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Addressing current limitations of household transmission studies by collecting contact data

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Abstract

Modeling studies of household transmission data have helped characterize the role of children in influenza and coronavirus disease 2019 (COVID-19) epidemics. However, estimates from these studies may be biased since they do not account for the heterogeneous nature of household contacts. Here, we quantified the impact of contact heterogeneity between household members on the estimation of child relative susceptibility and infectivity. We simulated epidemics of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-like and influenza virus-like infections in a synthetic population of 1000 households, assuming heterogeneous contact levels. Relative contact frequencies were derived from a household contact study according to which contacts are more frequent in the father–mother pair, followed by the child–mother, child–child, and finally child–father pairs. Child susceptibility and infectivity were then estimated while accounting for heterogeneous contacts or not. When ignoring contact heterogeneity, child relative susceptibility was underestimated by approximately 20% in the two disease scenarios. Child relative infectivity was underestimated by 20% when children and adults had different infectivity levels. These results are sensitive to our assumptions of European-style household contact patterns; but they highlight that household studies collecting both disease and contact data are needed to assess the role of complex household contact behavior on disease transmission and improve estimation of key biological parameters.

Key words: household study; respiratory infections; modeling; simulation; parameter estimation; infectivity; susceptibility.

Introduction

Households constitute an ideal setting for the study of respiratory disease transmission. Respiratory diseases generally transmit through infectious respiratory particles, with the risk of transmission generally increasing with time spent indoors in close proximity to a contagious case.[1] Within-household transmission represents a substantial fraction of disease transmission for a number of respiratory diseases.[2,3] In addition, the study of respiratory disease transmission is simplified in households because case contacts are well-defined, which facilitates their follow-up after exposure and the estimation of the secondary infection risk, often referred to as the secondary attack rate (SAR), and defined as the proportion of household contacts that are infected after the index case is detected.

Household studies have helped characterize the transmission of respiratory diseases caused by influenza viruses,[4] the respiratory syncytial virus,[5] and the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[6,7] These studies allowed the estimation of the serial interval, the SAR, and the identification of factors affecting individual infectivity and susceptibility. Mathematical models can improve inference by explicitly accounting for the possibility of community-acquired and tertiary infections. They have helped to quantify the role of children[4,8-11] by estimating their relative susceptibility and infectivity compared with adults. For example, child susceptibility was shown to be about half adult susceptibility for SARS-CoV-2 infections,[11,12] while children are about twice as susceptible to influenza virus infections as adults,[9,13,14] with differences also identified between newborns, children, and teenagers.[15,16] Mathematical models have also quantified the impact of direct [12,17] and indirect vaccination[12,14,17] on household transmission dynamics.[18]

The relative infectivity and susceptibility estimated in household studies can be caused by biological factors (eg, different levels of viral shedding when infected or different propensity

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to get infected when exposed) but also by the level of physical contact in the household.[19] So far, household transmission models have ignored this second source of heterogeneity, implicitly assuming that estimated values were indicative of different biological parameters between children and adults, essentially related to the maturity of the immune system. By doing so, models have allowed the estimation of the overall contribution of children to household transmission dynamics and have shown their epidemiologic importance; however, at the same time, their estimates of susceptibility and infectivity might not reflect biological factors.

To date, only one study has quantified mixing between household members according to their individual characteristics and relationship to one another.[20] Based on a contact survey administered from 2010 to 2011 to 318 Belgian households with at least 1 child under 12 and representative of the geographical area, day/weekend distribution, and age and gender of the youngest children, it concluded that, (1) the vast majority of contacts that occur in households are physical; (2) on average, children have less contact with their fathers than with other siblings; (3) the overall rate of household physical contact between children decreases with age; and (4) the magnitude of contacts decreases with household size. The study shows that the assumption of homogeneous mixing does not hold in the household environment, a finding supported by other studies using close-proximity electronic sensors.[21-23] As a result, part of the estimated differences between children and adults in households might be due to different mixing patterns in the household. It is important to determine by how much mixing patterns in households might bias estimates of biological susceptibility/infectivity estimated in household studies because these estimates are essential in pandemic contexts to guide recommendations on interventions such as testing protocols in schools and school closure.[18]

Here, we argue that contact patterns should be integrated in the collection and analysis of household transmission studies for respiratory diseases to ensure robust estimation. We thus investigate how heterogeneous contact patterns in households might bias estimates of respiratory diseases transmission, notably the transmission rate between household members, the relative susceptibility of children (defined as individuals aged ≤ 18 years old) compared with adults, and their relative infectivity. To this end, we simulated epidemics in households using realistic contact patterns from Belgium,[20] and we estimated key transmission parameters (considering the case of SARS-CoV-2 and influenza) while accounting or not for the heterogeneous nature of contact patterns.

Methods

Household composition in the simulated data set

We constituted a synthetic population of 1000 households. We derived the demographic structure and the index cases of the synthetic population from the multicenter household study RECOVER[16] by randomly sampling with replacement 1000 households from a subset of the households (n = 225) of the RECOVER study. From the RECOVER study, we retained households with 2 to 5 household members that correspond either to father–mother pairs, or to single-parent or hetero-parental 2-generation families. We excluded same-sex couples (n = 2) and homo-parental families (n = 2) because of the lack of estimates in the study by Goeyvaerts et al[20] on contact levels between partners of same-sex couples, and more specifically, between same-sex parents and their children. From the original household study RECOVER, we kept 2 types of information for each household member: (1) whether the individual is the index case, and (2) the role of the individual in the household (ie, mother, father, or child).

Simulation of household epidemics

In silico follow-up protocol

We assumed that the 1000 households from the synthetic population were recruited and followed up starting from the symptom onset of the index case, and for up to 20 days. Since our aim was to ascertain how the misspecification of contact intensity may influence the estimation of transmission rates, we decided to consider a simple inference context, assuming that all cases exhibit symptoms and testing is perfect.

Relative contact rates between household members

Given that the vast majority of contacts that occur in households are physical contacts, we used the odds ratios of physical contacts between pairs estimated during weekdays by Goeyvaerts et al.[20] For brevity, we refer to physical contacts as contacts in the rest of the manuscript. We used the father–mother pair as the reference, which means that for this type of pair the relative contact rate between the infector l and their recipient k is $\kappa_{k,l} = 1$. For the mother–child pairs, we assumed they were 10% less in contact compared with the father–mother pairs ($\kappa_{k,l} = 0.90$), father-child pairs were 58% less in contact ($\kappa_{k,l} = 0.42$), and pairs of children were 24% less in contact ($\kappa_{k,l} = 0.76$).

Force of infection within households

In the simulations, the probability that an individual k in household h gets infected between time t and time $t + dt$ with $dt > 0$ small is:

$$\Lambda_k\left(t, t+dt\right) = \alpha \times dt + \sum\nolimits_{l \in I_h\{\xi_j < t\}} \frac{\beta}{n/2} \kappa_{k,l} \mu_{s,k} \mu_{i,l} \int_t^{t+dt} f\left(u - \xi_l | s_l\right) du$$

where α is the instantaneous hazard of infection in the community; ξ_l is the infection date of case l that belongs to $I_h\left\{\xi_j < t\right\}$ the infected individuals in household h that were infected before time t; $\frac{\beta}{n/2}$ models the dependency between the baseline transmission rate β in the father–mother pair, and the household size n; $\kappa_{k,l}$ is the relative contact rate between recipient k and infector l according to the type of the pair; $\mu_{s,k}$ is the relative susceptibility of recipient k according to their age with adults as reference ($\mu_{s,adult} = 1$); $\mu_{i,l}$ is the relative infectivity of infector l according to their age with adults as reference ($\mu_{i,adult} = 1$); and $f\left(t - \xi_l | s_l\right)$ is the density probability function of the generation time conditioned on the incubation period s_l of infector l. Here, the generation time is defined as the distribution of the interval between the infection time of the infector and the infection time of the recipient. We used the distribution estimated by Ferretti et al[24] for SARS-CoV-2 infections.

If k gets infected between t and $t + dt$, its exact time of infection ξ_k is drawn uniformly between t and $t + dt$, and its incubation period s_k is drawn from a log-normal distribution with log-mean = 1.63 and log-standard deviation = 0.5, previously estimated by McAloon et al[25] for SARS-CoV-2 infections. If symptom onset occurs after the end of the follow-up, the individual is not detected. We simulated continuous times of infection and symptom onset. For realistic reasons, we discretized the time of symptom onset and kept only the day of symptom onset to perform the inference.

We tested two scenarios. The first corresponds to a SARS-CoV-2–like infection scenario, with children being 50% less susceptible than adults and 20% less infectious than adults (Table 1).[6,11,12,15]

Table 1. Parameter values used in the simulations for an analysis of the impact of household contact heterogeneity on the estimation of respiratory infections transmission dynamics

Parameter	SARS-CoV-2–like infection	Influenza virus–like infection
Hazard of infection in the community α	0.001	0.001
Secondary attack rate in father–mother pairs $1-\exp(-\beta)$	29%	13%
Relative susceptibility of children $\mu_{s,child}$	0.5	2
Relative infectivity of children $\mu_{i,child}$	0.8	1

Abbreviation: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

The second corresponds to an influenza-like infection scenario with children being twice as susceptible as adults and as infectious as adults.[4,9,13,14,26] For each scenario, we assumed similar generation times but different transmission rates. The value of the baseline transmission rate in father–mother pairs β was chosen so that the overall SAR was approximately 33%[7,16] (Table 1). Finally, we simulated epidemics in the synthetic household database 1000 times for each scenario.

Statistical inference

Statistical inference was performed in a Bayesian framework with data augmentation.[8] In the section above, we detailed the model by using adults as the reference. In the inference model, we used children as the reference because pairs of children were more numerous than pairs of adults, which provides more stable inference. We estimated the hazard of infection in the community α, the transmission rate between 2 children in a household of size 4 $\beta'_{child-child,4} = (\beta/(4/2))\,\kappa_{child,child}\mu_{s,child}\mu_{i,child}$, the relative susceptibility of adults compared with children $\mu'_{s,adult} = 1/\mu_{s,child}$, and the relative infectivity of adults compared with children $\mu'_{i,adult} = 1/\mu_{i,child}$ using a simple Metropolis-Hastings algorithm. For α, we assumed an exponential prior distribution with parameter equal to 500, which means that the instantaneous incidence rate is 200/100000 inhabitants in the population, and for $\beta'_{child-child,4}$, we assumed a uniform prior distribution between 0 and 10. We used a log-normal distribution with log-mean = 0 and log-standard deviation = 1 for $\mu'_{s,adult}$ and $\mu'_{i,adult}$.

Infection dates and symptom onset dates were augmented after each parameter iteration. Infection dates were sampled from the incubation period distribution estimated by McAloon et al,[25] and the exact time of symptom onset was sampled uniformly over the observed day of symptom onset.

For each simulation, we launched two Markov chain Monte Carlo (MCMC) chains assuming homogeneous mixing between household members (incorrect inference model) or heterogeneous mixing (correct inference model) using the parameter values of contact rates from the simulations. Each chain was run for 70 000 iterations. We discarded a burn-in of 7000 steps and applied a thinning of 40 for the estimation of the posterior distributions. Convergence was assessed visually and by calculating the effective sample size (ESS) using the *effectiveSize* function in the *coda* R package for every parameter of every MCMC chain. ESS values exceeded 500 for all parameters in all chains.

Comparison of simulated and estimated parameters

The estimates of β, $\mu_{s,child}$, and $\mu_{i,child}$ were compared with the values used in the simulations using 2 metrics: the mean relative bias in percentage defined as $MRB = \frac{1}{n}\sum_{i=1}^{n}\frac{1}{\theta_i}\left(\hat{\theta}_i - \theta_i\right) \times 100$; and the coverage in percentage defined as $coverage_{95\%} = \frac{1}{n}\sum_{i=1}^{n} 1_{\{\theta_i \in CrI_{95\%}(D_i)\}} \times 100$.

We denote n the number of simulations, θ_i the true value of the parameter, D_i the parameter posterior distribution, $\hat{\theta}_i$ the median posterior estimate, and $CrI_{95\%}$ the 95% credible interval.

Results

We explore two inference scenarios: a scenario where the heterogeneous contact patterns are accounted for in the inference model, and a scenario where contacts are assumed to occur at the same levels between all pairs of household members. In the coronavirus disease 2019 (COVID-19) scenario depicted in Figure 1, the 3 parameters of within household transmission are well estimated when the inference model accounts for heterogeneous contact patterns between household members ("correct" inference model in Figure 1). The transmission rate in father–mother pairs is relatively well estimated with a mean relative bias lower than 2% (Figure 1D) and a coverage of 94% (Figure 1G). The estimation of child relative susceptibility is also satisfying with a mean relative bias around −2% (Figure 1E) and a coverage of 94% (Figure 1H). Finally, the 20% reduction of child infectivity is correctly estimated with a mean relative bias of about 8% (Figure 1F) and a coverage of 89% (Figure 1I). The slight overestimation of the transmission rate in father–mother pairs mirrors the slight underestimation of child relative susceptibility as the 2 parameters are negatively correlated.

When the inference model does not account for contact heterogeneity ("incorrect" inference model in Figure 1), the estimation of the parameters of within household transmission is largely biased. The transmission rate is overestimated by 27% and the 95% credible interval contains the true value in only 1.7% of the simulations (Figure 1D and 1G). Child relative susceptibility and child relative infectivity are underestimated by around 20% (Figure 1E-F), and their coverage does not exceed 35% (Figure 1H-I). Given that father–mother pairs have the strongest level of contact in the simulations, their net transmission rate is higher than the net transmission rate in pairs of children or between parents and children. When the inference model assumes that all household members have the same level of contact, it has to compensate by a larger transmission rate in pairs of adults and a lower transmission rate between children and in parent–child pairs by increasing the transmission rate in father–mother pairs and reducing the susceptibility and infectivity of children. The extent of the bias that we observed results from the values used to model contact heterogeneity in the simulations.

We obtained similar results for the influenza scenario presented in Figure 2. When contact heterogeneity is accounted for, the transmission rate in father–mother pairs is well estimated (5% bias) with a coverage of 88% (Figure 2D and G). Child relative susceptibility is underestimated by about 6% with a coverage of

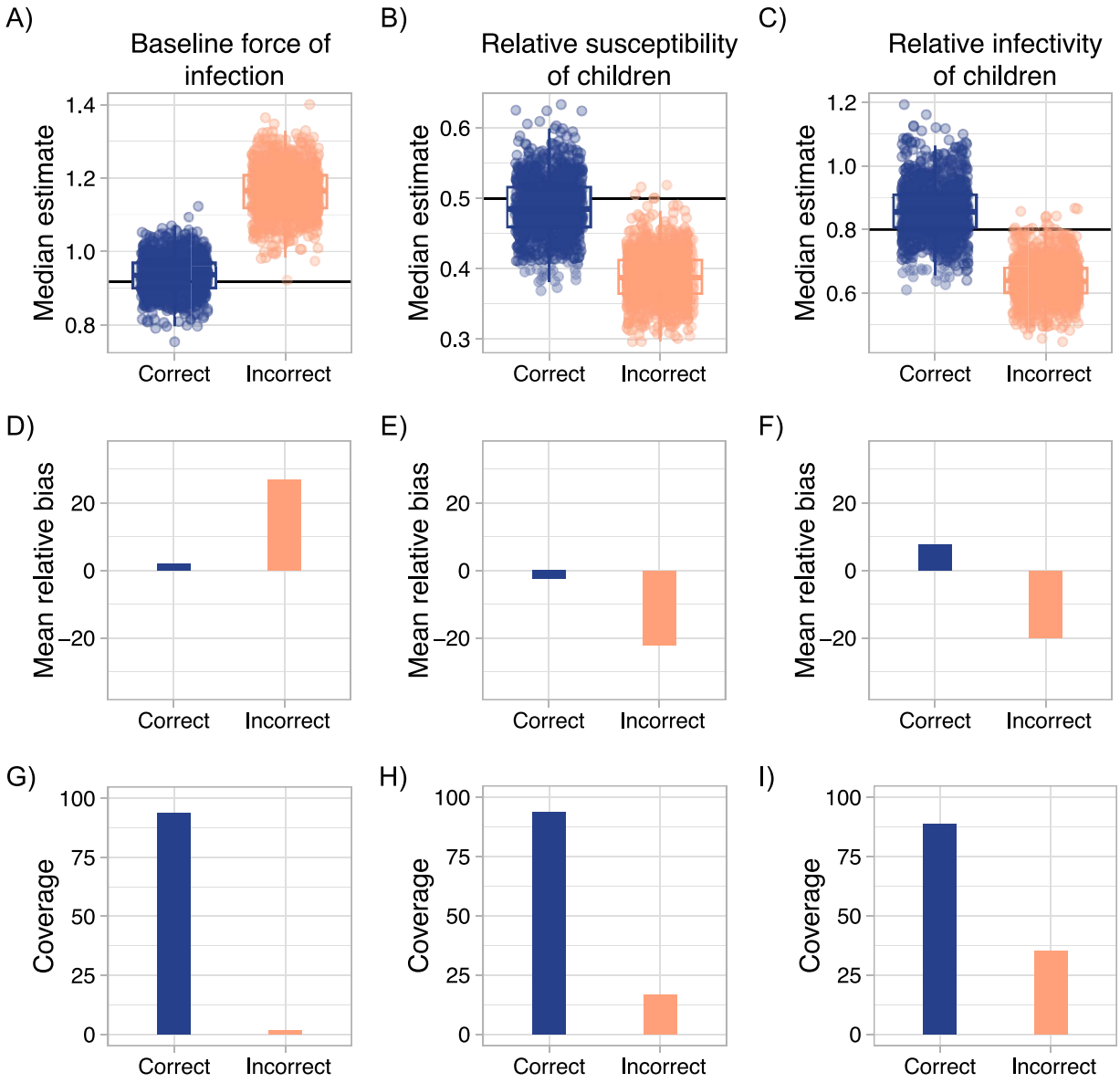

Figure 1. Impact of contact patterns on the estimation of within household transmission, child infectivity, and child susceptibility in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections. (A-C) Posterior median estimates of the transmission rate in father–mother pairs, child relative susceptibility, and child relative infectivity for the correct (heterogeneous mixing) inference model in dark blue (n = 1000), and the incorrect (homogeneous) inference model in light orange (n = 1000). The black horizontal line corresponds to the true value used in the simulations. (D-F) Relative bias between the posterior median estimate and the true value for the transmission rate in father–mother pairs, child relative susceptibility, and child relative infectivity. Positive values indicate overestimation and negative values underestimation. Relative bias is expressed in percentage. (G-I) Coverage of the transmission rate in father–mother pairs, child relative susceptibility, and child relative infectivity. Coverage is expressed in percentage.

85% (Figure 2E and H). In contrast, when homogeneous mixing between household members is assumed, the transmission rate in father–mother pairs is overestimated by 22% (Figure 2D) and child relative susceptibility is underestimated by 20% (Figure 2E) with a coverage that does not exceed 22% for both parameters (Figure 2G-H). Just like in the COVID-19 scenario, estimation bias in the incorrect inference model resulted from the compensation of contact heterogeneity in the simulations. The results for child relative infectivity are less clear in the influenza scenario in which adults and children have the same infectivity levels. Indeed, the parameter is overestimated by 5% with a coverage of 92% (Figure 2F and I) with the correct model, and it is underestimated by 10% with a coverage of 80% with the incorrect model (Figure 2F and I).

Discussion

In this study, we show that estimates of child relative susceptibility and infectivity derived in household studies can be biased when heterogeneous contact patterns between household members are not accounted for. When considering the transmission of SARS-CoV-2 or influenza virus in households with heterogeneous contacts derived from Goeyvaerts et al,[20] the incorrect assumption of homogeneous mixing in the inference model leads to the underestimation of child relative susceptibility and infectivity by approximately 20%. This underestimation compensates for the lower contact rate between children and other household members compared with the contact rate in father–mother pairs in the simulated epidemics.[20] Biased estimates of child relative susceptibility and infectivity may lead to an inaccurate picture of

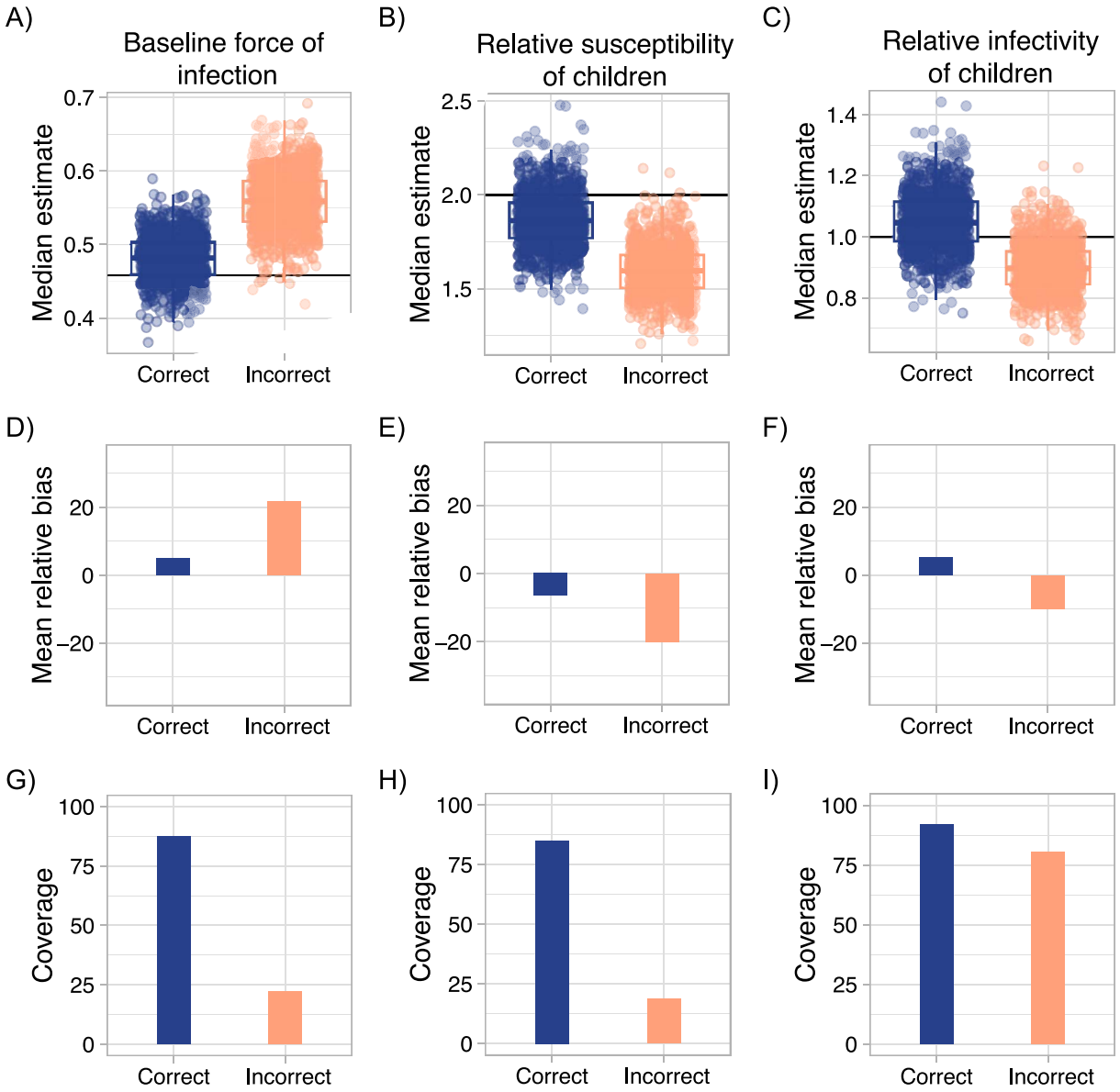

Figure 2. Impact of contact patterns on the estimation of within household transmission, child infectivity, and child susceptibility in influenza virus infections. (A-C) Posterior median estimates of the transmission rate in father–mother pairs, child relative susceptibility, and child relative infectivity for the correct (heterogeneous mixing) inference model in dark blue (n = 1000), and the incorrect (homogeneous) inference model in light orange (n = 1000). The black horizontal line corresponds to the true value used in the simulations. (D-F) Relative bias between the posterior median estimate and the true value for the transmission rate in father–mother pairs, child relative susceptibility, and child relative infectivity. Positive values indicate overestimation and negative values underestimation. Relative bias is expressed in percentage. (G-I) Coverage of the transmission rate in father–mother pairs, child relative susceptibility, and child relative infectivity. Coverage is expressed in percentage.

the biology of transmission within households, with direct implications on the parameterization of disease transmission models used for the design of intervention measures beyond households.

We emphasize that the intensity of the bias we quantified is conditional on our assumptions about contact patterns in households in our simulations. These assumptions were derived from the study of Belgian households by Goeyvaerts et al.[20] As a consequence, our results are expected to reflect contact patterns in Western Europe; the bias might be substantially different in other settings. For example, in low- and middle-income countries like South Africa, where there are more frequent contacts between children than between children and parents,[22] inference biases could be strongly modified. Even within Europe, we may expect that household contact patterns vary by country (eg, North vs South of Europe). We assumed that transmission rates were dependent on the intensity of physical contacts, defined as $\frac{\beta}{n/2}\kappa_{k,l}$ and measured by Goeyvaerts et al.[20] However, uncertainty remains about which type of contact (characterized by the duration, frequency, and distance of the contact) best explains transmission. In our analysis, we only considered droplet transmission that occurs during close contacts. Fomite and aerosol transmissions might also play a role in the transmission of influenza and SARS-CoV-2.[27] In particular fomite transmission might be an important mode of transmission for infants.[28] Accounting for those modes of transmission would necessitate alternative model formulations, and additional data should be collected to quantify the relative contribution of the different routes of transmission. In addition, we made simplifying assumptions in the simulation model. For example, we assumed that all infected individuals eventually develop symptoms and

that testing is perfect. We considered a single point estimate for the relative contact frequencies even though these frequencies are expected to vary by household and over time. Temporal dynamics of contact patterns can be caused by multiple factors, among which are the effect of the day of the week (weekday versus weekend)[20] and behavioral change following symptom onset.[29,30] We also assumed that all children had the same contact patterns and biological susceptibility/infectivity regardless of their age, even though contact rates with parents are presumably the highest during infancy[31] and decrease with age,[20] and biological susceptibility/infectivity vary with age as well.[15,16,32] For all these reasons, important uncertainties remain about how estimation of key biological parameters from household transmission studies may be affected when household contact patterns are being ignored; but our simulation study emphasizes that bias could be substantial and that further improvements to study design and data analysis are required to circumvent the problem.

To mitigate the risk of bias, we believe it is important to integrate information about contact patterns in household transmission studies and models. Using the results of a household contact survey such as Goeyvaerts et al.[20] to inform an observational study in a different country is problematic since household contact patterns likely vary across socioeconomic levels,[33] cultural practices,[21,22,34] and epidemic/pandemic contexts.[29] Ideally, the study design of household transmission studies should integrate the collection of data on contacts between household members. The behaviors of household members not only vary between weekdays and weekends[20] but may also change when one or multiple members develop symptoms; it is therefore important to monitor variations in contact patterns during the study period. In addition, behavioral change upon symptomatic infection may depend on socioeconomic factors and the role of the individuals in the household. For instance, physical distancing and self-isolation are not possible in crowded households,[35] and they are difficult if not impossible to apply when the symptomatic case is a young child. Finally, the way contact data are collected may affect results. Contact diaries are easy to put in place and can be repeated to capture behavioral changes but they may be subject to reporting bias because participants may underreport undesirable behaviors like not implementing physical distancing. Alternatively, wearable electronic devices that measure close-proximity face-to-face interactions are highly valuable in contexts with complex networks and for the study of infectious disease transmission.[36] Given that most contacts are physical in households, using devices to measure close contacts might not be relevant, especially in small accommodations. Besides, records typically do not exceed a few days due to the limited autonomy of these devices, and participants may raise concerns over the use of such devices, which could potentially limit compliance. For example, only 71% of index cases and 68% of household contacts complied with the sensors and had exploitable contact data in the study by Kleynhans et al.[22] While the collection of contact data seems essential to better disentangle the impact of biological versus behavioral factors, integration of these data to transmission assessment raises new questions. For example, different definitions of contact may be proposed to investigate transmission (eg, physical contact versus being < 1 meter away, short versus long duration of contact), and the optimal definition to measure transmission risk may depend on the infectious disease. The collection of these data, using contact diaries or electronic devices, will offer a unique opportunity to study the association between contact and transmission and assess how this association may vary with the context and the disease.

Here, we simulated epidemics in households so that around 33% of household contacts get infected. The choice of this value for the SAR is relatively arbitrary given that estimates from empirical data vary from a few percent to 45% for the historical variant of SARS-CoV-2,[6] and from 4% to 45% for influenza viruses.[9,37-39] Simulating epidemics with a lower SAR would reduce the number of infected pairs, and thus, the statistical power to estimate child relative susceptibility and child relative infectivity, but we do not expect the potential lack of statistical power in our simulations to reach the magnitude of the bias induced by contact patterns.

In conclusion, the heterogeneous nature of contacts in households is expected to bias estimates of key parameters that are estimated from household studies, such as the relative susceptibility and infectivity of children. It is therefore important that these complex household contact patterns be accounted for in future household studies. Data are scarce, and many knowledge gaps remain concerning the changes of household contact patterns that may occur following infections and certainly depend on age. Future household transmission studies should collect data on both disease and contact patterns (especially during the transmission period in the household), raising new challenges related to the study design, and model development.

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Conflict of interest

B.J.C. has consulted for AstraZeneca, Fosun Pharma, GSK, Haleon, Moderna, Pfizer, Roche, and Sanofi Pasteur. The authors report no other potential conflicts of interest.

Data availability

All R and C++ codes to reproduce the analyses are available at https://github.com/mlayan/heterogeneous_contacts.

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