{P_H}$ was multiplied $1\ \mathrm{min}/\Delta t$ times, where 1 minute is the duration of hand hygiene and Δt is the time-step length. Results using timesteps of 0.01 min and 0.001 min were compared to choose a timestep that resulted in similar doses as runs with smaller timesteps while balancing computational cost. Comparisons of timesteps and iterations resulted in Δt = 0.001 min being used. Dose was equated with the number of viruses that transitioned to the compartment representing the facial mucous membrane.

In the discrete event models, microbial transfer between hands and a fomite was only calculated when a hand-to-fomite contact occurred. Inactivation, however, was calculated for every event. During a hand-to-fomite contact, transfer in both directions was accounted for, and new concentrations at time t on the hand ($C_{h,t}$) and fomite ($C_{f,t}$) were calculated,

$$C_{f,t} = C_{f,t-1}e^{-k_f\Delta t} - S_h\left(\frac{A_h}{A_f}\right)\left(TE_{fh}e^{-k_f\Delta t}C_{f,t-1} - TE_{hf}e^{-k_h\Delta t}C_{h,t-1}\right) \quad (4)$$

$$C_{h,t} = C_{h,t-1}e^{-k_h\Delta t} - S_h\left(TE_{hf}e^{-k_h\Delta t}C_{h,t-1} - TE_{fh}e^{-k_f\Delta t}C_{f,t-1}\right) \quad (5)$$

Where k_f is the inactivation rate of viruses on the fomite, k_h is the inactivation rate of viruses on the hands, S_h is the fraction of total hand surface area of a single hand used for a hand-to-

fomite contact, A_h is the total hand surface area of a single hand, A_f is the fomite surface area (constant across the simulation where a value was randomly sampled for fomite A and fomite B separately), TE_{fh} is the fomite-to-hand transfer efficiency, and TE_{hf} is the hand-to-fomite transfer efficiency. Note that inactivation was accounted for, where the assumed time between events is 1 minute so that the simulated time of the discrete event models is consistent with the discrete Markov chain models. When an object was not contacted, its concentration per timestep was a function of what was remaining after inactivation occurring for that timestep. Dose (D) and a change in concentration on the hand at time t are calculated during a simulated hand-to-mouth contact,

$$D = TE_{hm} S_m A_h C_{h,t-1} e^{-k_h \Delta t} \quad (6)$$

$$C_{h,t} = (1 - TE_{hm} S_m) C_{h,t-1} e^{-k_h \Delta t} \quad (7)$$

Where TE_{hm} is the hand-to-mouth transfer efficiency, and S_m is the fraction of total hand surface area of a single hand used for the hand-to-mouth contact.

Because events were assumed to occur at 1-minute intervals, the simulated time for the discrete event model was consistent with the discrete Markov chain models. The models were implemented using Monte Carlo simulation to account for variability and uncertainty in the input parameters. For both models, the number of iterations was evaluated to balance computational cost and consistency in results. Upon investigation, 5,000 iterations was deemed appropriate for both models for the Monte Carlo simulations. Skewness in estimated dose distributions was calculated using the *e1071* R package and definition type 2 (19).

Per iteration of each model, transfer efficiencies, the fraction of hand used for contacts with fomites or the mouth, inactivation rates, total hand surface area, surface areas of fomites A and B, and hand hygiene efficacy were randomly sampled. For the Markov models, this meant that rates and transitional probability matrices were recalculated per iteration. For the discrete event models, the timing of the hand-to-mouth contact was randomly sampled per iteration. For

each iteration, Markov models 1-4 and discrete event models 1-4 were run using these same randomly selected inputs. These input parameters were then constant during the entire exposure simulation for that iteration.

Sensitivity Analysis

Monotonic relationships between randomly sampled input parameter values and estimated doses were evaluated using Spearman correlation coefficients, and the strength of these relationships were compared across models, where a larger absolute value of a Spearman correlation coefficient implies that a parameter is more influential on infection risk (assuming a monotonic relationship). This method has been used in other QMRA sensitivity analyses (9,10,20).

Additionally, the effect of differences in initial concentration between fomites A and B on changes in concentration for fomites A and B and on hands over time was evaluated by rerunning the models where starting concentrations on fomites A and B were randomly sampled so that their sum was 100 viral particles/cm^2. Changes in concentration over time were compared to those in the original models, where starting concentrations for fomites A and B were 100 viral particles/cm^2 and 5 viral particles/cm^2, respectively (Table 2). The distributions of the 1) starting concentration on the more frequently touched fomite in the asymmetrical models and 2) a ratio of concentration between the two fomites that resulted in the 15% largest doses were compared to distributions for all iterations.

Results

Concentrations on Hands and Fomites over Time

In all scenarios and for both modelling methods, the dynamics of the microorganism concentration on fomite A were similar (Figure 1), where fomite A was the more contaminated fomite initially (100 viral particles/cm^2 vs. 5 viral particles/cm^2) and, in asymmetrical contact frequency scenarios, was the more frequently contacted fomite (12 contacts vs. 4 contacts in per simulation). For fomite B, the dynamics of the microorganism concentration were quite

similar for the two modelling methods in scenarios 1 and 4 (Figure 1). The dynamics of the microorganism concentrations, however, differed between the two modelling methods in scenarios 2 and 3 (Figure 1). These scenarios are characterized by an asymmetrical distribution of contact patterns before and after the hand hygiene events in the discrete event model that align with the "steps" visible in Figure 1. Given the patterns observed, it appears that two modelling methods diverge in predicted fomite contamination for asymmetrical contact patterns, independent of how the Markov model represents hand hygiene.

Changes in concentrations on hands were most similar between the two modelling methods for scenarios 1 and 3, where the decreases in concentration due to hand hygiene events are visible (Figure 1). The dynamics of microorganism concentrations on hands estimated by discrete event model 2 were notably different than the other scenarios. In discrete event model 2 there was no accumulation of microorganisms after the second and fourth hand hygiene events (minutes 5-10 and 15-20), which is consistent with the contact patterns between the two fomites; accumulation occurred during the period with sequential contacts with the more contaminated fomite, fomite A (Table 1).

Dynamics of Cumulative Dose

Dynamics in mean cumulative dose over time were similar for the discrete event and Markov models, but mean dose was slightly greater over time for the discrete event models than for the Markov models (Figure 1). This is consistent with generally greater mean doses estimated with the discrete event models than for the Markov models (Table S1).

In 5.5% of simulations, the discrete event model estimated the dose to be zero. This occurred because hand-to-mouth contact was made with an uncontaminated hand; all preceding hand-to-fomite contacts had been made with the other hand. Excluding these results, the two modelling methods had central tendencies of the estimated $\log_{10}$ dose of similar orders of magnitude (Figure 2). Distributions of $\log_{10}$ estimated doses were slightly more skewed for discrete-event models. Across the four model scenarios, Markov models' skewness of $\log_{10}$

dose ranged from -0.80 to -0.72, and discrete-event model skewness of $\log_{10}$ ranged from -0.93 to -0.70.

Comparison of Dose across Contact Patterns

For both the Markov and discrete event models, larger mean and median doses were estimated for asymmetrical contact frequency models (models 3 and 4) (Table S1, Figure 2). When hand hygiene events were handled as independent events in the Markov model (models 1 and 3), the median dose for asymmetrical scenarios was 41% greater relative to symmetrical scenarios (model 3 vs. 1). The median dose for discrete event model 4 (0.86) was 121% greater relative to the median risk for discrete event model 2 (Table S1).

For symmetrical contact frequency models, median and mean doses were similar between the Markov and discrete event models, where the median dose for Markov model 1 was 20% greater relative to discrete event model 1 and where the mean dose for Markov model 1 was 40% smaller relative to discrete event model 1 (Table S1). Greater mean doses for discrete event models and greater median doses for Markov models were consistent across symmetrical and asymmetrical contact frequency scenarios, with the exception of Markov model 4, which produced a median dose slightly smaller than that produced by discrete model 4 (Table S1).

Comparison of Dose across Hand Hygiene Scenarios

The handling of hand hygiene had little impact on estimated median or mean doses for symmetrical contact Markov models (Table S1). However, when contact frequencies were asymmetrical, differences in median and mean doses were seen, where the median and mean doses for Markov model 3 were approximately 9% and 7% greater, respectively, relative to Markov model 4. The handling of sequences of events for discrete event models translated to little difference in estimated median or mean dose for symmetrical contact models. However, a greater difference in median dose was observed for asymmetrical contact models, where the

median dose for discrete event model 3 was 23% smaller than for discrete event model 4 (Table S1).

Characteristics of High Dose Iterations & Sensitivity Analysis

Among the simulations that yielded the highest 15% of dose estimates, 64% were from the discrete event framework and 36% were from the Markov chain framework, indicating that both modelling methods can capture “high risk” conditions. Among the Markov simulations with the highest doses, more were from model scenarios 3 and 4 (model 1: 21%, model 2: 19%, model 3: 32.5%, model 4: 27.5%), where there were more contacts with the more contaminated fomite (Tables 1 and 2). This was consistent for the discrete event models (model 1: 25%, model 2: 20%, model 3: 26%, model 4: 29%).

The model parameters most positively associated with cumulative dose estimates are fomite-to-hand transfer efficiency, hand-to mouth transfer efficiencies and the fraction of the hand used for fomite contacts (Table 3). The distributions of these variables among the simulations yielding the 15% highest dose estimates were notably different from the distributions of these parameters for all iterations combined (Figure 3).

Hand hygiene efficacy had a strong negative association with cumulative dose among all scenarios of the discrete event model, while the relationship was stronger in Markov models that time-averaged losses due to hand hygiene (models 2 and 4) (Table 3). One potential explanation for consistently strong negative associations for the discrete event models is the variability in hand-to-mouth contact moments in the discrete event models, where a dose for a hand-to-mouth contact directly following a hand hygiene event would be notably different than if the hand-to-mouth contact occurred right before the hand hygiene event. In the iterations resulting in the 15% highest doses, the frequency of hand-to-mouth contacts were not uniformly distributed across the simulation time (Figure 4).

In general, high risk hand-to-mouth contacts often occurred early in the simulation before reductions due to hand hygiene had taken effect. More specifically, the greatest number of

hand-to-mouth contacts occurred at the 5th event in the simulation. Because events were moved 1 minute forward after the insertion of a hand-to-mouth contact, a hand-to-mouth contact in the 5th minute maximizes the number of hand-to-fomite contacts made before a hand hygiene event, since the hand hygiene event that would have happened in the 5th minute is moved to the 6th minute in the simulation. While this hand-to-mouth contact timing was frequently represented among the iterations resulting in high doses, there were differences in distributions of hand-to-mouth contact timing among discrete models that resulted in highest doses, influenced by differences in concentration changes on the hands, driven by differences in hand-to-fomite contact sequences, contact frequencies with fomite A vs. fomite B, and in starting concentration between the fomites (Table 2, Figures 3 and 6). The sawtooth patterns of the hand-to-face contact timings that resulted in high doses mimic those of the changes in concentration on hands over time (Figures 1 and 4).

Unlike in the discrete event models, the reductions due to hand-to-mouth contacts in the Markov models were averaged over time. For the discrete event models only, distribution differences in hand hygiene efficacies were seen for the iterations producing the 15% greatest doses relative to all iterations (Figure 3). Scatterplots of dose vs. inputs can be seen in Figures S5-S15.

When the initial concentrations were allowed to vary between fomites A and B (but sum to 100 virus particles/cm^2, temporal changes in mean concentration on fomite A remained similar to the primary models (Figures 1 and S16). Temporal changes for fomite B were more similar to those of fomite A in this condition, than in the primary models where fomite A consistently had greater initial contamination than fomite B. The iterations producing the top 15% of dose estimates contained more instances of fomite A starting with large concentrations and fomite B starting with small concentrations, relative to distributions of starting concentrations for all iterations (Figure S17).

Discussion

Key Findings

The two modelling methods evaluated in this study yielded mean and median doses of similar orders of magnitude for all scenarios tested, and both were able to capture “high risk” events (Table S1, Figures 1 and 3). The dynamics of microorganism concentrations were similar between the two modelling methods when the Markov model treated hand hygiene as a periodic event, described in a separate transition probability matrix (Figure 1). The Markov models resulted in generally less skewed distributions of estimated $\log_{10}$ doses (Figure 2) while the discrete event models offered insights regarding the influence of the timing of hand-to-mouth events on dose (Figure 4).

For the discrete event model, mean estimated doses were less sensitive to the sequence of fomite contacts than to the distribution of contacts (symmetrical vs. asymmetrical) between the two fomites (Table S1). The doses estimated by the Markov models were also more sensitive to the symmetry of contacts with the two fomites than to the distribution of contacts, but the handling of hand hygiene had a greater effect on hand concentration dynamics than contact patterns (Figures 1 and 2, Table S1). Dose estimates from all models, regardless of framework type, were sensitive to the fraction of the hand used for hand-to-fomite contacts and the transfer efficiency from fomites to the hand and from the hand to the mouth (Table 3, Figure 3). While the fraction of the hand used for the hand-to-mouth contact would have been expected to be a more important parameter in estimating dose than the fraction of the hand used for hand-to-fomite contacts, the maximum of this distribution was 0.012 as opposed to 0.25 for the fraction of the hand used for hand-to-fomite contacts, meaning hand-to-mouth transfer efficiencies had a smaller range and allowed for smaller magnitudes of transfer than for hand-to-fomite contacts (Table 2). The way hand hygiene events were handled in the Markov model framework influenced the magnitude of monotonic relationships between hand hygiene efficacy and estimated dose, with stronger relationships seen when losses due to hand hygiene were time-averaged rather than treated as separate events (Table 3)

The discrete event model estimated doses of zero (Table S1) when one hand had been used for a series of contacts and the other was used for a later hand-to-mouth contact. This raises the issue of concentration dilution and how virus is spread homogeneously across a single hand or both hands over the course of the simulation. This issue has been addressed in previous modeling research (21), but is typically not accounted for in the frameworks used in this study. In the discrete event model, virus accumulation on each hand was tracked separately, while it was averaged across both hands in the Markov models over time. However, the Markov models could be further refined with the separation of the "hands" compartment into two compartments, representing the two hands. How specifically to track accruement on the whole hand or parts of the hand and the sensitivity of each of these frameworks to the handling of concentration dilution should be explored in future work, in addition to identifying human behaviour data gaps that may limit more detailed modelling of fomite-mediated exposures.

Limitations

To focus on the objective of this study – to compare the two modelling methods – decisions were made regarding sequences of events and distributions or point values for parameters that will not represent any specific or all potential exposure scenarios. This means that other choices could lead to conditions that produce greater or lesser differences in the performance of the modelling methods. For example, it was assumed that all events in the discrete event models occurred at a fixed interval of one minute. Varying this interval may affect differences between the discrete event and Markov models, as the latter represents events as occurring at time-averaged rates. However, the ability to model concentration changes at very short intervals are limited, in part, by the lack of data describing variability in contact duration during micro-activities, which occur on the time-scale of seconds (22), and lack of understanding of how microbial transfer efficiency is affected by duration of contact (pressure changes, uncertainties regarding concentration equilibrium between skin and fomite, etc.). Longer duration of contact between food and equipment surfaces has been associated with

greater microbial transfer in some cases (23) and not in others (24). Within the context of chemical exposures, there may be insignificant differences in transfer efficiency over small contact durations (2 sec vs. 20 sec contact duration (5,25)) but more meaningful differences for longer periods of contact (1 min vs. 60 min (26)). More transfer efficiency data and behaviour data connecting micro-activities to meso-activities, which occur on the timescale of minutes-to-hours, would potentially be needed to address the impact of contact duration on microbial transfer that would result in meaningful differences in microbial accruement on hands.

Recommendations and Considerations for Future Model Framework Choice

Exposure models have been used to understand exposure mechanisms in a variety of indoor environmental and occupational health contexts, including offices (27,28), healthcare environments (9,13,29), and publicly shared spaces (30,31). They are used to not only estimate exposures and subsequent risks but also to compare the relative contribution of one transmission route over another (9); to estimate intervention effectiveness (32); and to identify types of human behaviours, environmental conditions, and room designs that result in the greatest risks (33). Because of the wide application of exposure modeling, the accuracy and consistency in estimating exposures and describing human behaviours have important implications for infection prevention decision making.

The comparison of these frameworks offers insights into how each framework may respond to choices regarding hand hygiene events, symmetry of contacts with multiple fomites, and differences in the exposure insights each framework may offer. For the case studied in this research, either modelling method is appropriate for determining dose to the facial mucous membranes through the indirect contact pathway and to explore determinants of exposure. However, the Markov model should represent hand hygiene as distinct event with a unique transition probability matrix, rather than as a continuous rate of microorganism loss from the hand. If the objective of the model is to gain insights regarding how the timing of events yields

the highest doses or risks, the discrete event model may be more useful in providing these insights.

Future work is needed to further develop our understanding of the conditions under which different exposure models are appropriate. The two models used in this study are relatively common in QMRA applications (9,10,17,33–36), but other models are also used. For example, Environment Infection Transmission System (EITS) modeling framework combines compartments common to epidemiologic models (e.g., susceptible-infectious-recovered or S-I-R models) with environmental compartments (e.g. hands) to track pathogens (37). Thus, not only is there further need to challenge the Markov model and discrete event model under a wider variety of conditions, and against experimental or observational data, but to compare performance of other models. Despite these needs, exposure models remain a valuable tool to support infection prevention and public health decision making.

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References

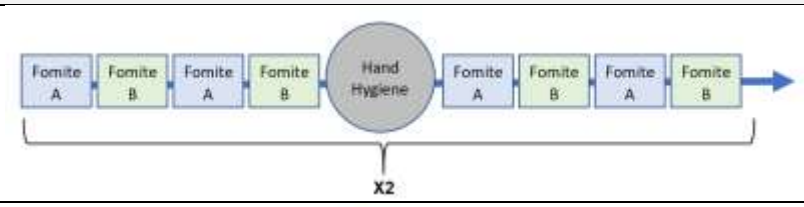
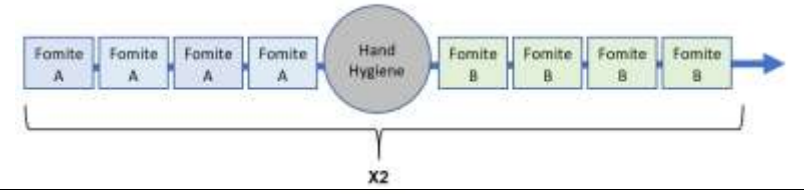
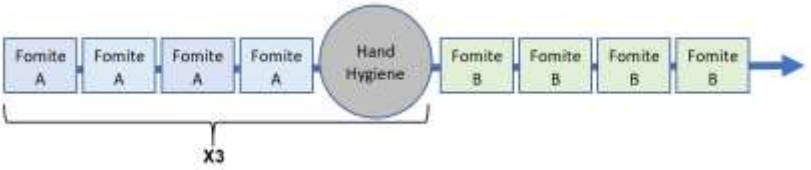
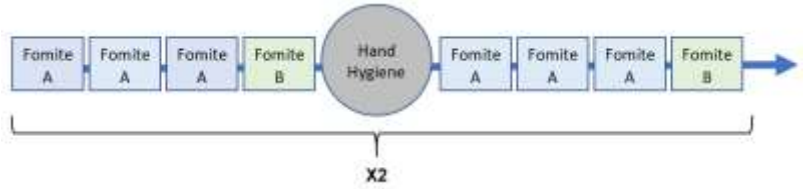
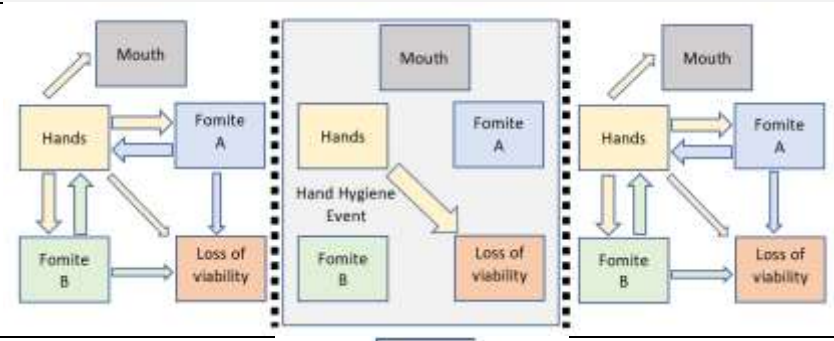
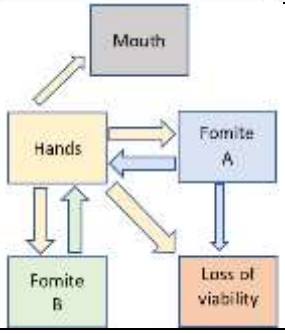
1. Weber DJ, Anderson DJ, Sexton DJ, Rutala WA. Role of the environment in the transmission of *Clostridium difficile* in health care facilities. Am J Infect Control. 2013;41(5 SUPPL.):S105–10. Available from: http://dx.doi.org/10.1016/j.ajic.2012.12.009
2. Collins AS. Chapter 41. Preventing Health Care – Associated Infections Definitions of Health Care-Associated Infections. In: Hughes R, editor. Patient Safety and Quality: An Evidence-Based Handbook for Nurses. Rockville, MD: Agency for Healthcare Research and Quality; 2008. p. 547–76. Available from: https://www.ncbi.nlm.nih.gov/books/NBK2683/
3. Lei H, Jones RM, Li Y. Exploring surface cleaning strategies in hospital to prevent contact transmission of methicillin-resistant *Staphylococcus aureus*. BMC Infect Dis. 2017;17:85. Available from: http://dx.doi.org/10.1186/s12879-016-2120-z
4. Tacconelli E, Cataldo MA. Vancomycin-resistant *enterococci* (VRE): transmission and control. Int J Antimicrob Agents. 2008;31:99–106. Available from: https://www.doi.org/ 10.1016/j.ijantimicag.2007.08.026.
5. Hubal EAC, Suggs JC, Nishioka G, Ivancic WA. Characterizing residue transfer efficiencies using a fluorescent imaging technique. J Expo Anal Environ Epidemiol. 2005;15(3):261–70. Available from: https//www.doi.org/ 10.1038/sj.jea.7500400.
6. Sahmel J, Hsu EI, Avens HJ, Beckett EM, Devlin KD. Estimation of hand-to-mouth transfer efficiency of lead. Ann Work Expo Heal. 2015;59(2):210–20. Available from: https://www.doi.org/10.1093/annhyg/meu088.
7. Hubal EAC, Sheldon LS, Burke JM, McCurdy TR, Berry MR, Rigas ML, et al. Children's exposure assessment: A review of factors influencing children's exposure, and the data available to characterize and assess that exposure. Environ Health Perspect. 2000;108(6):475–86. Available from: https://www.doi.org/10.1289/ehp.108-1638158.
8. Haas CN, Rose JB, Gerba CP. Quantitative Microbial Risk Assessment. John Wiley and Sons; 1999.
9. Jones RM. Relative contributions of transmission routes for COVID-19 among healthcare personnel providing patient care. J Occup Environ Hyg. 2020 Jul 9;17(9):408–15. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32643585
10. Julian TR, Canales RA, Leckie JO, Boehm AB. A model of exposure to rotavirus from nondietary ingestion iterated by simulated intermittent contacts. Risk Anal. 2009;29(5):617–32. Available from: https://www.doi.org/ 10.1111/j.1539-6924.2008.01193.x.
11. Wilson AM, King M-F, Clifton I, Proctor J, Reynolds KA, Noakes CJ. Modelling the influence of room orientation and care type on differences in norovirus exposure via an air-surface interface transmission route. In: The 16th Conference of the International Society of Indoor Air Quality & Climate (Indoor Air 2020). Seoul, Korea; 2020.
12. King M-F, Wilson AM, Weir MH, Lopez-Garcia M, Proctor J, Hiwar W, et al. Modelling the risk of SARS-CoV-2 infection through PPE doffing in a hospital environment. medRxiv. 2020; Available from: https://doi.org/10.1101/2020.09.20.20197368
13. King MF, Noakes CJ, Sleigh PA. Modeling environmental contamination in hospital single- and four-bed rooms. Indoor Air. 2015;25(6):694–707. Available from: https://www.doi.org/ 10.1111/ina.12186.
14. Wilson AM, Reynolds KA, Verhougstraete MP, Canales RA. Validation of a stochastic discrete event model predicting virus concentration on nurse hands. Risk Anal. 2019;39(8):1812–24. Available from: http://doi.wiley.com/10.1111/risa.13281
15. Canales RA, Reynolds KA, Wilson AM, Fankem SLM, Weir MH, Rose JB, et al. Modeling the role of fomites in a norovirus outbreak. J Occup Environ Hyg. 2019;16(1). Available from: https://www.doi.org/ 10.1080/15459624.2018.1531131.

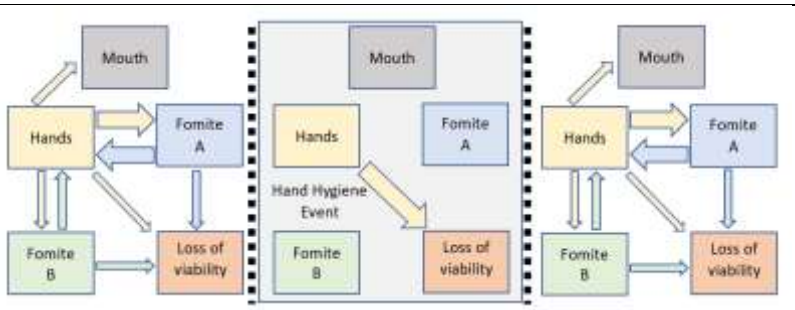
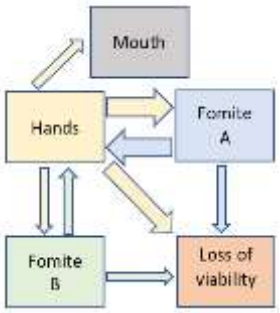
16. Canales RA, Wilson AM, Sinclair RG, Soto-Beltran M, Pearce-Walker J, Molina M, et al. Microbial study of household hygiene conditions and associated *Listeria monocytogenes* infection risks for Peruvian women. Trop Med Int Heal. 2019;24(7). Available from: https://www.doi.org/ 10.1111/tmi.13246.
17. Weir MH, Shibata T, Masago Y, Cologgi DL, Rose JB. Effect of surface sampling and recovery of viruses and non-spore-forming bacteria on a quantitative microbial risk assessment model for fomites. Environ Sci Technol [Internet]. 2016 Jun 7;50(11):5945–52. Available from: https://pubs.acs.org/doi/10.1021/acs.est.5b06275
18. Wilson AM, Jones RM, Lugo Lerma V, Abney SE, King M-F, Weir MH, et al. Respirators, face masks, and their risk reductions via multiple transmission routes for first responders within an ambulance. J Occup Environ Hyg. 2021;8(7):345-360. Available from: https://www.doi.org/ 10.1080/15459624.2021.1926468.
19. Meyer D, Dimitriadou E, Hornik K, Weingessel A, Leisch F, Chang C-C, et al. e1071: Misc Functions of the Department of Statistics, Probability Theory Group (Formerly: E1071), TU Wien [Internet]. 2021 [cited 2021 Mar 22]. Available from: https://cran.r-project.org/web/packages/e1071/index.html
20. Hamilton KA, Hamilton MT, Johnson W, Jjemba P, Bukhari Z, LeChevallier M, et al. Risk-based critical concentrations of *Legionella pneumophila* for indoor residential water uses. Environ Sci Technol. 2019;53(8):4528–41. Available from: http://pubs.acs.org/doi/10.1021/acs.est.8b03000
21. Canales RA. The cumulative and aggregate simulation of exposure framework. Stanford University; 2004. PhD dissertation.
22. Beamer PI, Luik CE, Canales RA, Leckie JO. Quantified outdoor micro-activity data for children aged 7 – 12-years old. J Expo Sci Environ Epidemiol. 2012;22(1):82–92. Available from: http://dx.doi.org/10.1038/jes.2011.34
23. Miranda RC, Schaffner DW. Longer contact times increase cross-contamination of Enterobacter aerogenes from surfaces to food. Appl Environ Microbiol. 2016;82(21):6490–6. Available from: https://www.doi.org/ 10.1128/AEM.01838-16.
24. Dawson P, Han I, Cox M, Black C, Simmons L. Residence time and food contact time effects on transfer of *Salmonella Typhimurium* from tile, wood and carpet: testing the five-second rule. J Appl Microbiol. 2007;102:945–53. Available from: https://www.doi.org/ 10.1111/j.1365-2672.2006.03171.x.
25. Hubal EAC, Nishioka MG, Ivancic WA, Morara M, Egeghy PP. Comparing surface residue transfer efficiencies to hands using polar and nonpolar fluorescent tracers. Environ Sci Technol. 2008;42(3):934–9. Available from: https://www.doi.org/ 10.1021/es071668h.
26. Rohrer CA, Hieber TE, Melnyk LJ, Berry MR. Transfer efficiencies of pesticides from household flooring surfaces to foods. J Expo Anal Environ Epidemiol. 2003;13(6):454–64. Available from: https://www.doi.org/10.1038/sj.jea.7500300.
27. Beamer PI, Plotkin KR, Gerba CP, Sifuentes LY, Koenig DW, Reynolds KA. Modeling of human viruses on hands and risk of infection in an office workplace using micro-activity data. J Occup Environ Hyg. 2015;12(4):266–75. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25436665
28. Zhang N, Su B, Chan P-T, Miao T, Wang P, Li Y. Infection spread and high-resolution detection of close contact behaviors. Int J Environ Res Public Health. 2020;17(4):1445. Available from: https://www.doi.org/ 10.3390/ijerph17041445.
29. Nicas M, Sun G. An integrated model of infection risk in a health-care environment. Risk Anal. 2006;26(4):1085–96. Available from: https://www.doi.org/ 10.1111/j.1539-6924.2006.00802.x.
30. Pitol AK, Julian TR. Community transmission of SARS-CoV-2 by surfaces: Risks and risk reduction strategies. Environ Sci Technol Lett. 2021;In print. Available from:

https://www.doi.org/10.1021/acs.estlett.0c00966.
31. Harvey AP, Fuhrmeister ER, Cantrell M, Pitol AK, Swarthout JM, Powers JE, et al. Longitudinal monitoring of SARS-CoV-2 RNA on high-touch surfaces in a community setting. Environ Sci Technol Lett. 2021;8(2):168-175. Available from: https://www.doi.org/10.1021/acs.estlett.0c00875.
32. Wilson AM, Reynolds KA, Canales RA. Estimating the effect of hand hygiene compliance and surface cleaning timing on infection risk reductions with a mathematical modeling approach. Am J Infect Control. 2019;47(12):1453–9. Available from: https://www.doi.org/10.1016/j.ajic.2019.05.023.
33. Wilson AM, King M-F, Clifton IJ, Proctor J, Reynolds KA, Noakes CJ. Effects of patient room layout on viral accruement on healthcare professionals' hands. Indoor Air. 2021; Online ahead of print. Available at: https://doi.org/ 10.1111/ina.12834.
34. Wilson AM, King M-F, López-García M, Weir MH, Sexton JD, Canales RA, et al. Evaluating a transfer gradient assumption in a fomite-mediated microbial transmission model using an experimental and Bayesian approach. J R Soc Interface. 2020 Jun 24;17(167):20200121. Available from: https://royalsocietypublishing.org/doi/10.1098/rsif.2020.0121
35. Nicas M, Jones RM. Relative contributions of four exposure pathways to influenza infection risk. Risk Anal. 2009;29(9):1292–303. Available from: https://www.doi.org/10.1111/j.1539-6924.2009.01253.x.
36. Julian TR, Pickering AJ. A pilot study on integrating videography and environmental microbial sampling to model fecal bacterial exposures in peri-urban. PLoS One. 2015;10(8):e0136158. Available at: https://www.doi.org/10.1371/journal.pone.0136158.
37. Kraay ANM, Hayashi MAL, Hernandez-Ceron N, Spicknall IH, Marisa C, Meza R, et al. Fomite-mediated transmission as a sufficient pathway: a comparative analysis across three viral pathogens. BMC Infect Dis. 2018;18(1):540. Available at: https://www.doi.org/10.1186/s12879-018-3425-x.
38. Julian TR, Leckie JO, Boehm AB. Virus transfer between fingerpads and fomites. J Appl Microbiol. 2010;109(6):1868–74. Available at: https://www.doi.org/0.1111/j.1365-2672.2010.04814.x.
39. Rusin P, Maxwell S, Gerba C. Comparative surface-to-hand and fingertip-to-mouth transfer efficiency of gram-positive bacteria, gram-negative bacteria, and phage. J Appl Microbiol. 2002;93(4):585–92. Available at: https://www.doi.org/10.1046/j.1365-2672.2002.01734.x.
40. AuYeung W, Canales RA, Leckie JO. The fraction of total hand surface area involved in young children’s outdoor hand-to-object contacts. Environ Res. 2008;108(3):294–9. Available at: https://www.doi.org/10.1016/j.envres.2008.07.010.
41. Wilson AM, Reynolds KA, Jaykus LA, Escudero-Abarca B, Gerba CP. Comparison of estimated norovirus infection risk reductions for a single fomite contact scenario with residual and nonresidual hand sanitizers. Am J Infect Control. 2020;48(5):538–44. Available at: https://www.doi.org/10.1016/j.ajic.2019.09.010.
42. Boone SA, Gerba CP. Significance of fomites in the spread of respiratory and enteric viral disease. Appl Environ Microbiol. 2007;73(6):1687–96. Available at: https://www.doi.org/10.1128/AEM.02051-06.
43. Ansari SA, Sattar SA, Springthorpe VS, Wells GA, Tostowaryk W. Rotavirus survival on human hands and transfer of infectious virus to animate and nonporous inanimate surfaces. J Clin Microbiol. 1988;26(8):1513–8. Available at: https://www.doi.org/10.1128/jcm.26.8.1513-1518.1988..
44. Wilson AM, Verhougstraete MP, Beamer PI, King M-F, Reynolds KA, Gerba CP. Frequency of hand-to-head, -mouth, -eyes, and -nose contacts for adults and children during eating and non-eating macro-activities. J Expo Sci Environ Epidemiol.

2020;31:34–44. Available from: http://dx.doi.org/10.1038/s41370-020-0249-8

Table 1. Descriptions of model scenarios, discrete event model contact patterns, and matrices used in Markov models*

Scenario	Contact Frequency Condition	Contact Pattern	Visual Description
Discrete Event Models			
1	Symmetrical	$(F_A F_B F_A F_B H F_A F_B F_A F_B)_{x2}$	
2	Symmetrical	$(F_A F_A F_A F_A H F_B F_B F_B F_B)_{x2}$	
3	Asymmetrical	$(F_A F_A F_A F_A H)_{x3} F_B F_B F_B F_B$	
4	Asymmetrical	$(F_A F_A F_A F_B H F_A F_A F_A F_B)_{x2}$	
Markov Models			
1	Symmetrical	$(P_1)_{xn} (P_H)_{x4} (P_1)_{xn}$	
2	Symmetrical	$(P_3)_{xn}$	

3	Asymmetrical	$(P_4)_{xn}\,(P_H)_{x4}\,(P_4)_{xn}$	
4	Asymmetrical	$(P_5)_{xn}$	

*Timing of hand-to-mouth contact events were randomly selected. Subsequent events were moved forward by 1 minute. F_1 indicates contact with fomite A. F_2 indicates contact with fomite B. H indicates hand hygiene event. Each contact pattern for discrete event models repeats until 21 events occur, with 4 hand hygiene events, 1 hand-to-mouth contact, and 16 fomite contacts. Markov models involved different one-step transition probability matrices to represent different contact patterns (P_1, P_2, etc.) and hand hygiene (P_H) multiplied iteratively.

Table 2. Model parameters, their distributions, and their sources

Model	Parameter	Distribution/Point Value	Source
All Models	Hand-to-surface transfer efficiency	Lognormal (meanlog= -2.1, sdlog=1.4), Left- and right-truncated at 0 and 1, respectively	(38)
	Surface-to-hand transfer efficiency	Lognormal (meanlog= -2.1, sdlog=1.4), Left- and right-truncated at 0 and 1, respectively	
	Hand-to-mouth transfer efficiency	Normal (mean=0.3390, sd=0.1318), Left- and right-truncated at 0 and 1, respectively	(39)
	Total Hand Surface Area	Uniform (min=445, max=535), cm^2	(40)
	Fraction of Total Hand Surface Area Used for Contact	Uniform (min=0.008, max=0.25)	(40)
	Fraction of Total Hand Surface Area Used for Hand-to-Mouth Contact	Uniform (min=0.008, max=0.012)	(40)
	Fomite A Surface Contamination	100 viral particles/cm^2	Assumed*
	Fomite B Surface Contamination	5 viral particles/cm^2	
	Hand Hygiene Efficacy (log_{10} reduction)	Normal (mean=1.06, sd =0.54), Left-and right-truncated at 0 and 1.89, respectively	(41)
	Exposure Duration	21 min	Assumed*
	Fomite Surface Area	Uniform (min=150, max=250), cm^2	Assumed*
	Inactivation Rate on Fomites	Uniform (0.0048, 0.013), hr^{-1}	(42)
	Inactivation Rate on Hands	Uniform (0.61, 1.7), hr^{-1}	(43)
	Frequency of Hand Hygiene Events	4 hand washes/20 min	Assumed*
	Hand-to-Mouth Contact Frequency	1 contact/20 min	(44)
Discrete Models 1 and 2, Markov Models 1 and 2	Frequency of Contacts with Fomite A	8 contacts/20 min	Assumed*
	Frequency of Contacts with Fomite B	8 contacts/20 min	Assumed*
Discrete Models 3 and 4, Markov Models 3 and 4	Frequency of Contacts with Fomite A	12 contacts/20 min	Assumed*
	Frequency of Contacts with Fomite B	4 contacts/20 min	Assumed*

Descriptions of how data from original sources were used to inform these distributions can be found in supplemental materials. *These values are used for demonstration of model comparison purposes and not intended to reflect reality

Figure 1. Dynamics in cumulative dose (mean± SD) and microbial concentrations (mean ± SD) on the hands, fomite A and fomite B predicted by the discrete event (discrete) and Markov models for scenarios 1-4. *Symmetrical hand contact frequency is reflected in scenarios 1 and 2, while asymmetrical hand contact frequency is reflected in scenarios 3 and 4. Differences in the handling of hand hygiene can be seen between scenarios 1 and 3 (hand hygiene treated as an event) and scenarios 2 and 4 (hand hygiene loss is time-averaged across the simulation) for the Markov models.

Figure 2. Distributions of estimated doses for discrete event and Markov chain models for the 4 scenarios described in Table 1.

Table 3. Spearman correlation coefficients

		Input Parameter										
		Hand-to-Fomite TE	Fomite-to-Hand TE	Hand-to-Mouth TE	Total Hand SA	SA of Fomite A	SA of Fomite B	Inactivation Rate on Fomites	Inactivation Rate on Hands	Fraction of hand used in fomite contacts	Fraction of hand used in mouth contacts	Hand Hygiene Efficacy
Markov Models	1	-0.0092	0.78	0.30	0.049	0.043	-0.0094	-0.018	0.0021	0.47	0.10	-0.14
	2	-0.007	0.75	0.30	0.048	0.049	-0.0012	-0.021	0.00032	0.45	0.10	-0.30
	3	-0.0089	0.78	0.31	0.049	0.050	-0.011	-0.019	0.0013	0.46	0.11	-0.15
	4	-0.0065	0.73	0.31	0.047	0.059	-0.014	-0.022	-0.0012	0.44	0.11	-0.32
Discrete-event Models	1	0.014	0.44	0.19	0.039	0.024	-0.016	-0.0037	-0.0038	0.27	0.056	-0.20
	2	-0.0050	0.43	0.17	0.045	0.025	0.0016	0.0027	-0.021	0.27	0.066	-0.28
	3	-0.0077	0.42	0.20	0.030	0.041	-0.0015	0.0031	-0.012	0.25	0.072	-0.26
	4	-0.023	0.44	0.19	0.040	0.062	0.0064	-0.0057	-0.022	0.27	0.068	-0.22

Figure 3. Distributions of fomite-to-hand transfer efficiency, fraction of the hand used for a fomite touch, hand-to-mouth transfer efficiency, and $\log_{10}$ hand hygiene efficacy* for iterations producing the 15% largest doses and for all iterations

*Distributions of $\log_{10}$ hand hygiene efficacies are only shown for the discrete event model iterations among the 15% producing the largest doses since hand hygiene efficacy did not have as large of an effect on estimated doses in the Markov models

Figure 4. Distributions of discrete-event hand-to-face contact timing for iterations producing the 15% largest doses and for all iterations