Annals of Epidemiology 77 (2023) 44–52

Contents lists available at ScienceDirect

Annals of Epidemiology

journal homepage: sciencedirect.com/journal/annals-of-epidemiology

Original article

Modeling shield immunity to reduce COVID-19 transmission in long-term care facilities

Adriana Lucia-Sanz, PhD [a,1], Andreea Magalie, BA [a,b,1], Rogelio Rodriguez-Gonzalez, BS [a,b,1], Chung-Yin Leung, PhD [a,c,2], Joshua S. Weitz, PhD [a,c,*]

[a] *School of Biological Sciences, Georgia Institute of Technology, Atlanta, GA*
[b] *Interdisciplinary Graduate Program in Quantitative Biosciences, Georgia Institute of Technology, Atlanta, GA*
[c] *School of Physics, Georgia Institute of Technology, Atlanta, GA*

ARTICLE INFO

Article history:
Received 1 April 2022
Revised 11 October 2022
Accepted 19 October 2022
Available online 7 November 2022

Keywords:
SARS-CoV-2
COVID-19
Bipartite network
Compartmental epidemiological model
Long-term care facility
Cohorting
Mitigation strategy
Variant
Reproductive number
Viral testing

ABSTRACT

Purpose: Nursing homes and long-term care facilities have experienced severe outbreaks and elevated mortality rates of COVID-19. When available, vaccination at-scale has helped drive a rapid reduction in severe cases. However, vaccination coverage remains incomplete among residents and staff, such that additional mitigation and prevention strategies are needed to reduce the ongoing risk of transmission. One such strategy is that of “shield immunity”, in which immune individuals modulate their contact rates and shield uninfected individuals from potentially risky interactions.
Methods: Here, we adapt shield immunity principles to a network context, by using computational models to evaluate how restructured interactions between staff and residents affect SARS-CoV-2 epidemic dynamics.
Results: First, we identify a mitigation rewiring strategy that reassigns immune healthcare workers to infected residents, significantly reducing outbreak sizes given weekly testing and rewiring (48% reduction in the outbreak size). Second, we identify a preventative prewiring strategy in which susceptible healthcare workers are assigned to immunized residents. This preventative strategy reduces the risk and size of an outbreak via the inadvertent introduction of an infectious healthcare worker in a partially immunized population (44% reduction in the epidemic size). These mitigation levels derived from network-based interventions are similar to those derived from isolating infectious healthcare workers.
Conclusions: This modeling-based assessment of shield immunity provides further support for leveraging infection and immune status in network-based interventions to control and prevent the spread of COVID-19.

Introduction

SARS-CoV-2 remains a global threat as of March 2022 with more than 79M documented cases and 975K fatalities in the US alone, and more than 480M cases and 6.1M fatalities worldwide. In the US, nursing homes and long-term care facilities have experienced severe outbreaks and elevated death rates [1]. Both residents and staff have been disproportionately affected by SARS-CoV-2 compared to other population groups [2,3,4]. Coronavirus disease (COVID-19) affects the elderly far more severely, on average, than younger individuals [5]. Besides age, other high-risk factors for COVID-19 severity in nursing homes and long-term health care facilities (which we refer to as LTCs) include co-occurring conditions, such as cardiovascular disease, chronic respiratory disease, and diabetes [6,7]. This increased risk is evident in the gap between cases and fatalities in the US: as of March 2021, LTCs had 4% of total COVID-19 cases but accounted for 34% of total COVID-19 fatalities [8]; in aggregate, 23% of total COVID-19 deaths (>200,000) occurred in LTCs through January 2022 [1].

Abbreviations: CDC, Centers for Disease Control and Prevention; COVID-19, coronavirus disease 2019; HCW, healthcare worker; LTC, long-term care facility; PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SD, standard deviation.

Authors declare no conflict of interest.

* Corresponding author. School of Biological Sciences, Georgia Institute of Technology, Atlanta, GA 30332.

E-mail address: jsweitz@gatech.edu (J.S. Weitz).

[1] These authors contributed equally to this work.

[2] Current address: Systems Modeling and Translational Biology, GSK, Stevenage SG1 2NY, UK.

https://doi.org/10.1016/j.annepidem.2022.10.013
1047-2797/

From the outset, there have been acute challenges in preventing and responding to COVID-19 outbreaks in LTCs. As of early May 2020, thousands of LTCs across the U.S. reported cases of COVID-19 among residents and staff, given limitations to prevention policies, facility-wide testing, and support for staff [9]. Data from June 2020 reported that 71% of 13,167 US nursing homes had at least one case among residents and/or staff and 27% of facilities reported an outbreak [10]. As of October 2022, a state-level average of 99.6% of nursing homes had at least one case (range from 92.6% to 100%); with a state-level average of approximately 50% of nursing homes reporting at least one case in the four weeks preceding August 21, 2022 [11]. Understaffing [10] and staff movement across facilities [12] have shown to be important factors for COVID-19 outbreaks among nursing homes. The combination of those high-risk factors, vulnerable residents sharing space and requiring prolonged and intense contact with staff seem to have been critical for the severity of the COVID-19 pandemic in LTCs [13,14].

The increasing availability of highly effective and safe vaccines has contributed to the rapid decline in severe cases of COVID-19 amongst vulnerable individuals [15,16]. However, vaccine coverage remains incomplete, amongst residents and especially among staff (e.g. only 42% of staff per facility are up to date with recommended booster vaccines as of August 15, 2022 [11]). Critically, receiving a booster has been shown to reduce the near-term risk of severe illness caused by the omicron variant [17] even if the efficacy is reduced relative to protection against the original strain and even if such protection can wane over time. Protection of healthcare workers (HCWs) who are at increased risk to become infected by COVID-19 [18,19] is of paramount importance for the care of residents and might be fundamental to control ongoing and future outbreaks [20,21]. Hence, enhanced protocols are urgently needed to combat COVID-19 transmission in nursing homes and other LTCs. Amongst non-pharmaceutical interventions, recommendations have centered on testing, cohorting and restricting movement across and within facilities. Facility-wide surveillance testing, either via antigen or molecular viral testing, provides a mechanism to identify and isolate residents as well as to reduce the risk that infected staff interact with other staff members and vulnerable residents [22]. As a complementary approach, models of staff cohorting could lead to fewer infections among HCWs [23]. However, designing cohorting interventions based, in part, on immune status (rather than infection status alone) remains under-explored.

One way to leverage testing to improve infection control is to restructure which HCWs care for which residents based on both disease and immune status. The intent of such restructuring is to minimize potential risky interactions that could facilitate transmission. Shield immunity represents one strategy to leverage immune status to reduce transmission risk, such that recovered/vaccinated individuals increase their contact rates, including with susceptible individuals [24]. As a result, the frequency of potential risky interactions between individuals of unknown status (including susceptible and infectious individuals) are reduced. Subsequent modeling work extended the proof-of-concept shield immunity model [24] and showed that restructuring interactions as a means to reduce transmission can retain effectiveness at population scales even with high-quality, albeit imperfect tests [25] and could help balance public health and socioeconomic outcomes [26]. However, adapting a shield immunity strategy for implementation in LTCs requires specifying which HCWs care for which residents as part of a dynamic epidemic network model (*sensu* [27]) rather than assuming random interactions.

Here, we use a network model approach to study the effectiveness of shield immunity in reducing outbreak size in LTCs. We propose an immune shielding rewiring algorithm that implements cohorting and workload assignments between HCWs and residents based on disease status. In doing so, we also address the workload constraints imposed by re-assigning interactions in a bipartite network (i.e., representing interactions between HCWs and residents). Consistent with prior work, we find that outbreak size can be reduced when immunized HCWs care for infected residents. Network simulations show that when immune shielding rewiring is implemented weekly, then outbreak sizes are reduced beyond that achieved by viral testing alone. We also develop a preventative "prewiring" intervention and show that cohorting susceptible HCWs with recovered or vaccinated residents could prevent future outbreaks - because an inadvertent introduction of SARS-CoV-2 is less likely to spread when susceptible HCWs provide care for immune residents. This prewiring intervention may provide one route to decrease risks of outbreaks in partially vaccinated populations of HCWs. Overall, this network modeling study provides further evidence that identifying and leveraging disease status to personalize interventions can be a critical part of ongoing efforts to control and prevent COVID-19 in the face of the evolution of variants and heterogeneous levels of immunity, especially amongst vulnerable populations.

Methods

Summary

We simulate the spread of SARS-CoV-2 in a nursing home via a stochastic network-based model. The facility is represented as a network consisting of two sets of nodes: HCWs and residents. We use an SEIR representation of disease states. Every individual is represented by a node which can be either susceptible S, exposed E (contracted SARS-CoV-2 but not yet infectious), infectious I, or recovered R (acquired immunity to SARS-CoV-2 and no longer infectious). The model assumes that individuals who recovered from COVID-19 during an outbreak acquire immunological memory that at least lasts until the end of the outbreak. We note that the I class contains both symptomatic and asymptomatic individuals. Every time step (10 minutes), individuals interact with exactly one of their neighbors with probability $P_{contact}$. This means that in one day, every individual averages $\beta = 0.5$ contacts through which infection can spread. Infection spreads strictly by interactions between I and S individuals and newly infected individuals enter the E class. Further, at every time step exposed individuals become infectious with probability P_{EI} and infectious individuals recover with probability P_{IR}. We note that a full treatment of heterogeneity in interaction intensity (e.g., between HCWs based on work category and duties as well as between residents based on room location) is beyond the scope of the present model (see Discussion for more details on potential extensions).

The proposed mitigation strategies (immune shielding, prewiring, and isolation) depend on determination of the infection status of individuals. We distinguish 3 possible test status states for every individual:

- Susceptible: PCR negative and seronegative/not vaccinated
- Infected: PCR positive or positive antigen test
- Recovered: PCR negative/negative antigen test after infection or seropositive/vaccinated

We assume that exposed individuals are grouped with susceptible individuals given that their PCR test status is likely to be negative. We also note that antigen tests can be used along with PCR tests as an indicator of infected status, but that we do not assume that a negative antigen test is, in and of itself, a barometer of susceptibility. Our models make the following implicit assumptions: the disease status of individuals is obtained at the same frequency as the mitigation interventions are applied (e.g. weekly viral testing is required for weekly immune shielding), the disease status of an individual does not change between when testing is performed and when the intervention is applied (i.e., delays obtaining test results are not incorporated in the model), and recovered individuals cannot be reinfected during the same outbreak in which they were infected. In this analysis we do not consider the impacts of false positives and/or false negative on intervention outcomes (but note that prior work showed the robustness of strategies for imperfect, albeit high quality tests [25]). In order to apply immune shielding on a weekly basis, individuals are tested once a week and then residents are re-assigned to HCWs based on the proposed immune shielding strategy and test status. Specific details on the simulations and model assumptions are described in the sections below.

Stochastic SEIR model

We use a frequency dependent SEIR epidemiological model on a bipartite network (i.e., where interactions occur between HCWs and residents). We choose a frequency dependent model (rather than density-dependent model) to mimic social distancing guidelines in LTCs. Hence, we assume that within a time step of 10 minutes, an individual is in close contact with at most one other individual irrespective of the size of the facility. Depending on contact rates, individuals need not have a close contact within a particular 10 minute window.

Nodes can change their disease status at every time step based on the following three events:

1. E→I: With probability P_{EI}, an exposed E node will become infectious.
2. I→R: With probability P_{IR}, an infected I node will become recovered.
3. S→E: With probability $P_{contact}$, a susceptible S node will have a potentially infectious contact with a random neighbor. If that neighbor is infected I, the susceptible node becomes exposed E.

The transition probabilities per time step (P_{EI}, P_{IR}, $P_{contact}$) are derived from underlying parameters, e.g., the infectious contact rate $\beta = 1/2$ day^{-1}, exposed to infected rate of $\gamma_E = 1/2$ day^{-1} and recovery rate of $\gamma_R = 1/6$ day^{-1} [24], as follows:

$$P_{EI} = 1 - e^{-\gamma_E \Delta t}$$

$$P_{IR} = 1 - e^{-\gamma_R \Delta t}$$

$$P_{contact} = 1 - e^{-\beta \Delta t}$$

The choice of a low infectious contact rate $\beta = 1/2$ day^{-1} reflects the use of personal protective equipment (PPE) by staff and, in some cases, by residents. The expected R_0 for an equivalent deterministic model is $R_0 = \beta/\gamma = 3$ since the contact rate is independent of the degree of each node. We also consider the possibility of interventions against a more transmissible SARS-CoV2 variant ($\beta = 0.7$ day^{-1}, $R_0 = 4$) [28]. In both cases, these baseline values can be reduced through mitigation steps beyond that imposed by testing. Further, note that the realized threshold criterion for epidemic spread in a network differs from that in a deterministic model, and depends on the network connectivity (for more details, see [29]). To show the impact of network connectivity in the reproductive number we calculate the final size of outbreaks and use this to infer a network-equivalent reproductive number using the final size equation $R_t = N^*\log(S_0/S_\infty)/(N-S_\infty)$, where N is the total number of individuals in the LTC; S_0 and S_∞ are the initial and final number of susceptible individuals in the simulated outbreak. The ensembled averaged network-equivalent reproductive number is typically smaller than R_0 (Figure S3).

Testing

To identify S or I individuals, high sensitivity and specificity PCR diagnostic tests need to be performed before applying mitigation. Antigen tests can also be used to identify I individuals – an issue we revisit in the Discussion. We assume that the PCR test correctly identifies S and I individuals (assuming high specificity and sensitivity, respectively) and will identify E individuals as S (assuming that E is of short duration and individuals in this compartment do not have sufficient viral load to generate a positive PCR result). To identify R individuals, facilities could use antibody tests, vaccination status or presume immunity within a fixed period of time since a confirmed infection (e.g., 4-6 months). Since antibody status is maintained for an extended period of time, antibody testing could be done at a lower frequency than diagnostic testing [30].

Network setting

We consider a bipartite network consisting of 100 healthcare workers (HCWs) and 100 residents yielding a 1:1 ratio consistent with levels of care in skilled nursing facilities. We also consider variation in staff levels reflecting observed variation in LTCs, spanning 1:3, 1:5 and 1:10 (ratios denote HCWs:residents). Note that all synthetic bipartite networks have a mean of 1000 total links and a total size of 200 nodes. Keeping the size of the LTC and the number of links constant while increasing the number of residents per HCW automatically implies an increase in staff workload concomitant with a decrease in the level of patient care (Supplementary Table 1). The choice of a bipartite network is motivated by the strict social distancing guidelines in LTCs, assuming only necessary care-centered interactions take place. We subsequently relax this assumption and allow connections between HCWs. We use two kinds of network structures: (i) random interactions between HCWs and residents; (ii) small-world social networks for interactions amongst HCWs. We construct a random bipartite network with an average degree of 10 [31], in practice this yields a binomial degree distribution with minimum degree 3 and maximum degree 20. When HCW-HCW interactions are considered (e.g., as a result of relaxing social distancing restrictions among HCWs), we simulate the network of interactions as a Watts-Strogatz social interaction network with average degree 10 and edge rewiring probability $p = 0.02$ [32].

Mitigation strategies

Immune shielding rewiring algorithm

We adapt a network ‘rewiring’ algorithm which provides an efficient and unbiased method to randomize connections between nodes while preserving their degree [33]. The adaptation focuses on rewiring to fulfill two key objectives (i) Minimize $I_{Resident}$ – S_{HCW} connections; (ii) Minimize $S_{Resident}$ – I_{HCW} connections. To minimize $I_{Resident}$ – S_{HCW} connections, we find all residents that are in the I state and all residents that are in either the R or S state. We use the notation $I_{Resident}$ as well as $R_{Resident}$ or $S_{Resident}$ to refer to a resident drawn from these sets, respectively. We use a similar notation to refer to healthcare workers. Given N_I infected residents and N_{RS} recovered or susceptible residents, we perform the following algorithm $N_I * N_{RS}$ times (Supplementary Figure S1):

1. Randomly select an $I_{Resident}$ and a $R_{Resident}$ or $S_{Resident}$.
2. Find all S_{HCW} connected to the $I_{Resident}$, but not to the $R_{Resident}$ or $S_{Resident}$ and all R_{HCW} or I_{HCW} connected to the $R_{Resident}$ or $S_{Resident}$ but not to the $I_{Resident}$.
3. Randomly reconnect the S_{HCW} with the $R_{Resident}$ or $S_{Resident}$, and R_{HCW} or I_{HCW} with the $I_{Resident}$. These reconnections are termed a ‘swap’.

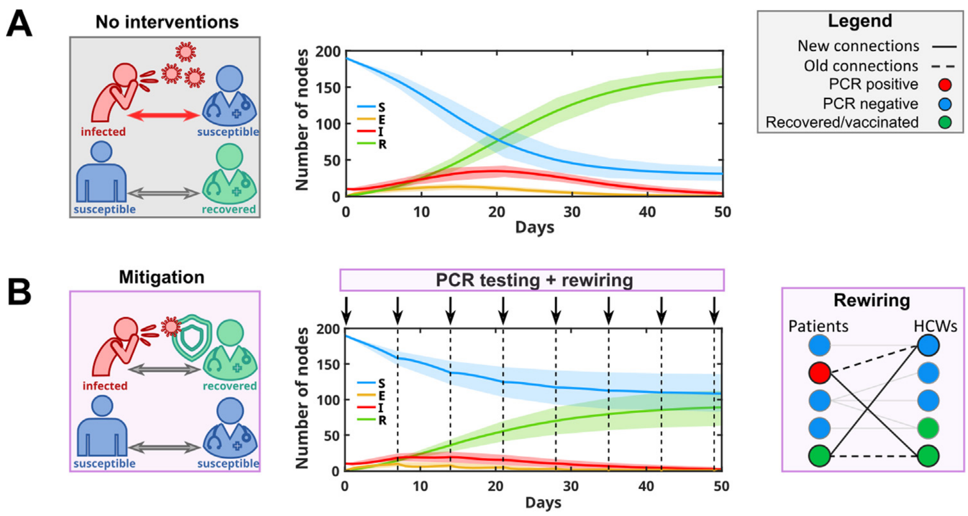

Fig. 1. Shield immunity as a mitigation intervention in a LTC setting. Schematics (*left*), SEIR dynamics on a bipartite network (*middle*), and an example of shield immunity as a mitigation "rewiring" strategy (*right*). SEIR dynamics show the number of nodes in S (*blue*), E (*orange*), I (*red*), and R (*green*) epidemic states. The LTC facility is represented as a bipartite network with nodes of two types: residents and HCWs. Interactions among HCWs and residents are represented as connections between nodes. Node colors show individuals PCR/antigen test or immunization status as depicted in the legend. (*A*) Case with no interventions: we seed the epidemic with 5% of the total population (10 nodes) and simulate the outbreak over 50 days. Solid lines show the average of 500 simulation runs and shaded areas represent the standard deviation of the runs. (*B*) Shield immunity as a mitigation strategy: We seed the epidemic as in *A*. Arrows and vertical dashed lines indicate when PCR testing and rewiring are applied during the outbreak (weekly). The network shows an example of the rewiring algorithm. It deletes SI and RR (or RS) connections (*dashed bold line*) and replaces them with RI and SR (or SS) connections (*solid bold line*). For a complete schematic see Supplementary Figure S1. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

At the completion of this sequence of steps, the network is rewired while preserving the degree for each HCW and each resident; hence the workload balance of HCWs is maintained and each resident receives the same level of care (see Figure 1b).

Prevention prewiring algorithm

We extend the rewiring algorithm to a 'prewiring' intervention which is applied to a scenario with no ongoing outbreak (all nodes are in the S or R state). The goal of prewiring is to reconfigure interactions to minimize both the likelihood and size of an outbreak in the event of an introduced case into a facility. At the network level, the prewiring algorithm minimizes the number of R-R connections while maintaining the degrees of all nodes constant. In effect, prewiring replaces R-R and S-S connections with R-S and S-R connections (Figure 4b). We adapt our immune shielding algorithm in the following way. First, we find all $R_{Resident}$ and all $S_{Resident}$. Second, given N_R recovered residents and N_S susceptible residents, we perform the following algorithm $N_R * N_S$ times:

1. Randomly select a $R_{Resident}$ and a $S_{Resident}$.
2. Find all R_{HCW} connected to the $R_{Resident}$ but not to the $S_{Resident}$, and all S_{HCW} connected to the $S_{Resident}$ but not to the $R_{Resident}$.
3. Randomly reconnect R_{HCW} with the $S_{Resident}$ and S_{HCW} with the $R_{Resident}$.

Isolation of infected HCWs

The isolation intervention is implemented when infectious HCWs are identified via viral testing and become "isolated" such that they do not interact with anyone until they recover from the infection. Confirmed infectious residents are not isolated and continue to receive the same levels of care. Similar to immune shielding, isolation can be implemented at different frequencies (i.e., daily, weekly). When isolated, HCWs transition to recovered (with probability P_{IR} at every time step), at which point they reconnect with their previous neighbors. Because we do not distinguish between symptomatic and asymptomatic cases, HCWs do not isolate at symptom onset but when they receive a positive PCR or antigen test.

Numerical Simulation

The network model is implemented in MATLAB 9.7.0.1296695 (R2019b) Update 4. We run the simulation with a time step of 10 minutes and total time of 100 days. For ensemble analysis, a total of 500 simulations are run to compute the mean and standard deviations of outcomes. All outbreak simulations begin with 10 infected HCWs (10% of total HCWs) selected at random and the rest of the population susceptible, unless otherwise mentioned. We choose these initial conditions to avoid stochastic fade-out in our simulations. Prewiring based interventions assume different levels of recovered individuals as described in the Results. Code is available via https://github.com/WeitzGroup/Networks_Immune_Shielding.

Results

Immune shielding through rewiring infected individuals protects susceptible individuals

We evaluated the performance of the shield immunity rewiring strategy on a bipartite network (N = 200), where half of the nodes represent residents and the other half represent HCWs. To do so, we simulated an outbreak on the network over 100 days with and without applying a dynamic rewiring strategy that leverages immune shielding on a weekly basis; resulting dynamics are shown in Figure 1. In all cases, we focus on outbreaks with an initial size of 10, intended to evaluate the effect on interventions conditional upon epidemic liftoff. Applying the rewiring intervention weekly resulted in a 45% reduction in the epidemic peak (epidemic peak without intervention, mean = 33 infectious people, SD = 9 infectious people vs. epidemic peak with weekly immune shielding intervention, mean = 18 infectious people, SD = 7 infectious people) and a 48% reduction in the final outbreak size (outbreak size without intervention, mean = 160 people, SD = 8 people vs. outbreak size with immune shielding intervention, mean = 83 people, SD = 27 people). In effect, the rewiring strategy decreases the risk

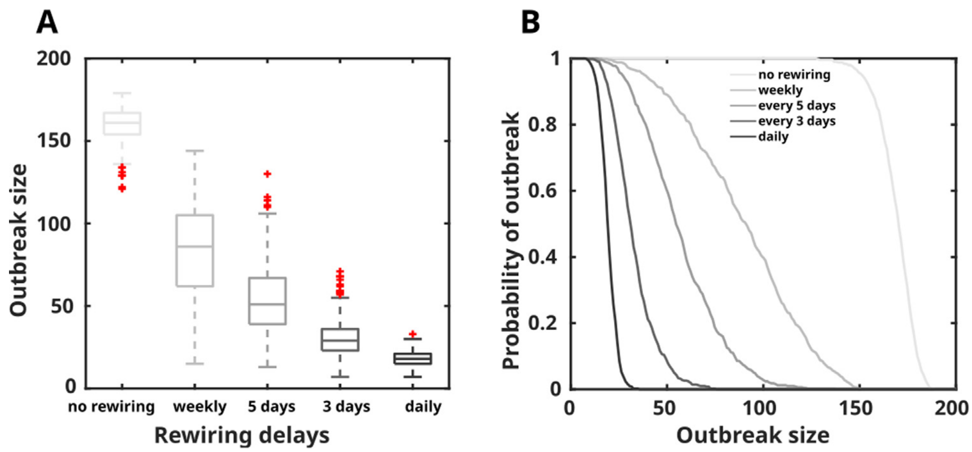

Fig. 2. Rewiring frequency effects on outbreak size. (*A*) Distribution of the final outbreak size of 500 realizations for different testing frequencies (daily, every 3 days, every 5 days, weekly, and never); darker-gray lines represent more frequent rewiring schedules. In all cases we seed the epidemic with 10 infected HCWs. Boxes represent the IQR range. The mark on the box represents the median (50th percentile). Upper and lower whiskers represent 0th and 100th percentile, respectively. Outliers are above or below the 1.5 the interquartile range and are shown in red "+" signs. (*B*) Probability density curves of having an outbreak of size greater or equal to the number of individuals indicated on the *x*-axis. The outbreak size does not include the 10 nodes (5% of total population) initially used to seed the epidemic. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

that infectious residents are cared for by susceptible HCWs compared to immune HCWs.

Immune shielding efficacy increases with testing frequency

Next, we evaluated the feasibility of a shield immunity rewiring strategy by assessing the impact of different testing frequencies on the final outbreak size in a network context. To do so, we simulated the SEIR epidemic model given the same bipartite network structure as described above over 100 days. We then applied the rewiring intervention described in Figure 1b (see Methods for details) at different frequencies spanning tests that occur daily, every three days, every five days, and weekly. As anticipated, an increase in testing decreased the final outbreak size (Figure 2a). For example, when rewiring was applied every three days instead of every week, the mean outbreak size was 30 people (SD = 10) compared to the mean outbreak size of the scenario without intervention of 160 people (SD = 8); this corresponds to a reduction of 81% of the outbreak size. As stated in the previous section, weekly rewiring shows effectiveness reducing the final outbreak size by more than 45% on average.

Immune shielding is potentially more effective than isolation in controlling outbreaks

We compared four scenarios to determine the impacts of a network-based shield immunity rewiring strategy in a LTC facility or nursing home, in comparison to and in addition to preexisting interventions such as the isolation of infected HCWs. To do so, we ran 500 simulations of the epidemiological, network model of a COVID-19 outbreak in four scenarios: (i) baseline; (ii) isolation only; (iii) shield immunity only; (iv) both isolation and shield immunity together. The baseline scenario already incorporates social distancing and other measures (e.g., partial PPE compliance) that reduces the rate of transmission. For all scenarios, we compared the distribution of outbreak sizes (see Figure 3a). Notably, when used on its own, shield immunity-based rewiring is more effective than isolation of HCWs: reducing the probability of having larger outbreaks (Figure 3b) and reducing the median size of outbreaks (84 people vs. 122 people). We also find that combining isolation and rewiring together reduces the probability of an outbreak but does not provide a significant additional benefit in reducing outbreak sizes when outbreaks do occur. These comparative results imply that restructuring interactions is effective (see Figure 3), even when compared to standard mitigation practice. We also investigated the impacts of shield - immunity rewiring strategies when confronting a more transmissible variant. As expected, the outbreak sizes in the baseline and intervention scenarios are larger when R_0=4. Conducting weekly tests, rewiring alone is no longer more effective than isolation (median size of outbreaks 157 people vs. 164 people) (Supplementary Figure S2, weekly). However, the effectiveness of rewiring over isolation alone is regained when test frequency is increased to twice weekly (median size of outbreaks: 77 people vs. 135 people) (Supplementary Figure S2, twice a week). Network-based rewiring strategies are robust to plausible changes in R_0 values, we show the reduction of the final epidemic sizes in Supplementary Figure S3.

Prevention of COVID-19 outbreaks in nursing homes and long-term care facilities

The growing rate of population immunity via recovery from prior infections and, critically, from increasing vaccination coverage suggests that it may be possible to prewire interactions to reduce the chance and size of an outbreak before outbreaks are detected. To do so, we propose a prewiring intervention that preferentially connects immune individuals with susceptible individuals to maximize immune shielding (see Methods, prewiring for details). We first compare SEIR dynamics on bipartite networks with and without applying prewiring. We simulate an outbreak with 1 infected HCW and 30% immunized individuals in the LTC (Figure 4). We observed a reduction in the outbreak size of 44% (outbreak size without intervention, mean = 34 individuals, SD = 40 individuals vs. outbreak size with prewiring, mean = 19 individuals, SD = 27 individuals) due to prewiring. To further compare this preventive intervention with the baseline case, we calculated total number infections when we seed the epidemic with 1 infected HCW and 20, 40, 60, 80 and 100 immunized individuals: including HCW and residents (10%, 20%, 30%, 40% and 50% of the LTC). We also calculated the probability density of an outbreak given the above conditions.

We find that preventive immune shielding significantly reduces outbreak size when immunity levels exceed 20% (Figure 5). However, prewiring interventions do not significantly reduce outbreak size when immunity levels exceed 50%; note that in such cases the outbreak size is low, even for the baseline case, in part because

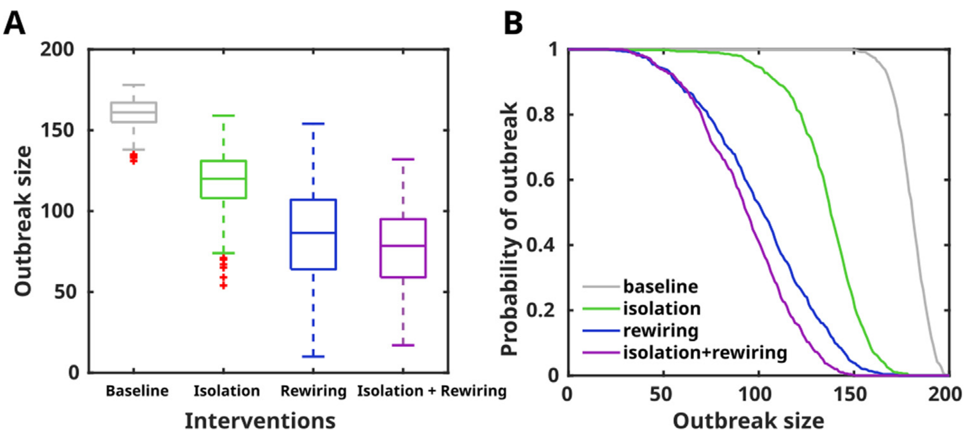

Fig. 3. Comparison of different interventions applied on a weekly basis. (*A*) Distribution of the final outbreak size of 500 realizations for different interventions when we seed the epidemic with 10 infected HCWs. Boxes represent the IQR range. The mark on the box represents the median (50th percentile). Upper and lower whiskers represent 0th and 100th percentile, respectively. Outliers are above or below the 1.5 the interquartile range and are shown in red "+" signs. (*B*) Probability density curves of having an outbreak of size greater or equal to the number of individuals indicated on the *x*-axis. All interventions are applied on a weekly basis. The outbreak size does not include the 10 nodes (5% of total population) initially used to seed the epidemic. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

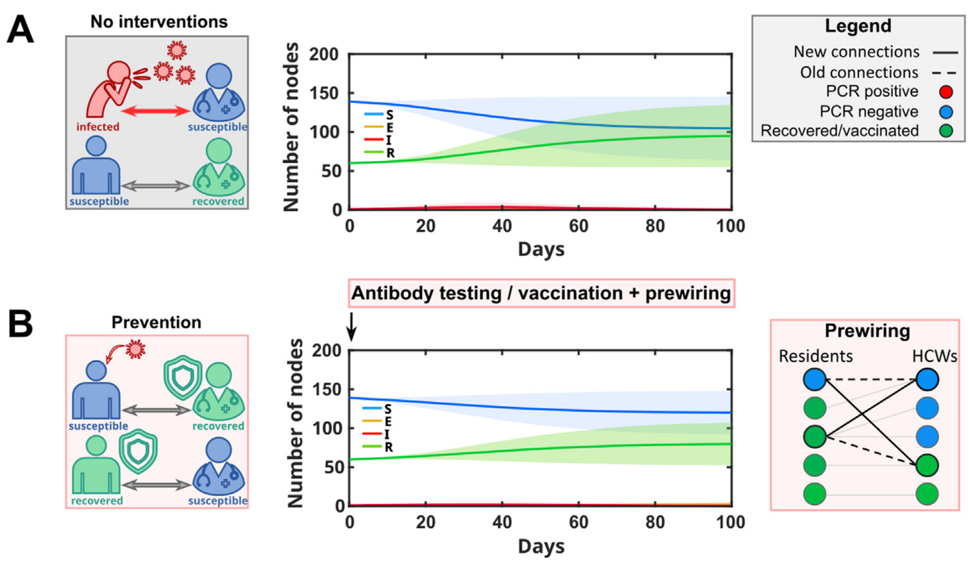

Fig. 4. Shield immunity as a preventive intervention in a LTC setting. Schematics (*left*), SEIR dynamics on a bipartite network (*middle*), and an example of shield immunity as a preventive prewiring strategy (*right*). SEIR dynamics show the number of nodes in S (*blue*), E (*orange*), I (*red*), and R (*green*) epidemic states. A second outbreak initiates with one infected HCW and 60 immunized (recovered/vaccinated) individuals (30% of the LTC). We simulate the epidemic over 100 days. Solid lines show the average of 500 simulation runs and shaded areas represent the standard deviation of the runs. The LTC facility is represented as a bipartite network with nodes of two types: residents and HCWs. Interactions among HCWs and residents are represented as connections between nodes. Node colors show individuals PCR or immunization status as depicted in the legend. (*A*) Case with no interventions. (*B*) Shield immunity as a prevention strategy: The arrow indicates prewiring is applied only before the outbreak starts. Prewiring rewires SS connections (*dashed bold lines*) and replaces them with SR connections (*bold lines*). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

of the effect of preexisting susceptible depletion on disease transmission. We further compare the prewiring strategy with targeted interventions, i.e., isolation and rewiring. We show that when the immunized fraction of individuals is low (20% or less), targeted interventions (with weekly surveillance testing) are necessary to reduce the probability and size of the outbreak (Supplementary Figure S4a). However, when the immunized fraction exceeds 35%, we find that prewiring intervention is as efficient as isolating infected HCWs (Supplementary Figure S4b). Hence, there is an intermediate range of preexisting immunity (through natural infection and/or vaccination) in which prewiring interventions may help to reduce outbreak size in partially vulnerable populations – we note that such intermediate levels of effective immunity may point to periods of opportunity to deploy shield - immunity preventative wiring strategies in light of waning immunity.

Generalized prevention of COVID-19 outbreaks given staff-staff interactions and staff levels

Thus far we have focused our dynamical model on risk of infection between HCWs and residents. However, previous studies have estimated that approximately 50% of nursing home cases are attributable to cross-facility staff movement, hence attention to highly connected nursing facilities is warranted [12]. In order to incorporate staff movement, we extended our model to include the potential for interactions between HCWs by allowing connec-

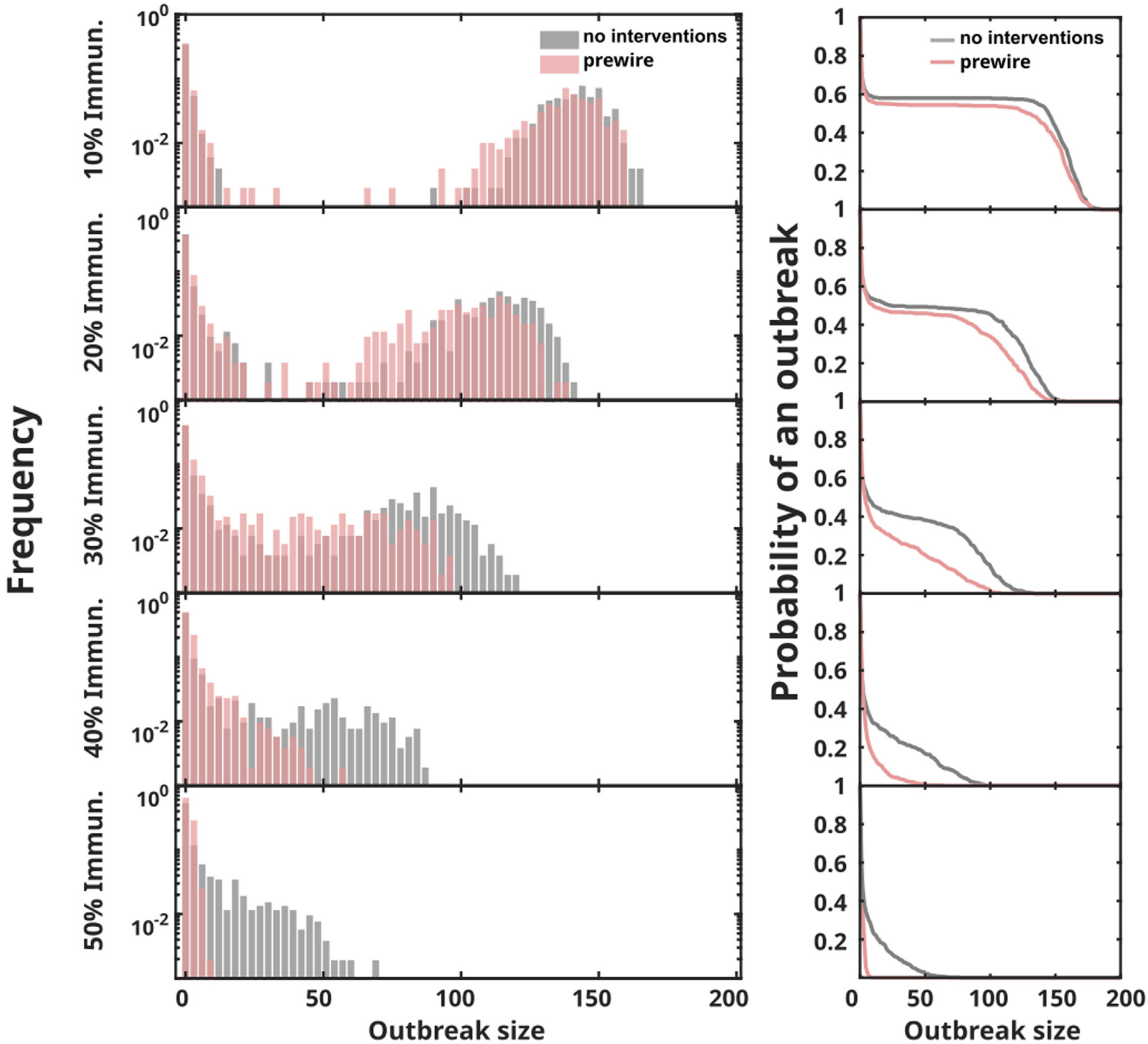

Fig. 5. Outbreak size distributions and probability of an outbreak depending on the immunization level. Distributions of the total infected and probability densities of an outbreak for 10%, 20%, 30%, 40%, and 50% of immunized individuals in the LTC when no interventions (*gray*) and a preventive immune shielding (prewiring, *pink*) strategy is applied before the outbreak starts. The epidemic initiates with one infected HCW. We simulate the epidemic over 100 days and perform 500 simulation runs. A two-sample Kolmogorov-Smirnov test was performed to look for a statistically significant difference of outbreak distributions with and without prewiring. *P*-values for 10%, 20%, 30%, 40%, and 50% of immunized individuals are: less than 0.05 for 10% and less than 0.001 for the rest of immune levels. The distributional differences are associated with statistically significant differences in mean outbreak sizes for all but the 10% case, as quantified by a one-sided *t*-test with 99% confidence interval; *P*-values for 10%, 20%, 30%, 40%, and 50% of immunized individuals are: 0.056 for 10%, less than 0.01 for 20%, and less than 0.001 for the rest of immune levels. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

tions within HCWs in addition to the connections between HCWs and residents. To do so, we augmented the bipartite network interactions with a small-world network representation of HCW interactions (see Methods). In Supplementary Figure S5a, we show that including additional flexibility of staff interactions lead to an increase in cases and may require increasing the frequency of rewiring to control outbreaks and/or the inclusion of multiple prewiring steps to prevent outbreaks.

Finally, we extend our analysis to include different staffing levels consistent with 1:3, 1:5, and 1:10 HCW per resident ratios, consistent with the recommended standards for LTC [34]. The model predicts that shield immunity-based rewiring continues to be effective even while decreasing the HCW:resident ratio from 1:1 to 1:5 and generally shows fewer infections when staffing levels are low in comparison to the 1:1 HCW per resident ratio (Supplementary Figure S5b). The bipartite structure we use to describe the LTC network assumes that residents are isolated in their rooms and can only interact with staff that follows strict social distancing guidelines. As a result, the outbreak exhibits a sequential pattern for infection propagation, where an infected resident infects a HCW and vice versa. Reducing the number of propagators through a reduction in the HCW per resident ratio helps to reduce the overall size of the epidemic. However, we note that there is a latent impact of decreases in staff levels, implying that lower ratios may actually improve infection control even in the absence of other measures given that staff may (unwittingly) mobilizing infection in a facility – the consequence is that patient care decreases and workload per HCW increases (Supplementary Table S1). As expected, reduced staffing levels also resulted in a larger fraction of infected HCWs during the outbreak. Additional studies are necessary to evaluate the balance between patient care, infection control, and staffing levels.

Discussion

As of February 2022, residents and staff of LTCs represent more than 20% of all COVID-19 fatalities in the United States [1]. These populations are likely to remain vulnerable in light of the evolution of variants, waning immunity from vaccines, and partial vaccination within LTC residents and staff. Developing strategies to control and prevent outbreaks in LTCs is critical given the disproportionate impacts of severe illness in these vulnerable communities. The present analysis leverages viral testing to inform network-based mitigation strategies that restructure who care for whom based on disease status. We find that restructuring interactions during or before an outbreak can reduce outbreak size significantly – rivaling if not exceeding that of standard mitigation practices (like case isolation). The key principle underlying the effectiveness of such interventions is that disease status can be used to minimize the number of risky connections (i.e., between susceptible and infectious individuals) as well as increase the number of potentially epidemic-blocking connections (i.e., between susceptible and immune individuals). Reducing risky connections helps to control ongoing outbreaks for the same reason that isolation can be effective. Notably, our proposed preventative rewiring strategy leverages the intentional increase in epidemic-blocking connections to reduce the transmission via an inadvertent introduction of an infectious case. Preventative rewiring increases the odds that an outbreak is restrained because someone who was susceptible and becomes infected is already connected to an immune individual – whether due to recovery and/or vaccine derived immunity. Together, we show that such strategies are feasible using weekly testing and given realistic network and epidemiological conditions associated with LTCs.

At present, best practices to prevent and monitor outbreaks in nursing homes and LTCs include a combination of practices including the use of PPE, support for staff, as well as viral surveillance testing of staff and residents [35–37]. Our findings contrast with early suggestions to cohort susceptible HCWs (in PPE) with infectious residents while having recovered HCWs not wear PPE when dealing with other residents [38]. Such strategies may have been prudent given prior limitations on PPE availability. However, we note that PPE alone is not 100% effective and mixing susceptible and infectious residents is likely to accelerate disease spread. In contrast, our proposed implementation of cohorting strategies aims to reduce transmission across connections– thereby benefiting the population as a whole. In doing so, the rewiring strategies leverage high-quality viral tests (analogous to a PCR test) which requires considerations of trade-offs between test rate, turnaround speed, and accuracy. We note that the inclusion of antigen tests can accelerate identification of infectious individuals (given high test specificity), but caution should be used if using negative test results from antigen tests to guide cohorting (give relatively lower test sensitivity). As is apparent, knowing both the disease and immunization status of individuals can inform shield immunity interventions. Hence, our findings also suggest the value of considering large-scale antibody testing of staff to inform immunity-based cohorting to reduce transmission risk, particularly in context in which vaccine mandates are not feasible, not permitted, not effective or are otherwise impractical. Moreover, network-based rewiring may also be relevant given low compliance with booster recommendations. For example, only ∼38% of residents and ∼51% of HCWs in LTCs nationwide complied with CDC booster recommendations as of August 2022, even if ∼87% of residents and staff in LTC are considered fully vaccinated with the initial recommended dose [11]. Therefore, the use of both viral and antibody tests combined with vaccination mandates or surveys for vaccination status could help inform care schedules to reduce the risk of transmission of SARS-CoV-2 in nursing homes and other LTCs.

Indeed, our network-based intervention model comes with caveats. Our focus on interventions to reduce risk of SARS-CoV-2 does not consider risks for other infections like influenza, norovirus, and antibiotic resistant pathogens. In practice, shield immunity interventions would have to be balanced with cohorting and care protocols that account for other co-circulating pathogens and specialized resident care necessities. In addition, network-based interventions require changes in staff care and availability, exploration of feasibility will require extending the current framework to reflect constraints in staff expertise, numbers, and supply. Moreover, we have assumed that recovered individuals and vaccinated individuals have protective immunity from onward transmission over the period of the epidemic outbreak (here modeled as 100 days). The duration of effective immunity has been estimated to be on the order of 6-8 months [39]. The duration of effective immunity is likely to change over time as new variants emerge and vaccine and booster recommendations change. As such, monitoring the effective period of immunity in vulnerable populations will be critical to leveraging both prior infection status and vaccination status to guide cohorting.

In summary, we have developed a network-based approach to cohort both residents and HCW in light of their infection and immune status as a means to reduce the risk of active transmission or the future risk associated with the inadvertent introduction of SARS-CoV-2 into a vulnerable population. In doing so, this study reinforces a persistently under-explored opportunity: to use testing at scale as a guide for targeted mitigation rather than a passive indicator of the status of an outbreak. Here, viral testing and assessment of immune status (whether through antibody testing or via vaccination status) are combined to inform the active ‘rewiring’ or preventative ‘prewiring’ of resident to healthcare worker interactions with a central goal: reducing the size and severity of outbreaks. With the increasing but still partial coverage of vaccines and their limited effectiveness against new variants, the present study advances the goal of informing behavioral strategies to reduce the disproportionate impact of severe illness and SARS-CoV-2 associated fatalities in vulnerable, elderly populations.

Conclusions

We developed a network-based cohorting intervention that leverages both disease status and recovery/immunization status to reduce and prevent outbreaks in nursing homes and LTCs. Using a network-based intervention, we find that cohorting the care of infected residents with immunized HCWs (either via natural infection or vaccination) can significantly reduce the size of an outbreak. In doing so, the network intervention extends prior modeling efforts to establish the benefits of antibody testing as part of a ‘shield immunity’ mitigation [24–26]. Using the network-based modeling framework, we also show that shield immunity principles can be applied as a preventative measure in advance of an outbreak via a prewiring step in which susceptible HCWs provide cohorted care for immune residents. This prewiring step helps to reduce the frequency and severity of outbreaks by reducing the risk that an inadvertent introduction of SARS-CoV-2 into a facility via a potentially asymptomatic HCW spreads to vulnerable residents (and then to susceptible staff). Such prewiring steps could potentially be used to improve the targeted efficacy of vaccination mandates and immunity passes [40]. Finally, the use of weekly testing and either prewiring or rewiring to control an outbreak suggests that network-based cohorting interventions are likely feasible given partial population immunity – particularly when used to protect vulnerable populations.

Author contributions

AL, AM, RR, CYL, JSW designed methods; AL, AM, RR, CYL developed simulations; AL, AM, RR, CYL implemented simulations; AL, AM, RR, JSW analyzed model results; AL, AM, RR, JSW wrote the paper; CYL and JSW designed the overall project.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We thank Jonathan Dushoff, Sang Woo Park, Scott Fridkin, Ben Lopman, Carly Adams, and Weitz group members for feedback on the manuscript. This work was enabled by support from the Centers for Disease Control and Prevention (75D30121P10600) and the Army Research Office (W911NF1910384).

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.annepidem.2022.10.013.

References

[1] Chidambaram P. Over 200,000 residents and staff in long-term care facilities have died from COVID-19. Kaiser Family Foundation 2022. (Coronavirus). https://www.kff.org/policy-watch/over-200000-residents-and-staff-in-long-term-care-facilities-have-died-from-covid-19/. [Accessed 3 February 2022].

[2] Lau-Ng R, Caruso LB, Perls TT. COVID-19 deaths in long-term care facilities: a critical piece of the pandemic puzzle. J Am Geriatr Soc 2020;68(9):1895–8. doi:10.1111/jgs.16669.

[3] Sugg MM, Spaulding TJ, Lane SJ, Runkle JD, Harden SR, Hege A, et al. Mapping community-level determinants of COVID-19 transmission in nursing homes: a multi-scale approach. Sci Total Environ 2021;752:141946. doi:10.1016/j.scitotenv.2020.141946.

[4] Ouslander JG, Grabowski DC. COVID-19 in nursing homes: calming the perfect storm. J Am Geriatr Soc 2020;68(10):2153–62. doi:10.1111/jgs.16784.

[5] Verity R, Okell LC, Dorigatti I, Winskill P, Whittaker C, Imai N, et al. Estimates of the severity of Coronavirus Disease 2019: a model-based analysis. Lancet Infect Dis 2020;20(6):669–77. doi:10.1016/S1473-3099(20)30243-7.

[6] Dessie ZG, Zewotir T. Mortality-related risk factors of COVID-19: a systematic review and meta-analysis of 42 studies and 423,117 patients. BMC Infectious Disease 2021;21:855. doi:10.1186/s12879-021-06536-3.

[7] Li X, Xu S, Yu M, Wang K, Tao Y, Zhou Y, et al. Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. J Allergy Clin Immunol 2020;146(1):110–18. doi:10.1016/j.jaci.2020.04.006.

[8] Kaiser Family Foundation Report. https://www.kff.org/coronavirus-covid-19/issue-brief/state-covid-19-data-and-policy-actions/#longtermcare. [Accessed 09 March 2022].

[9] Grabowski DC, Mor V. Nursing home care in crisis in the wake of COVID-19. JAMA 2020;324(1):23–4. doi:10.1001/jama.2020.8524.

[10] Gorges RJ, Konetzka RT. Staffing levels and COVID-19 cases and outbreaks in U.S. nursing homes. J Am Geriatr Soc 2020;68(11):2462–6. doi:10.1111/jgs.16787.

[11] AARP data table using CDC data; last accessed October 6, 2022 URL: https://www.aarp.org/ppi/issues/caregiving/info-2020/nursing-home-covid-states.html.

[12] Chen MK, Chevalier JA, Long EF. Nursing home staff networks and COVID-19. Proc Natl Acad Sci 2021;118(1):e2015455118. doi:10.1073/pnas.2015455118.

[13] Strausbaugh LJ, Sukumar SR, Joseph CL, High KP. Infectious disease outbreaks in nursing homes: an unappreciated hazard for frail elderly persons. Clin Infec Dis 2003;36:870–6. doi:10.1086/368197.

[14] Barnett ML, Grabowski DC. Nursing homes are ground zero for COVID-19 pandemic. JAMA Health Forum 2020;1(3):e200369. doi:10.1001/jamahealthforum.2020.0369.

[15] Rossman H, Shilo S, Meir T, Gorfine M, Shalit U, Segal E, et al. COVID-19 dynamics after a national immunization program in Israel. Nat Med 2021;27:1055–61. doi:10.1038/s41591-021-01337-2.

[16] Amit S, Regev-Yochay G, Arnon A, Yitshak K, Eyal E. Early rate reductions of SARS-CoV-2 infection and COVID-19 in BNT162b2 vaccine recipients. Lancet 2021;397(10277):875–7. doi:10.1016/S0140-6736(21)00448-7.

[17] Andrews N, Stowe J, Kirsebom F, Toffa S, Rickeard T, Gallagher E, et al. Covid-19 vaccine effectiveness against the Omicron (B.1.1.529) variant. N Engl J Med 2022;386:1532–46. doi:10.1056/NEJMoa2119451.

[18] Nguyen LH, Drew DA, Graham MS, Joshi AD, Guo CG, Ma W, et al. Risk of COVID-19 among front-line health-care workers and the general community: a prospective cohort study. Lancet Public Health 2020;5:475–83. doi:10.1016/S2468-2667(20)30164-X.

[19] Hartmann S, Rubin Z, Sato H, Yong KO, Terashita D, Balter S. Coronavirus disease 2019 (COVID-19) infections among healthcare workers, Los Angeles County, February–May 2020. Clin Infec Dis 2020;73(7):e1850–4. doi:10.1093/cid/ciaa1200.

[20] Darbon A, Colombi D, Valdano E, Savini L, Giovannini A, Colizza V. Disease persistence on temporal contact networks accounting for heterogeneous infectious periods. Soc Open Sci 2019;6(1):181404. doi:10.1098/rsos.181404.

[21] Meyers LA, Newman MEJ, Martin M, Schrag S. Applying network theory to epidemics: control measures for mycoplasma pneumoniae outbreaks. Emerg Infect Dis 2003;9(2):204–10. doi:10.3201/eid0902.020188.

[22] Telford CT, Onwubiko U, Holland DP, Turner K, Prieto J, Smith S, et al. Preventing COVID-19 outbreaks in long-term care facilities through preemptive testing of residents and staff members. MMWR 2020;69:1296–9. doi:10.15585/mmwr.mm6937a4external.

[23] Sanchez-Taltavull D, Candinas D, Roldan E, Beldi G. Modelling strategies to organize healthcare workforce during pandemics: Application to COVID-19. Journal of Theoretical Biology 2021;523:110718. doi:10.1016/j.jtbi.2021.110718.

[24] Weitz JS, Beckett SJ, Coenen AR, Demory D, Dominguez-Mirazo M, Dushoff J, et al. Modeling shield immunity to reduce COVID-19 epidemic spread. Nat Med 2020;26:849–54. doi:10.1038/s41591-020-0895-3.

[25] Kraay ANM, Nelson KN, Zhao CY, Demory D, Weitz JS, Lopman BA. Modeling serological testing to inform relaxation of social distancing for COVID-19. Nat Commun 2021;12:7063. doi:10.1038/s41467-021-26774-y.

[26] Li G, Shivam S, Hochberg ME, Wardi Y, Weitz JS. Disease-dependent interaction policies to support health and economic outcomes during the COVID19 epidemic. Iscience 2021;24(7):102710. doi:10.1016/j.isci.2021.102710.

[27] Bansal S, Grenfell BT, Meyers LA. When individual behaviour matters: homogeneous and network models in epidemiology. J R Soc Interface 2007;4:879–91. doi:10.1098/rsif.2007.1100.

[28] Ito K, Piantham C, Nishiura H. Relative instantaneous reproduction number of Omicron SARS-CoV-2 variant with respect to the Delta variant in Denmark. J Med Virol 2022;94(5):2265–8. doi:10.1002/jmv.27560.

[29] Meyers LA, Pourbohloul B, Newman MEJ, Skowronski DM, Brunham RC. Network theory and SARS: predicting outbreak diversity. J Theor Biol 2004;4(1):71–81. doi:10.1016/j.jtbi.2004.07.026.

[30] Shioda K, Lau MSY, Kraay ANM, Nelson KN, Siegler AJ, Sullivan PS, et al. Estimating the cumulative incidence of SARS-CoV-2 infection and the infection fatality ratio in light of waning antibodies. Epidemiology 2021;32(4):518–24. doi:10.1097/EDE.0000000000001361.

[31] Erdös P, Rényi A. On random graphs. Public Math 1959;6:290–7.

[32] Watts D, Strogatz S. Collective dynamics of 'small-world' networks. Nature 1998;393:440–2. doi:10.1038/30918.

[33] Strona G, Nappo D, Boccacci F, Fattorini S, San-Miguel-Ayanz JA. A fast and unbiased procedure to randomize ecological binary matrices with fixed row and column totals. Nat Commun 2014;5:4114. doi:10.1038/ncomms5114.

[34] Harrington C, Dellefield ME, Halifax E, Fleming ML, Bakerjian D. Appropriate nurse staffing levels for U. S. nursing homes. Health Ser Insights 2020;13:117863292093478. doi:10.1177/1178632920934785.

[35] Dorritie R, Quigley D, Agarwal M, Tark A, Dick A, Stone P. Support of nursing homes in infection management varies by US state Departments of Health. J Hosp Infect 2020;105(2):258–64. doi:10.1016/j.jhin.2020.02.007.

[36] Chatterjee P, Kelly S, Qi M, Werner RM. Characteristics and quality of US nursing homes reporting cases of coronavirus disease 2019 (COVID-19). JAMA Netw Open 2020;3(7):e2016930. doi:10.1001/jamanetworkopen.2020.16930.

[37] White EM, Kosar CM, Feifer RA, Blackman C, Gravenstein S, Ouslander J, et al. Variation in SARS-CoV-2 prevalence in U.S. skilled nursing facilities. J Am Geriatr Soc 2020;68(10):2167–73. doi:10.1111/jgs.16752.

[38] Holmdahl I, Kahn R, Hay JA, Buckee CO, Mina MJ. Estimation of transmission of COVID-19 in simulated nursing homes with frequent testing and immunity-based staffing. JAMA Netw Open 2021;4(5):e2110071. doi:10.1001/jamanetworkopen.2021.10071.

[39] Dan JM, Mateus J, Kato Y, Hastie KM, Yu ED, Faliti CE, et al. Immunological memory to SARS-CoV-2 assessed for up to 8 months after infection. Science 2021;371(6529):eabf4063. doi:10.1126/science.abf4063.

[40] Ward JK, Gauna F, Gagneux-Brunon A, Botelho-Nevers E, Cracowski JL, Khouri C, et al. The French health pass holds lessons for mandatory COVID-19 vaccination. Nat Med 2022;28:232–5. doi:10.1038/s41591-021-01661-7.