



Predicting consequences of COVID-19 control measure de-escalation on nosocomial transmission and mortality: a modelling study in a French rehabilitation hospital

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SUMMARY

Introduction: Infection control measures are effective for nosocomial COVID-19 prevention but bear substantial health-economic costs, motivating their “de-escalation” in settings at low risk of SARS-CoV-2 transmission. Yet consequences of de-escalation are difficult to predict, particularly in light of novel variants and heterogeneous population immunity.

Aim: To estimate how infection control measure de-escalation influences nosocomial COVID-19 risk.

Methods: An individual-based transmission model was used to simulate SARS-CoV-2 outbreaks and control measure de-escalation in a French long-term care hospital with multi-modal control measures in place (testing and isolation, universal masking, single-occupant rooms). Estimates of COVID-19 case fatality rates (CFRs) from reported outbreaks were used to quantify excess COVID-19 mortality due to de-escalation.

Results: In a population fully susceptible to infection, de-escalating both universal masking and single rooms resulted in hospital-wide outbreaks of 114 (95% CI: 103–125) excess infections, compared with five (three to seven) excess infections when de-escalating only universal masking or 15 (11–18) when de-escalating only single rooms. When de-escalating both measures and applying CFRs from the first wave of COVID-19, excess patient mortality ranged from 1.57 (1.41–1.71) to 9.66 (8.73–10.57) excess

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deaths/1000 patient-days. By contrast, when applying CFRs from subsequent pandemic waves and assuming susceptibility to infection among 40–60% of individuals, excess mortality ranged from 0 (0–0) to 0.92 (0.77–1.07) excess deaths/1000 patient-days.

Conclusions: The de-escalation of bundled COVID-19 control measures may facilitate widespread nosocomial SARS-CoV-2 transmission. However, excess mortality is probably limited in populations at least moderately immune to infection and given CFRs resembling those estimated during the ‘post-vaccine’ era.

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Introduction

Infection control measures adopted to prevent SARS-CoV-2 transmission in healthcare settings have proven widely effective for nosocomial COVID-19 prevention [1–3]. However, stringent measures are difficult to sustain over extended periods, as they bear substantial economic costs, impose occupational burden on healthcare workers (HCWs), and can interfere with patient health and wellbeing [4]. Social isolation during COVID-19 quarantines and lockdowns, for example, has been associated with worsened mental health outcomes among people living and working in healthcare facilities [5,6]. Such health and economic costs motivate decision makers to consider scaling back or ‘de-escalating’ COVID-19 control measures in facilities not experiencing significant COVID-19 burden, or those deemed at low risk of nosocomial spread. In many healthcare settings worldwide, COVID-19 control measures have already been lifted or largely scaled back. Yet benefits of de-escalation must be weighed against potential costs, including the exacerbation of SARS-CoV-2 outbreak risk and any excess infection burden that may result.

In the face of high levels of community SARS-CoV-2 transmission, but great declines in COVID-19 morbidity and mortality since the early days of the pandemic, it is difficult to predict to what extent the de-escalation of infection control measures such as universal masking may amplify nosocomial spread and imperil patient safety [7]. A recent retrospective cohort study evaluating the relaxation of universal SARS-CoV-2 testing in a Singaporean hospital highlights challenges in estimating de-escalation’s impacts in real-world settings, in particular given high rates of asymptomatic infection and potential asynchrony in the timing of de-escalation and local surges in transmission [8].

Mathematical models have been used extensively to predict the epidemiological impacts of COVID-19 control measures in healthcare settings when real-world clinical evidence has been lacking [9]. It seems obvious from simple models that de-escalating COVID-19 control measures could create the epidemiological conditions necessary for a large nosocomial outbreak, with consequences of de-escalation depending on population-specific levels of susceptibility to infection and disease (Supplementary Box A1). However, while simple models are helpful for conceptualizing epidemic risk in a general sense, robust models fitted to detailed empirical data are needed to capture realistic nosocomial transmission dynamics, and to provide more credible estimates of de-escalation risk in specific settings. For example, a model of nursing homes in the USA predicted that de-escalating routine asymptomatic SARS-CoV-2 testing is likely to be safe in facilities with high

vaccine coverage, especially when community infection incidence is low [10]. However, it remains unclear how de-escalating diverse COVID-19 control interventions is likely to impact outbreak risk in different types of healthcare settings, and in particular given the emergence of novel variants circulating among patients and HCWs with increasingly complex immunological histories.

Here, to investigate impacts of COVID-19 control measure de-escalation on nosocomial COVID-19 risk, we conducted a mathematical modelling study using an individual-based SARS-CoV-2 transmission model fitted to high-resolution inter-individual contact data from a long-term care hospital in France.

Methods

Simulating SARS-CoV-2 outbreaks using an individual-based transmission model

SARS-CoV-2 outbreaks were simulated using CTCmodeler (‘the model’), a previously developed, stochastic, individual-based SARS-CoV-2 transmission model programmed in C++. This model is designed to reproduce the demography and contact behaviours of patients and HCWs in a five-ward, 170-bed rehabilitation hospital in northern France. It has been used previously to simulate COVID-19 outbreaks and evaluate control interventions in the long-term care hospital setting [11,12]. Briefly, the model simulates: (i) synthetic contact networks, describing inter-individual contact among patients and staff in the hospital; (ii) the potential transmission of SARS-CoV-2 within the hospital during contacts between infectious and susceptible individuals; and (iii) the natural progression of SARS-CoV-2 infection, following a modified Susceptible-Exposed-Infectious-Recovered process accounting for various infection pathways. In the Supplementary data, we describe our model according to the MInD-Healthcare framework [13], including details on our modelling assumptions regarding SARS-CoV-2 infection, symptom profiles and the management of COVID-19 cases. A model schematic is provided in Supplementary Figure S2 and model parameters are reported in Supplementary Table S3.

Contact networks simulated by the model are dynamic and describe all contacts that all individuals in the facility have with one another over time, within a distance of 1.5 m and over 30-s time intervals. These synthetic contact networks are fitted to high-resolution, close-proximity interaction data recorded within the hospital by radio frequency identification devices worn by approximately 90% of all patients and staff over a three-month period. These data were originally collected in

2009 from a rehabilitation hospital in Berck-sur-Mer, France, as part of the i-Bird (Individual-Based Investigation of Resistance Dissemination) study. Note that the patient population of this hospital was relatively mobile, and most patients shared rooms and participated in social activities. This translates to high rates of patient–patient contact relative to standard acute-care facilities. See Duval *et al.* for a detailed description of these contact data [14].

COVID-19 control measures implemented

We implemented a range of COVID-19 control measures in the model. First, we assumed increased availability of standard infection prevention and control (IPC) resources (e.g., for hand hygiene, droplet precautions) among HCWs relative to pre-pandemic baseline. Second, we implemented routine symptomatic reverse transcription polymerase chain reaction (RT-PCR) testing with imperfect diagnostic sensitivity among patients presenting with COVID-19 symptoms. Patients diagnosed with COVID-19 were isolated from other patients while maintaining their necessary daily contacts with HCWs. For members of staff, we assumed a policy of at-home rapid diagnostic testing upon COVID-19 symptom onset, and assumed that staff with positive tests were put on mandatory sick leave and replaced for the duration of their illness by stand-by staff. Third, we implemented universal masking among both patients and staff, which was assumed to reduce SARS-CoV-2 transmission risk during inter-individual contact by 80% relative to no-intervention baseline, as estimated by Liang *et al.* [15]. Finally, we considered single patient rooms as an intervention designed to reduce the risk of patient-to-patient transmission. This was conceptualized as the installation of materials that improve ventilation and/or physically separate individuals inhabiting the same room (e.g., curtains, tarps), and was implemented in the model as the severing of overnight patient–patient contacts.

De-escalation scenarios, simulation initialization and sensitivity analyses

Model simulations were conducted to quantify nosocomial COVID-19 burden across a range of epidemiological scenarios. In each scenario, we varied the COVID-19 control measures in place in order to estimate the impact of de-escalation on nosocomial disease dynamics. We included enhanced IPC availability and routine symptomatic COVID-19 testing in all scenarios, under the assumption that these measures bear relatively little health-economic burden and are less likely to be de-escalated. In our baseline scenario, we further included universal masking and single rooms. Across three de-escalation scenarios, we considered the lifting of universal masking, the lifting of single rooms, and the simultaneous lifting of both universal masking and single rooms.

Simulations across each scenario were initialized by introducing a single patient infected with SARS-CoV-2 – the index case – into the hospital, followed by a low rate of subsequent introductions equivalent to one patient infected with SARS-CoV-2 being admitted into the hospital every 12.5 days. We also assumed that each susceptible HCW had a daily probability of 0.04% of becoming infected while not at work. These parameters were calibrated to reflect a period of moderate

community SARS-CoV-2 transmission and importation risk into the hospital [12]. Simulations were run for four weeks, after which it was assumed that facilities brought nosocomial SARS-CoV-2 transmission under control. Due to this short time horizon, we assumed that simulated outbreaks were caused by a single SARS-CoV-2 variant and that no instances of re-infection occurred. To account for vaccination and past infection, we varied the population's level of susceptibility to infection at simulation outset, ranging from 0% to 100% by increments of 20%, and accounting for potentially asymmetric susceptibility across patients and staff.

In sensitivity analyses, we considered alternative index cases (members of staff infected in the community) and simulation time horizons (two weeks, 12 weeks), and included the cancellation of social activities as an alternative 'social distancing' intervention to single rooms. This was implemented as the severing of all patient triads, i.e., all contacts involving more than two patients simultaneously, as considered in previous work [12]. For each combination of variables (four de-escalation scenarios, three time horizons, two types of index case, two social distancing interventions, six levels of patient immunity, six levels of staff immunity), we ran 100 independent stochastic simulations, resulting in a total of 172,800 distinct outbreaks.

Epidemiological outcomes

Epidemiological outcomes calculated from outbreak simulations were the index reproduction number (R_i), the number of wards with hospital-acquired (HA) infection (W), the cumulative number of HA infections (C), and the population-adjusted incidence rate (I). The index reproduction number was calculated as the number of individuals within the hospital to whom the index case transmitted infection. The number of wards with HA infection was calculated as the number of wards in which at least one individual acquired infection from someone else in the hospital by the end of simulation time. Cumulative infection numbers were calculated as the total number of HA infections among both patients and staff within the hospital by the end of simulation time. The incidence rate per 1000 person-days was calculated for patients as the cumulative number of patient infections divided by the cumulative number of patient bed-days in the hospital over simulation time ($I^{pat} = C^{pat} \times 1000/d^{pat}$), and for staff as the cumulative number of staff infections divided by the cumulative number of staff working-days ($I^{hchw} = C^{hchw} \times 1000/d^{hchw}$).

Excess mortality due to de-escalation

To quantify excess COVID-19 mortality due to de-escalation, we multiplied the incidence of excess patient infections caused by de-escalation, $I_{\rho}^{pat} - I_0^{pat}$, by the case fatality rate (CFR) of nosocomial COVID-19, τ (see [Supplementary Box A1](#)). As excess mortality was estimated retrospectively from simulated daily outbreak data, we implicitly assumed that death occurs after the infectious period and that deceased patients are not replaced by susceptible patients over the simulated outbreak period. A range of CFR estimates were used, extracted from clinical studies describing nosocomial SARS-CoV-2 outbreaks in aged care facilities. Studies screened were those identified in two systematic reviews by Hashan *et al.* The first describes SARS-CoV-2 outbreaks in aged care facilities occurring during

the ‘first wave’ of the COVID-19 pandemic reported in studies published by September 2020 [16], and the second describes SARS-CoV-2 outbreaks in aged care facilities during the ‘post-vaccine period’ in studies published from December 2020 to April 2022 [17]. All studies reporting incident cases of patient SARS-CoV-2 infection and mortality were included. Data extracted include the date of the first reported infection, the number of patient infections and deaths, and the SARS-CoV-2 variant(s) that caused the outbreak. For each outbreak, the CFR was estimated as the number of deaths among patients infected with COVID-19 divided by the number of patient infections. Studies reporting <20 patient infections and outbreaks caused by an unreported SARS-CoV-2 variant were excluded. All outbreaks during the first wave were assumed to be caused by the same index virus.

Statistical reporting

Each outcome is reported as the mean and its 95% confidence interval (CI), calculated from raw simulation output data (Supplementary Figure S3) using bootstrap resampling with $N = 10,000$ replicates. For each de-escalation scenario, we also calculated the absolute difference of each outcome relative to the baseline scenario ($\Delta R_i, \Delta W, \Delta C, \Delta I$), again using bootstrap resampling with $N = 10,000$ replicates to calculate means and 95% CIs.

Ethical approval

The i-Bird study obtained all authorizations required by French regulations regarding medical research and information processing. All French IRB-equivalent agencies accorded the i-Bird programme official approval (CPP 08061; Afssaps 2008-A01284-51; CCTIRS 08.533; CNIL AT/YPA/SV/SN/GDP/AR091118 No. 909036). Signed consent by patients and staff was not required according to the Ethics Committee to which the project was submitted.

Results

COVID-19 control measures limit nosocomial outbreak risk

The COVID-19 control measures in place at baseline effectively prevented nosocomial SARS-CoV-2 transmission, even when assuming complete susceptibility to infection among all patients and staff at simulation outset. In this scenario, infected patients admitted into the hospital from the community infected on average $R_i = 0.40$ (95% CI: 0.24, 0.60) other patients and HCWs during their hospital stay. These index cases resulted in on average $C = 0.84$ (95% CI: 0.54, 1.20) cumulative SARS-CoV-2 infections among patients and staff at four weeks. This translates to an incidence of $I^{pat} = 0.12$ (95% CI: 0.08, 0.18) HA patient infections per 1000 patient-days and $I^{hCW} = 0.04$ (95% CI: 0.02, 0.06) HA staff infections per 1000 staff-days (across on average 4506 patient-days and 6945 staff-days included over the baseline four-week outbreak period). SARS-CoV-2 transmission was less likely when index cases were members of staff infected in the community as opposed to patients (Supplementary Figure S4), due to their lower cumulative rates of contact in this facility.

De-escalating multiple control measures compounds outbreak risk

Individually, de-escalating either universal masking or single rooms led to significant increases in SARS-CoV-2 transmission (Figure 1). Lifting universal masking increased the index reproduction number to $R_i = 1.01$ (95% CI: 0.71, 1.34), resulting in $\Delta C = 4.88$ (95% CI: 3.22, 6.73) excess infections across $\Delta W = 1.05$ (95% CI: 0.72, 1.39) additional hospital wards, or $\Delta I^{pat} = 0.65$ (95% CI: 0.40, 0.94) excess patient infections/1000 patient-days and $\Delta I^{hCW} = 0.28$ (95% CI: 0.19, 0.38) excess staff infections/1000 staff-days. Lifting single rooms increased the index reproduction number to $R_i = 1.53$ (95% CI: 1.21, 1.87), resulting in $\Delta C = 14.72$ (95% CI: 11.46, 18.11) excess infections across $\Delta W = 1.37$ (95% CI: 1.06, 1.70) additional wards, or $\Delta I^{pat} = 2.79$ (95% CI: 2.17, 3.44) excess patient infections/1000 patient-days and $\Delta I^{hCW} = 0.31$ (95% CI: 0.24, 0.40) excess staff infections/1000 staff-days. In a sensitivity analysis considering an alternative social distancing intervention, single rooms was found to be a more effective intervention for SARS-CoV-2 transmission prevention than the cancellation of group activities (Supplementary Figure S5).

COVID-19 control measures are synergistic, such that increases in SARS-CoV-2 transmission resulting from de-escalating multiple measures simultaneously are much greater than the sum of increases resulting from de-escalating each measure independently (Figure 1). When both universal masking and single rooms were lifted, the index reproduction number increased to $R_i = 3.79$ (95% CI: 3.16, 4.56), resulting in $\Delta C = 114.31$ (95% CI: 102.68, 125.44) excess infections across $\Delta W = 4.03$ (95% CI: 3.75, 4.29) additional hospital wards, for an excess $\Delta I^{pat} = 18.39$ (95% CI: 16.62, 20.13) excess patient infections/1000 patient-days and $\Delta I^{hCW} = 4.53$ (95% CI: 4.01, 5.04) excess HCW infections/1000 staff-days. However, it is important to note that any such increases depend on the population’s degree of susceptibility to infection. For instance, when only 60% of patients and staff were susceptible, lifting both masking and single rooms increased the index reproduction number to a lesser extent: from $R_i = 0.21$ (95% CI: 0.11, 0.33) to $R_i = 2.39$ (95% CI: 1.98, 2.84), resulting in $\Delta C = 30.69$ (95% CI: 25.81, 35.73) excess infections across $\Delta W = 2.69$ (95% CI: 2.34, 3.03) additional wards. When assuming only 20% were susceptible, the index reproduction number increased from $R_i = 0.08$ (95% CI: 0.03, 0.14) to $R_i = 0.95$ (95% CI: 0.72, 1.22), resulting in just $\Delta C = 2.42$ (95% CI: 1.78, 3.09) excess infections across $\Delta W = 0.76$ (95% CI: 0.60, 0.92) additional wards. Asymmetric levels of immunization among patients and staff further impacted transmission dynamics, with de-escalation being considerably riskier when patient immunization was lower than HCW immunization in this facility (Supplementary Figure S6).

Excess mortality due to de-escalation is highly context specific

We included COVID-19 CFRs from 36 studies (23 from the first wave, 13 from subsequent waves) describing SARS-CoV-2 outbreaks occurring in aged care facilities across 14 countries (Supplementary Table S4). CFRs varied substantially across healthcare facilities and pandemic periods, ranging from 0.085 to 0.525 over the first wave and from 0 to 0.173 over

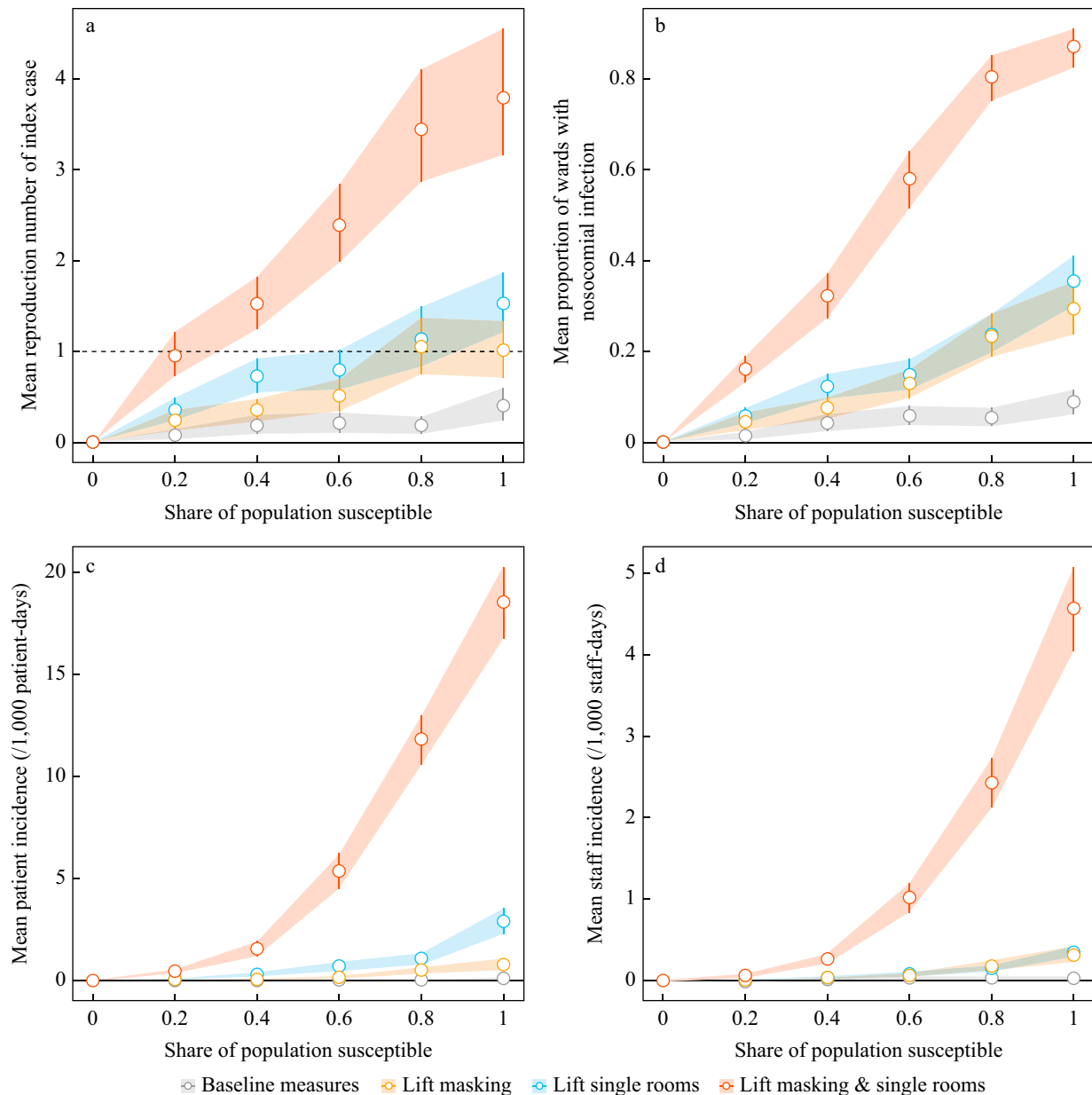


Figure 1. Epidemiological impacts of COVID-19 control measure de-escalation depend on the population's degree of susceptibility to infection. When lifting only universal masking (yellow) or single rooms (blue), the reproduction number of index cases only increased above one ($R_t > 1$) when approximately $\geq 80\%$ of the population was susceptible to infection (a). However, when both control measures were lifted simultaneously (red), the reproduction number increased above one when just $\geq 20\%$ of the population was susceptible to infection. Lifting both measures thus generally resulted in large increases in the probability of multi-ward outbreaks (b) and large increases in infection incidence (c, d). Here, the same share of patients and staff are assumed to be susceptible to infection upon outbreak outset (x-axis). Points represent means and error bars represent 95% confidence intervals across $N = 100$ outbreak simulations, calculated using bootstrap resampling with 10,000 replicates.

subsequent waves (Figure 2a). CFRs were applied to our simulated outbreaks for the full de-escalation scenario, i.e., assuming the relaxation of both universal masking and single rooms. Heterogeneity in CFR estimates translated to substantial heterogeneity in the estimated burden of excess mortality due to de-escalation (Figure 2b). In the context of a patient population wholly susceptible to infection, and when applying CFRs from the first wave of COVID-19, excess mortality ranged from 1.57 (95% CI: 1.41, 1.71) to 9.66 (95% CI: 8.73,

10.57) excess patient deaths/1000 patient-days. By contrast, when applying CFRs from subsequent pandemic waves, and assuming susceptibility to infection among 40–60% of the population, excess mortality ranged from 0 (95% CI: 0, 0) to 0.92 (95% CI: 0.77, 1.07) excess patient deaths/1000 patient-days. It should be noted that these incidence estimates represent the rate of excess mortality during the outbreak period (four weeks), while lower incidence estimates result when capturing only early outbreak dynamics (two weeks) or a

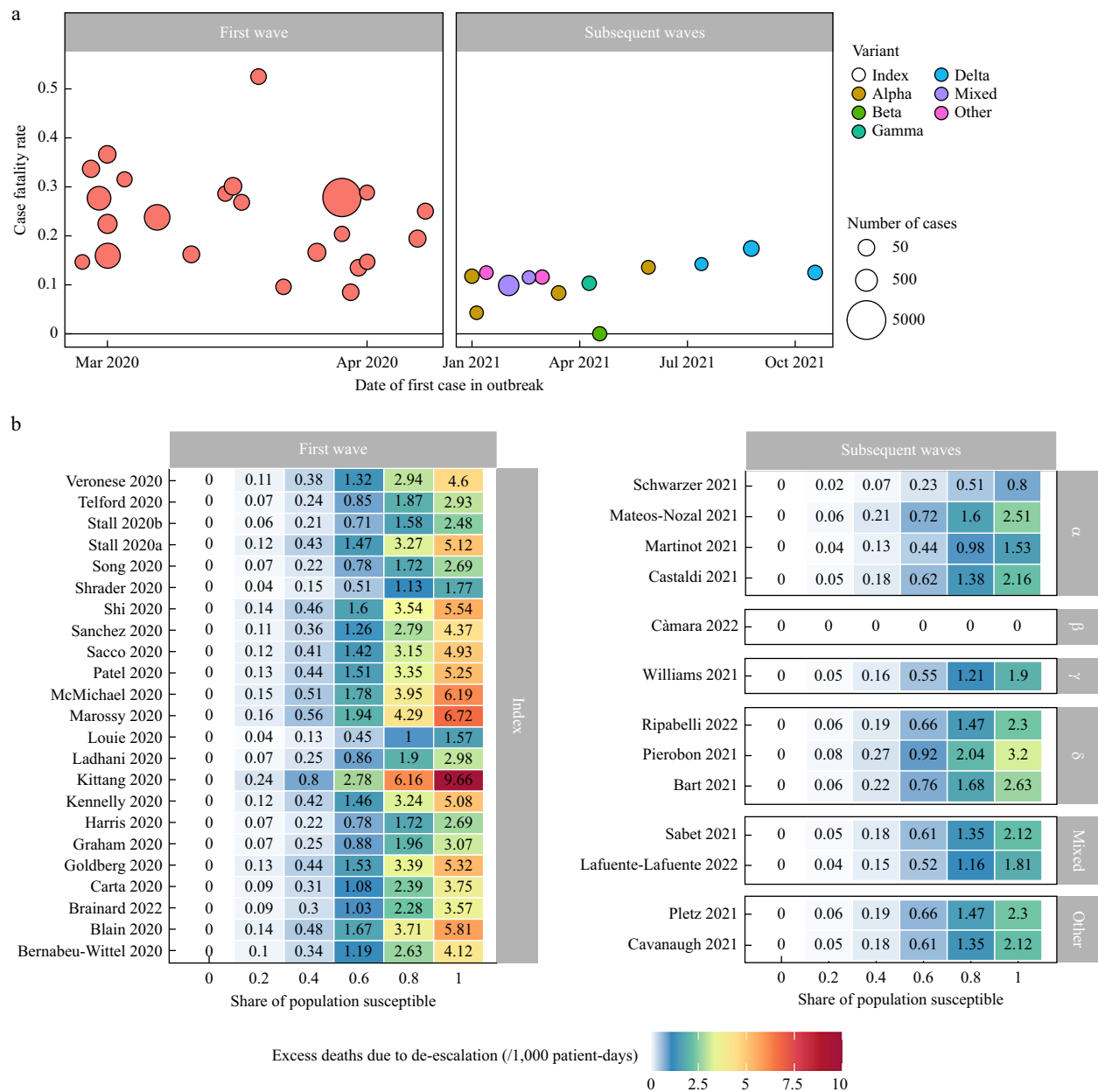


Figure 2. Impacts of de-escalation on excess mortality depend on the case fatality rate (CFR) of COVID-19, which has been highly variable across healthcare settings and over successive pandemic periods. CFRs were estimated from published studies describing nosocomial SARS-CoV-2 outbreaks in aged care facilities (a). Mean excess mortality due to de-escalation was calculated by applying these CFR estimates to the mean excess incidence of nosocomial SARS-CoV-2 infection among hospital patients (b), as estimated by the transmission model. Here, de-escalation includes the de-escalation of both universal masking and single rooms.

timespan exceeding most nosocomial transmission (12 weeks) (Supplementary Figure S7).

Discussion

This study provides estimates of excess nosocomial COVID-19 burden due to control measure de-escalation relative to variable CFR estimates from nosocomial outbreaks over the first several waves of the COVID-19 pandemic. Using an individual-based SARS-CoV-2 transmission model fitted to high-resolution contact data from a French rehabilitation hospital, we found that de-escalating multiple control measures

simultaneously could lead to an exponential increase in SARS-CoV-2 transmission risk relative to de-escalating separate measures independently. However, our model predicts that de-escalating multiple measures is none the less relatively low risk among well-immunized patient populations. When roughly half (40–60%) of the population was susceptible to infection, and when the CFR was representative of outbreaks during the ‘post-vaccine era’, de-escalating both universal masking and single rooms led to <1 excess deaths/1000 patient-days over the outbreak period. However, when the population was wholly susceptible to a variant exhibiting a CFR similar to outbreaks observed during the first wave of the COVID-19 pandemic, de-

escalation led to approximately two to 10 excess deaths/1000 patient-days over the outbreak period. This suggests that the excess burden of COVID-19 mortality due to de-escalation may be more than an order of magnitude greater among populations with high susceptibility to locally circulating variants (i.e., a novel and antigenically distinct variant) relative to populations with moderate to low susceptibility. These findings are consistent with emerging empirical evidence suggesting high attack rates, but limited mortality, in recent nosocomial epidemics occurring during periods of high immunization prevalence and reduced COVID-19 control measure adherence [18–20].

Our results highlight why up to date estimates of population susceptibility to COVID-19 are essential for predicting consequences of control measure de-escalation. However, forecasting nosocomial COVID-19 in any particular setting remains a great challenge due to its multi-factorial nature. Risks of infection and disease depend jointly on the prevalence and virological characteristics of locally circulating variants [21], the demographic profiles of patients and HCWs [22], their immunological histories and individual-level risk factors [23], their behaviours and interactions [24], their access to antiviral therapies [25], and impacts of any IPC measures in place [26]. Notwithstanding epistemic uncertainty underlying how these and other factors combine to influence COVID-19 risk, there is also a lack of data from clinical trials quantifying how the escalation or de-escalation of IPC measures influence epidemiological outcomes [27]. For these reasons, decision-making around hospital infection control often relies on crude estimates of viral importation risk (e.g., estimates of the reproduction number in the community) and population susceptibility (e.g., vaccination histories or serosurveys). In the face of such uncertainty, mathematical modeling has emerged as an important tool to support decision-making around nosocomial COVID-19 risk management, providing in-silico evidence regarding the potential costs and benefits of different infection control strategies [9].

We stress that our results represent estimates of excess COVID-19 burden due to de-escalation in a simulated long-term care hospital, using CFR values from reported outbreaks in aged care facilities published by April 2022 [16,17]. It was deemed inappropriate to meta-analyze these CFR estimates due to inconsistency across studies in terms of the definitions and reporting of COVID-19 cases and deaths. Based on the data available, it was also not possible to estimate levels of susceptibility to infection in each respective population at the start of each outbreak, nor to update model parameters to represent the specific epidemiological characteristics of particular SARS-CoV-2 variants (e.g., transmission rates, incubation periods). For these reasons, our findings do not represent a-posteriori estimates of de-escalation impact for specific outbreaks, settings or pandemic periods. Rather, our findings may serve as a guide to inform de-escalation risk for future waves of SARS-CoV-2, representing estimates of de-escalation impact across a broad range of possible levels of population susceptibility to infection and severe disease. For populations with access to effective antiviral therapies, excess COVID-19 mortality due to de-escalation may be even lower than predicted here, at least in the context of SARS-CoV-2 variants no more virulent than major mid-pandemic lineages such as Alpha and Delta.

Further, it seems likely that estimates of excess death due to de-escalation would be further reduced in the context of the Omicron variant and its various sub-lineages. Although a systematic review of nosocomial SARS-CoV-2 outbreaks since the emergence of Omicron is not (yet) available, there is clear evidence of reduced rates of severe disease and death relative to prior variants of concern, due to both reduced viral pathogenicity and increased population immunity [28,29]. We also note that the control measures implemented in our simulations at baseline are underpinned by assumptions of high efficacy and adherence. This is consistent with findings from a study conducted during the first wave of COVID-19 in a long-term care hospital in Paris, in which the basic reproduction number of SARS-CoV-2 was estimated to drop from approximately 8.7 to 1.3 subsequent to the implementation of multi-modal infection control measures [30]. None the less, while many healthcare facilities have successfully contained or avoided nosocomial SARS-CoV-2 transmission coincident with the implementation of strict IPC measures, many others have continued to experience outbreaks despite a range of theoretically effective measures being firmly in place.

Future work is needed to address a range of outstanding questions regarding risks of infection control measure de-escalation. Key interventions not considered here or in previous work include visitor restrictions, HCW cohorting, and hand-hygiene interventions [10]. Due to a lack of data, it was also not possible to consider economic outcomes, nor secondary impacts of COVID-19 control measures on health-related quality of life. COVID-19 control measures may also influence the transmission dynamics of pathogens other than SARS-CoV-2, including multi-drug-resistant bacteria and other common causes of healthcare-associated infections [31–33]. Finally, it is unclear how generalizable our findings are to acute healthcare facilities globally, particularly those in low- and middle-income settings. For instance, our model assumes sufficient laboratory capacity to return RT-PCR test results within 24 h of symptom onset, and sufficient resources to subsequently isolate positive COVID-19 cases from others in the facility. We also included a 'single room' intervention in our model, because the presence of multi-bedded rooms has been identified as an important risk factor for nosocomial COVID-19, and because many facilities throughout the pandemic have implemented extensive barriers in shared rooms to isolate patients from one another [34]. However, many facilities globally lack even basic IPC resources such as facemasks and alcohol-based hand rub, let alone the capacity and resources needed to test, trace and isolate potentially large numbers of patients and staff.

In conclusion, this study has estimated the excess epidemiological burden associated with de-escalating COVID-19 control interventions in a long-term care hospital. Just as bundling multiple interventions together can create synergistic resilience against nosocomial transmission [35], we show how the simultaneous de-escalation of multiple measures can lead to an exponential increase in SARS-CoV-2 transmission risk. However, impacts of de-escalation in any particular setting depend most importantly on risks of susceptibility to infection and severe disease in that population. Such parameters are not only difficult to estimate but will continue to evolve through future waves of SARS-CoV-2, in turn leading to oscillation between periods where control measures have a large impact on COVID-19 prevention and should be escalated, and those where COVID-19 risk is minimal, prompting de-escalation. This

entails an imperative to optimize health-economic investment in COVID-19 control measure implementation by dynamically reacting to real epidemic risk. Future efforts to optimize COVID-19 control measure implementation will benefit from relevant clinical trial data and improved real-time forecasting of nosocomial SARS-CoV-2 transmission risk.

Author contributions

D.R.M.S., L.O., L.T., M.A. and S.H. conceived the study. A.D. developed the simulation model. R.G. extracted outbreak data. D.R.M.S. developed methodology, conducted analyses, rendered figures and wrote the first draft. All authors contributed to interpreting results and revising the final draft.

Conflict of interest statement

None declared.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jhin.2024.02.020>.

References

- [1] World Health Organization. Infection prevention and control guidance for long-term care facilities in the context of COVID-19: interim guidance. 2021. Available at: https://www.who.int/publications/i/item/WHO-2019-nCoV-IPC_long_term_care-2021.1 [last accessed August 2023].
- [2] Lim RHF, Htun HL, Li AL, Huiling GUO, Kyaw WM, Hein AA, et al. Fending off Delta – hospital measures to reduce nosocomial transmission of COVID-19. *Int J Infect Dis* 2022;117:139–45.
- [3] Baker MA, Rhee C, Tucker R, Badwaik A, Coughlin C, Holtzman MA, et al. Rapid control of hospital-based severe acute respiratory syndrome coronavirus 2 omicron clusters through daily testing and universal use of N95 respirators. *Clin Infect Dis* 2022;75:e296–9.
- [4] Barker RO, Astle A, Spilsbury K, Hanratty B. COVID-19 testing during care home outbreaks: the more the better? *Age Ageing* 2021;50:1433–5.
- [5] Wang C, Song W, Hu X, Yan S, Zhang X, Wang X, et al. Depressive, anxiety, and insomnia symptoms between population in quarantine and general population during the COVID-19 pandemic: a case-controlled study. *BMC Psychiatry* 2021;21:99.
- [6] Farooq S, Tunmore J, Wajid Ali M, Ayub M. Suicide, self-harm and suicidal ideation during COVID-19: A systematic review. *Psychiatry Res* 2021;306:114228.
- [7] Klompas M, Baker MA, Rhee C. Is nosocomial SARS-CoV-2 still worth preventing? *JAMA Netw Open* 2023;6:e2344704.
- [8] Ong LS, Aung AH, Chow A. Remaining agile - post-pandemic prevention of SARS-CoV-2 nosocomial transmission. *J Hosp Infect* 2023;143:224–6.
- [9] Smith DRM, Chervet S, Pinettes T, Shirreff G, Jijón S, Oodally A, et al. How have mathematical models contributed to understanding the transmission and control of SARS-CoV-2 in healthcare settings? A systematic search and review. *J Hosp Infect* 2023;141:132–41.
- [10] Singh BK, Walker J, Paul P, Reddy S, Gowler CD, Jernigan J, et al. De-escalation of asymptomatic testing and potential of future COVID-19 outbreaks in US nursing homes amidst rising community vaccination coverage: a modeling study. *Vaccine* 2022;40:3165–73.
- [11] Smith DRM, Duval A, Pouwels KB, Guillemot D, Fernandes J, Huynh B, et al. Optimizing COVID-19 surveillance in long-term care facilities: a modelling study. *BMC Med* 2020;18:386.
- [12] Smith DRM, Duval A, Zahar JR, Opatowski L, Temime L, Modelling EM-MWGoNS-C-. Rapid antigen testing as a reactive response to surges in nosocomial SARS-CoV-2 outbreak risk. *Nat Commun* 2022;13:236.
- [13] Slayton RB, O’Hagan JJ, Barnes S, Rhea S, Hilscher R, Rubin M, et al. Modeling Infectious Diseases in Healthcare Network (MInD-Healthcare) framework for describing and reporting multidrug-resistant organism and healthcare-associated infections agent-based modeling methods. *Clin Infect Dis* 2020;71:2527–32.
- [14] Duval A, Obadia T, Martinet L, Boëlle PY, Fleury E, Guillemot G, et al. Measuring dynamic social contacts in a rehabilitation hospital: effect of wards, patient and staff characteristics. *Sci Rep* 2018;8:1686.
- [15] Liang M, Gao L, Cheng C, Zhou Q, Uy JP, Heiner K, et al. Efficacy of face mask in preventing respiratory virus transmission: a systematic review and meta-analysis. *Travel Med Infect Dis* 2020;36:101751.
- [16] Hashan MR, Smoll N, King C, Ockenden-Muldoon H, Walker J, Wattiaux A, et al. Epidemiology and clinical features of COVID-19 outbreaks in aged care facilities: a systematic review and meta-analysis. *EClinicalMedicine* 2021;33:100771.
- [17] Hashan MR, Smoll N, Chapman G, King C, Walker J, Kirk M, et al. Epidemiology of COVID-19 outbreaks in aged care facilities during post-vaccine period: a systematic review and meta-analysis. *SSRN* 2022. <https://doi.org/10.2139/ssrn.4181714>.
- [18] Gopal Rao G, Jinjika S, James D, Mukombe N, Patel B, Chietcheu A, et al. Nosocomial outbreak in a respiratory ward caused by the SARS-CoV-2 Omicron BA.5.2.1 subvariant associated with non-severe illness in vaccinated patients. *Epidemiol Infect* 2023;151:e171.
- [19] Dave N, Sjöholm D, Hedberg P, Ternhag A, Granath F, Verberk JDM, et al. Nosocomial SARS-CoV-2 Infections and Mortality During Unique COVID-19 Epidemic Waves. *JAMA Netw Open* 2023;6:e2341936.
- [20] Pak TR, Rhee C, Wang R, Klompas M. Discontinuation of universal admission testing for SARS-CoV-2 and hospital-onset COVID-19 infections in England and Scotland. *JAMA Intern Med* 2023;183:877–80.
- [21] Vihta KD, Pouwels KB, Peto TEA, Pritchard E, House T, Studley R, et al. Omicron-associated changes in SARS-CoV-2 symptoms in the United Kingdom. *Clin Infect Dis* 2022;76:e133–41.
- [22] O’Driscoll M, Ribeiro Dos Santos G, Wang L, Cummings DAT, Azman AS, Paireau J, et al. Age-specific mortality and immunity patterns of SARS-CoV-2. *Nature* 2021;590:140–5.
- [23] COVID-19 Forecasting Team. Past SARS-CoV-2 infection protection against re-infection: a systematic review and meta-analysis. *Lancet* 2023;401:833–42.
- [24] Temime L, Gustin MP, Duval A, Buetti N, Crépey P, Guillemot D, et al. A conceptual discussion about the basic reproduction

- number of severe acute respiratory syndrome coronavirus 2 in healthcare settings. *Clin Infect Dis* 2021;72:141–3.
- [25] Cao Z, Gao W, Bao H, Feng H, Mei S, Chen P, et al. VV116 versus nirmatrelvir-ritonavir for oral treatment of Covid-19. *N Engl J Med* 2023;388:406–17.
- [26] Haller S, Güsewell S, Egger T, Scanferla G, Thoma R, Leal-Neto OB, et al. Impact of respirator versus surgical masks on SARS-CoV-2 acquisition in healthcare workers: a prospective multicentre cohort. *Antimicrob Resist Infect Control* 2022;11:27.
- [27] Jafari Y, Yin M, Lim C, Pople D, Evans S, Stimson J, et al. Effectiveness of infection prevention and control interventions, excluding personal protective equipment, to prevent nosocomial transmission of SARS-CoV-2: a systematic review and call for action. *Infect Prev Pract* 2022;4:100192.
- [28] Ward IL, Bermingham C, Ayoubkhani D, Gethings OJ, Pouwels KB, Yates T, et al. Risk of covid-19 related deaths for SARS-CoV-2 omicron (B.1.1.529) compared with delta (B.1.617.2): retrospective cohort study. *BMJ* 2022;378:e070695.
- [29] Sigal A. Milder disease with Omicron: is it the virus or the pre-existing immunity? *Nat Rev Immunol* 2022;22:69–71.
- [30] Shirreff G, Zahar JR, Cauchemez S, Temime L, Opatowski L. SARS-CoV Em-MwgotNMo. Measuring basic reproduction number to assess effects of nonpharmaceutical interventions on nosocomial SARS-CoV-2 transmission. *Emerg Infect Dis* 2022;28:1345–54.
- [31] Lastinger LM, Alvarez CR, Kofman A, Konnor RY, Kuhar DT, Nkwata A, et al. Continued increases in the incidence of healthcare-associated infection (HAI) during the second year of the coronavirus disease 2019 (COVID-19) pandemic. *Infect Control Hosp Epidemiol* 2023;44:997–1001.
- [32] Rosenthal VD, Myatra SN, Divatia JV, Biswas S, Shrivastava A, Al-Ruzzieh MA, et al. The impact of COVID-19 on health care-associated infections in intensive care units in low- and middle-income countries: International Nosocomial Infection Control Consortium (INICC) findings. *Int J Infect Dis* 2022;118:83–8.
- [33] Smith DRM, Shirreff G, Temime L, Opatowski L. Collateral impacts of pandemic COVID-19 drive the nosocomial spread of antibiotic resistance: a modelling study. *PLoS Med* 2023;20:e1004240.
- [34] Leal J, O’Grady HM, Armstrong L, Dixit D, Khawaja Z, Snedeker K, et al. Patient and ward related risk factors in a multi-ward nosocomial outbreak of COVID-19: Outbreak investigation and matched case-control study. *Antimicrob Resist Infect Control* 2023;12:21.
- [35] Pincock T, Bernstein P, Warthman S, Holst E. Bundling hand hygiene interventions and measurement to decrease health care-associated infections. *Am J Infect Control* May 2012;40:S18–27.