**Failure to balance social contact matrices can bias models of infectious disease transmission**

**Short title:** Imbalanced social contact matrices can bias transmission models

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**ABSTRACT**

Transmissible infections such as those caused by SARS-CoV-2 spread according to who contacts whom. Therefore, many epidemic models incorporate contact patterns through contact matrices. Contact matrices can be generated from social contact survey data. However, the resulting matrices are often imbalanced, such that the total number of contacts reported by group A with group B do not match those reported by group B with group A. We examine the theoretical influence of imbalanced contact matrices on the estimated basic reproduction number (*R0*). We then explore how imbalanced matrices may bias model-based epidemic projections using an illustrative simulation model of SARS-CoV-2 with two age groups (<15 and 15+). Models with imbalanced matrices underestimated the initial spread of SARS-CoV-2, had later time to peak incidence, and smaller peak incidence. Imbalanced matrices also influenced cumulative infections observed per age group, and the estimated impact of an age-specific vaccination strategy. Stratified transmission models that do not consider contact balancing may generate biased projections of epidemic trajectory and impact of targeted public health interventions. Therefore, modelling studies should implement and report methods used to balance contact matrices for stratified transmission models.

Contact patterns (i.e., who contacts whom) are a fundamental component of infectious disease transmission dynamics. Such patterns, and the role of highly connected subgroups, can determine the size of epidemics, the incidence of infection among subgroups of a population, and whether epidemics emerge and persist (1). Mathematical models are widely used to study transmission dynamics and evaluate public health interventions; therefore, such models are often structured to consider population and contact heterogeneity (2-6).

Models with population and contact heterogeneity require estimates of contact within and between subgroups, represented through a contact matrix. Data to generate contact matrices are often obtained from contact diaries and surveys, with the POLYMOD social contact study (7) among the most commonly used data sources for models of respiratory pathogens (2-5). POLYMOD collected data on daily age-stratified social contacts of almost 8000 individuals across 8 European countries. To enable broader application of POLYMOD data, several techniques were then developed to project contact matrices to other countries (8-10). For example, Prem et al. (8, 9) used a Bayesian hierarchical model with country-specific data on population demographic structure, school enrollment, workforce participation, and household makeup to project POLYMOD contact matrices to 177 different countries around the world.

When using empirical contact data to structure the underlying contact patterns in a population, analysts must consider the balanced (i.e., reciprocal) nature of measured contacts (11, 12). In reality, the total number of contacts that individuals in subgroup *i* form with individuals in subgroup *j* must be equal to the total number of contacts that individuals in subgroup *j* form with individuals in subgroup *i*, such that:

|  |  |  |
| --- | --- | --- |
|  |  | (1) |

where *Cij* is the number of contacts an individual in subgroup *i* forms with individuals in subgroup *j* per day; *Ni* is the size of subgroup *i;* and likewise for *Cji*and *Nj.* Here “measured contacts”, which may not always lead to transmission, are distinguished from “effective contacts”, which do lead to transmission (by definition). The measured contact matrix (“who contacts whom”) must be balanced, but the transmission matrix (“who infects whom”) is often asymmetrical(13). This is because effective contacts that lead to transmission are a function of measured contacts and biological probabilities of transmission per contact (i.e., infectiousness and susceptibility, e.g., modified by vaccination). However, perfect reciprocity is rarely observed in in measured contacts from survey data. Imbalances in empirical contact data often arise due to measurement error in survey responses (e.g., recall bias or social desirability bias). However, even when measurement error is absent, imbalances can arise due to selection bias (e.g., differential sampling of subgroups across the network). That is, contact surveys rarely sample from closed, perfectly defined networks, and sampling frames are seldom designed to reflect network structures (11, 12).

Numerous mathematical transmission models have used contact data from POLYMOD and Prem et al., but many lack description of methods applied to handle the imbalanced (i.e., non-reciprocal) nature of these matrices (6, 14-16). For example, in some early models examining age-based prioritization of SARS-CoV-2 vaccination, there was either no mention of whether or not measured contacts were balanced or how they were balanced (6, 14-16). As such, it is not always clear if and when age-structured transmission models used balanced or imbalanced contact patterns. Moreover, how imbalanced contact matrices affect modelling projections has yet to be quantified.

We sought to examine how imbalances in measured contact matrices influence infection transmission dynamics. First, we examined the theoretical influence of imbalanced contact matrices on the estimated basic reproduction number (*R0*). We then conducted an illustrative simulation study, using a SARS-CoV-2 age-stratified compartmental model as an example, to explore the influence of imbalanced contact matrices on the temporal epidemic dynamics, cumulative infections among age groups, and potential impact of age-specific vaccination strategies.

**METHODS**

**Study design**

We conducted an analytic and simulation (mathematical modeling) study to examine three key characteristics of a model’s underlying transmission dynamics that can be modified by a network structure: the basic reproduction number, the temporal pattern of an epidemic, and the epidemic size. First, we compared the basic reproduction number R0 of an epidemic in a population stratified into two age groups (<15 and 15+) when parameterized with imbalanced versus balanced contact matrices across all 177 demographic settings studied by Prem et al. (8). We used contact matrices from Prem et al. to inform parametrization because of their use in most SARS-CoV-2 transmission models to date.

Next, we conducted a theoretical SARS-CoV-2 simulation study using an SEIR (susceptible-exposed-infectious-recovered) mathematical model in three demographic settings where imbalanced contacts reported by 15+ with <15 were a) larger than (Singapore), b) equal to (Luxembourg), and c) less than (Gambia) balanced contacts between 15+ and <15. We compared the timing and magnitude of peak infection incidence, cumulative infections after one year of seeding, and cumulative infections averted in the context of age-specific vaccination strategies after one year of seeding, when models were parameterized with imbalanced versus balanced matrices.

**Age-stratified social contact data**

We obtained age-stratified social contact matrices and population data from Prem et al (8). Raw matrices were imbalanced, and stratified into 16 age groups, with each matrix element, *Cij,* representing the mean number of contacts that a person in age group *i* reported with a person in age group *j* per day. To simplify our analysis, we transformed the age-structure of the matrices into two age groups: individuals less than 15 years of age, and 15 and older. Imbalanced contact matrices for these age groups were derived by calculating the population-weighted average contacts per person per day of contributing age groups (e.g. 0-4, 5-9 and 10-14 for the new age group <15) from the raw, imbalanced, contact matrices from Prem et al.

**Derivation of balanced social contact matrices**

As has been done previously (10, 17, 18), we estimated the balanced contacts between individuals in age groups *i* and *j* (*C’ij*) per day by averaging reported contacts from Prem as follows:

|  |  |  |
| --- | --- | --- |
|  |  | (2) |

**Derivation of R0**

We used methodology from Diekmann et al. (19) to calculate R0. In brief, R0 is the dominant eigenvalue of the next generation matrix (i.e. the number of secondary infectious persons that result in each age group). In a population divided into two age groups, the dominant eigenvalue is the maximum solution of:

|  |  |  |
| --- | --- | --- |
|  |  | (3) |

where *i* and *j* denote the two age groups (i.e., <15 and 15+), and *R0,ij*is the number of secondary infectious individuals in age group *i* that result from contact with an infectious person in age group *j* in a completely susceptible population, calculated as:

|  |  |  |
| --- | --- | --- |
|  |  | (4) |

where *β* is the probability of transmission of an infectious disease upon contact, and *D* is the duration of infectiousness. We calculated *R0* with imbalanced and balanced matrices from 177 demographic settings studied in Prem (8). We then calculated a relative R0 (*RR0*) under imbalanced versus balanced conditions where:

|  |  |
| --- | --- |
|  | (5) |

We assumed the probability of transmission and the duration of infectiousness was constant across age groups (and therefore had no impact on the *relative* reproduction number); thus, our estimate of the influence of imbalanced matrices is independent of a specific infectious disease.

**SEIR transmission model**

For our simulations, we used a deterministic, compartmental transmission model of SARS-CoV-2 using a simplified SEIR system. Susceptible individuals transitioned to an exposed health state (E) via a force of infection, defined by a probability of contact and probability of transmission per contact with a person in the infectious (I) health state. Individuals in the exposed health state became infectious (I) after a latent period. After an average period of infectiousness, individuals in the infectious health-state moved to the recovered health state (R), where they could not be re-infected. Model equations and details are outlined in **S1 Appendix** material(supplementary equations S1 to S4). **Table 1** summarizes model parameter values.

We made three key assumptions to simplify our model and focus the analysis on the influence of imbalanced matrices. First, we assumed the population size was fixed (i.e. the model simulates a closed system with no births or deaths) to avoid changes in the probability of contact over time. Second, we assumed there were no interventions to mitigate the spread of SARS-CoV-2 (e.g. isolation of infected individuals, reduction in contacts in response to increases in infection rates) as we were interested in isolating the effect of imbalanced matrices rather than infection prevention and control strategies. Finally, we assumed the probability of transmission of, and duration of infectiousness with, SARS-CoV-2 was fixed across age groups to estimate the impact of imbalanced matrices independent of infection properties by age.

**Simulation of SARS-CoV-2 transmission**

We simulated SARS-CoV-2 transmission in three demographic settings from Prem et al. (8), where imbalanced contacts that 15+ reported with <15 were: larger than (Singapore), equal to (Luxembourg), and less than (Gambia) balanced contacts between 15+ and <15 (**S1 Fig**). Models were seeded with 1 individual in the infectious state per age group for all simulations. We then compared the magnitude and time to peak incidence, and the percent difference in cumulative infections 1 year after seeding, when models were parameterized with imbalanced versus balanced matrices.

*Transmission impact of a targeted public health intervention*

To explore the influence of imbalanced matrices on the impact of prioritized public health interventions, we simulated two age-specific SARS-CoV-2 vaccination scenarios in all models: one in which vaccines were administered to individuals <15, and another where vaccines were administered to individuals 15 and older. We assumed 50% of the vaccinated age group were immune prior to seeding, and all vaccinated individuals could not be infected (i.e. were permanently immune). We compared cumulative infections overall and per age group in the presence and absence of vaccination over 1 year, to calculate cumulative infections averted from vaccination. Then, we calculated the percent difference in cumulative infections averted between models parameterized with imbalanced versus balanced matrices.

**Validation analyses**

To validate robustness of findings, we conducted two additional analyses. First, we assessed how imbalanced matrices affected R0 in a population stratified into different age groups: individuals less than 40, and 40 and older. Next, we assessed how imbalanced matrices affected R0 when biases in raw contact matrices were opposite to original observations from Prem et al. (8). For example, if reported contacts between <15 and 15+ were larger than balanced contacts between <15 and 15+ (e.g. Gambia), we forced <15 to underestimate contacts with 15+. We conducted this analysis to assess how systematic bias in contact patterns from Prem may have influenced our results.

**RESULTS**

**Imbalance in contact matrices by demographic setting**

In comparison to balanced matrices, imbalanced matrices from countries with older populations overestimated total contacts reported by 15+ with <15 (**Fig 1A, red**), and underestimated total contacts reported by <15 with 15+ (**S2A Fig, blue**). The opposite pattern was observed in countries with younger populations, where contacts reported by <15 with 15+ were overestimated (**S2A** **Fig, red**) and contacts reported by 15+ with <15 were underestimated (**Fig 1A, blue**). For example, in Singapore (median age 42.2 years) the number of imbalanced contacts reported by 15+ with <15 were 1.5 times balanced contacts between 15+ and <15, whereas in Gambia (median age 17.8 years), imbalanced contacts reported by 15+ with <15 were 0.45 times balanced contacts between 15+ and <15.

**Influence of imbalanced contact matrix on R0 and epidemic trajectory**

In comparison to models with balanced matrices, models with imbalanced matrices consistently underestimated R0 (**Fig 1B, S2B Fig**). For example, R0 was 5.7% and 3.1% smaller in Gambia and Singapore respectively, when matrices were imbalanced versus balanced. Models with imbalanced matrices also underestimated the magnitude of, and had delayed time to, peak incidence of SARS-CoV-2 (**Fig 2**). Peak incidence was most dampened and delayed among the age group that underestimated their contacts (i.e., 15+ in Gambia and <15 in Singapore).

When imbalanced and balanced contacts between 15+ and <15 were similar, there was minimal influence on R0 and on the epidemic trajectory of SARS-CoV-2. For example, in Luxembourg imbalanced contacts reported by 15+ with <15 were 0.99 times balanced contacts; therefore, R0 was nearly the same under imbalanced and balanced conditions (% difference in R0 = 0.0003%).

**Influence of imbalanced contact matrix on cumulative infections after 1 year of transmission**

Models with imbalanced contacts consistently overestimated cumulative infections in the age group that overestimated their contacts, and underestimated cumulative infections in the age group that underestimated their contacts (**Fig 3**). For example, cumulative infections were 3.2% larger among <15 and 6.7% smaller among 15+ in imbalanced versus balanced models in Gambia; whereas, cumulative infections were 1.6% larger among 15+ and 10.2% smaller among <15 in imbalanced versus balanced models in Singapore.

**Influence of imbalanced contact matrix on age-specific vaccination strategies**

Imbalanced matrices also directly and indirectly biased projected infections averted from age-specific SARS-CoV-2 vaccination strategies (**Fig 4**). For example, when vaccines were prioritized to individuals <15, imbalanced models underestimated infections averted among 15+ in Gambia (percent difference = -24.4) and overestimated infections averted among 15+ in Singapore (percent difference = 38.8). When vaccines were prioritized to individuals 15+, imbalanced models overestimated infections averted among <15 in Gambia (percent difference = 20.2) *and* Singapore (percent difference = 25.5).

**Validation analyses**

Our results were robust to changes in stratification of age groups (**S3A** **Fig**). For example, imbalanced contacts reported by 40+ with <40 were 1.4 and 0.38 times balanced contacts reported by 40+ with <40 in Singapore and Gambia respectively. In these two settings, models with imbalanced matrices underestimated R0 by 2.5% and 5.4% respectively.

Results were also robust to assumptions regarding which age group over- or underestimated their contacts (**S3B** **Fig**). For example, when we forced imbalanced contacts reported by 15+ with <15 to be 0.48 and 1.6 times balanced contacts between 15+ and <15 in Singapore and Gambia respectively (i.e. opposite the original imbalance direction observed in Prem et al.), models with imbalanced matrices still underestimated R0 by 3.0% and 5.8% respectively.

**DISCUSSION**

Using a combination of analytic and simulation methods, we found that the use of imbalanced contact matrices reshaped the underlying transmission dynamics of SARS-CoV-2. Models with imbalanced matrices consistently underestimated R0, leading to: 1) biased time to, and magnitude of peak infection incidence, 2) biased estimates of subgroup specific cumulative infections, and 3) biased impact of age-specific SARS-CoV-2 vaccination strategies. Biases resulting from imbalanced matrices persisted as we varied age group definitions, and as we transformed assumptions regarding which age group over- or underestimated their contacts per demographic setting.

The finding that R0 is always smaller when models are parameterized with imbalanced versus balanced matrices can be explained mathematically. In simplifying equation 3, we see that R0 is monotonically related to the product of R0,ij and R0,ji (proof provided in **S1 Appendix;** supplementary equations S5 to S8). We can also see that R0,ij and R0,ji are proportionate to CijNi and CjiNj, respectively (i.e., equation 4). Following the isoperimetric theorem for rectangles, given a fixed sum of population contacts between age groups *i* and *j* (i.e., CijNi + CjiNj), the product of CijNi and CjiNj will be maximized when CijNi = CjiNj (i.e., equation 1; conditions for balanced mixing). Since we assumed all other parameters in equation 4 were fixed across age groups, and the sum of population contacts was constant between imbalanced and balanced matrices (i.e., equation 2), the product of R0,ij, and R0,ji will maximize when CijNi and CjiNj are equal. Therefore, under our model and assumptions, R0 will always be largest under balanced conditions.

It may also be intuitive that biases in cumulative infections per age group are related to biases in contact patterns from imbalanced matrices. The number of infections among subgroup *i* is dependent on the “force of infection” ():

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| --- | --- | --- |
|  |  | (5) |

As Cij increases or decreases, the force of infection among subgroup *i* will also increase or decrease, as will the number of infections observed within the subgroup.

Given infection transmission dynamics were biased by imbalanced contact patterns, it was expected that they would also bias impact of subgroup specific public health interventions. This is because biases in contact patterns influence both risk of infection acquisition *and* transmission potential once infected. That is, if a model underestimates contacts that subgroup *i* makes with subgroup *j*, the model also underestimates the transmission potential of subgroup *j* to subgroup *i.* This was most notable when vaccine was administered to 50% of the population <15, where models that underestimated transmission potential of <15 underestimated infections averted among 15+ (i.e. Gambia) and models that overestimated transmission potential of <15 overestimated infections averted among 15+ (i.e. Singapore). Counterintuitively, when vaccine was administered to 50% of the population 15+, imbalanced models overestimated infections averted among <15 in both Gambia and Singapore (i.e. regardless of direction of bias in transmission potential of 15+). We hypothesize imbalanced models from Singapore overestimated infections averted among <15 (despite underestimating transmission potential of 15+) because of indirect bias in infection transmission dynamics. In addition to underestimating transmission potential of 15+, imbalanced models from Singapore overestimated transmission potential of <15. Therefore, in the absence of vaccination, there were more infections observed among 15+ in imbalanced models from Singapore. This provided more opportunity for vaccination to stop transmission of infection from 15+ to <15.

To our knowledge, this is the first study to quantitatively assess bias associated with *imbalanced* contact matrices on compartmental models of infectious diseases. Our work builds on a previous study by Arregui et al. that demonstrated the way in which contact matrices are balanced and projected to new demographic settings can influence the epidemic trajectory observed (10). The issue of non-reciprocity has been well-recognized in survey data on sexual partnerships, where various methods have been developed to balance sexual partnerships, and balancing is an established component of the modeling of sexually transmitted infections (11, 20, 21). However, the importance of balanced contacts has been less discussed, nor established, as part of standard practice and reporting of transmission modeling studies with non-sexually transmitted infections (22). Given imbalanced matrices can create error in model projections, and models with population heterogeneity are increasingly used to inform public health decisions (23-25), modellers should ensure and report on balancing of their contact matrices.

**Limitations**

The simplicity of our analytic study and simulation model allowed us to quantitatively assess and interpret the influence of imbalanced versus balanced matrices irrespective of other infection transmission parameters. As such, important sources of variability in transmission risk that lead to asymmetry in effective contact matrices could potentially amplify or dampen the influence of imbalanced measured contact matrices, and would benefit from further examination. Our results may also vary when studied in open populations (with births, deaths and/or movement of individuals) or when considering infection prevention and control measures such as school closures or isolation procedures. Bias may also vary when considering heterogeneity in biological characteristics, such as immunity to infection, duration of infectiousness, and probability of transmission once infected. For example, we assumed the probability of transmission and duration of infectiousness was constant across age groups. If older individuals were more likely to transmit SARS-CoV-2 than younger age groups, and had a longer duration of infectiousness, they would have greater transmission potential and we may see even greater bias in models that overestimate contacts that <15 made with 15+. Our examination was restricted to direct transmission of respiratory pathogens in the context of close contacts and thus, via droplet or close-range aerosolized transmission. Other modes of transmission, such as transmission via fomites, blood products, or in the context of waterborne (e.g. fecal-oral) pathogens require different types of contacts in their force of infection. The survey data used to generate symmetric measured contact matrices also do not capture the potential for point-source transmission events, including those that may occur via long-range aerosolized pathogens.

There are different ways to balance a measured contact matrix. Thus, differences in epidemic dynamics between models with imbalanced versus balanced matrices could differ based on the balancing method used. We used a population weighted average of reported contacts given the matrices were synthetic (8). However, when using survey data [e.g., POLYMOD (7)], it is more common to calculate respondent weighted averages of population contacts (10), or use statistical techniques to infer patterns across the population according to participant demographic information (12). Therefore, the balancing method used may change the extent to which raw contacts are considered imbalanced, and thus the magnitude and direction of potential bias. Finally, our balancing approach (as with many others) assumes that self-reported numbers from each group is equally subject to measurement error. That is, no age-group’s answers are more or less reliable than any other.

**Conclusions**

We show that compartmental models of infectious diseases parameterized with imbalanced contact matrices may produce biased estimates of initial epidemic characteristics (e.g., R0), epidemic trajectory (e.g., timing and magnitude of peak infection incidence), cumulative impact on populations (e.g., cumulative infections per age group), and impact of prioritized public health interventions. To avoid biases in projections, stemming from how the model is parameterized, modellers should account for and report reciprocity of contact matrices in their stratified transmission models.

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**TABLE**

**Table 1.** Model parameters.

|  |  |  |  |
| --- | --- | --- | --- |
| **Parameter** | **Symbol** | **Value** | **Source** |
| Probability of transmission per contact | β | 0.015 | (19) |
| Contact rate per day | Cij | Supplementary data\* | (8) |
| Duration of pre-infectious (latent) period | 1/Ω | 5.5 days | (20)(21) |
| Duration of infectious period | 1/γ | 10 days | (22) |
| Population size | Ni | Supplementary data\* | (8) |

\*Parameter varies by age group. Supplementary data are available at <https://github.com/mishra-lab/imbalanced-contact-matrices>.

**FIGURE CAPTIONS**

**Fig 1. Models with imbalanced contact matrices underestimate R0.** (A) Direction and magnitude of imbalance in synthetic contact matrix per country. (B) Underestimation of R0 in models with imbalanced contact matrices. R0, basic reproduction number; C, population contact rate; o, “old”, 15+; y, “young”, <15; imbal, imbalanced; bal, balanced.

**Fig 2. Bias in SARS-CoV-2 epidemic trajectory overall and among age groups according to imbalance in synthetic contact matrix.** Models were run among a closed population for 1 year in the absence of public health interventions. Models were seeded with 1 infected individual per age group.

**Fig 3. Imbalanced contact matrices bias estimates of cumulative SARS-CoV-2 infections overall and among subgroups.** (A) Direction and magnitude of imbalance in synthetic contact matrices from Gambia, Luxembourg and Singapore. (B) Percent difference in cumulative infections overall, and per age group from models parameterized with imbalanced versus balanced contact matrices. One infected individual was seeded per age group per model. Cumulative infections were compared one year after seeding in a completely susceptible and closed population in the absence of public health interventions. Imbal, imbalanced; bal, balanced.

**Fig 4. Imbalanced contact matrices bias impact of age-specific SARS-CoV-2 vaccination strategies.** (A) Percent difference in cumulative infections averted in models parameterized with imbalanced versus balanced contact matrices when 50% of population <15 was vaccinated (B)Percent difference in cumulative infections averted in models parameterized with imbalanced versus balanced contact matrices when 50% of population 15+ was vaccinated. One infected individual was seeded per age group, per model. Cumulative infections averted were compared one year after seeding in a completely susceptible and closed population, in the absence of additional public health interventions other than vaccination. Imbal, imbalanced; bal, balanced.