Quantifying the COVID #19 endgame: Is a new normal within reach?

FAST TRACK

Quantifying the COVID-19 endgame: Is a new normal within reach?

Hazhir Rahmandad* and John Sterman

Abstract

Eradication of COVID-19 is out of reach. Are we close to a "new normal" in which people can leave behind restrictive non-pharmaceutical interventions (NPIs) yet face a tolerable burden of disease? The answer depends on the ongoing risks versus communities' tolerance for those risks. Using a detailed model of the COVID-19 pandemic spanning 93 countries, we estimate the biological and behavioral factors determining the risks and responses, and project the likely course of COVID-19. Infection fatality rates have fallen significantly due to vaccination, prior infections, better treatments, and the less severe Omicron variant. Yet based on their estimated tolerance for deaths, most nations are not ready to live with COVID-19 without any NPIs. Across the world the increased transmissibility of Omicron, combined with the decay of immunity, leads to repeated episodes of reinfections, hospitalizations, and deaths, complicating the emergence of a new normal in many nations.

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Introduction

The COVID-19 pandemic disrupted nearly every aspect of life around the world, resulting in more than 6.3 million officially recognized deaths by June 2022 per the Johns Hopkins dashboard (Dong *et al.*, 2020); overloaded hospitals, burnout among frontline health workers, and delayed care for non-COVID-19 conditions; costly business shutdowns, supply chain disruptions, and unemployment; interruptions to education; aggravated political polarization; and large increases in stress, mental health issues, and long-COVID, among others. Moreover, the pandemic's global extent, substantial asymptomatic transmission, gradual loss of immunity from prior infection and vaccination, emerging variants, lack of access to vaccines (primarily in developing nations), and vaccine hesitancy mean eradication is highly unlikely (Kofman *et al.*, 2021). In response to these harms and challenges

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the global community made impressive progress in vaccine design and administration (Kashte *et al.*, 2021), new drug development (Borah *et al.*, 2021), and non-pharmaceutical interventions (NPIs) including masking, testing, voluntary isolation, and mandated actions that kept the toll of the pandemic well below what it would have been otherwise. That progress, along with the emergence of a milder dominant variant of SARS-Cov-2, Omicron, gives hope that a transition to living with COVID-19 is feasible and imminent. People around the world are eager to move into a "new normal" in which life largely returns to pre-pandemic conditions, with tolerable, low rates of infection, hospitalization, and death.

Any new normal will entail an ongoing burden of disease and some changes to our routines compared to the pre-pandemic era. Whether, and when, a community is willing to bear those harms and costs depends on the magnitude of the harms and costs and its willingness to accept the ongoing burden of disease and death. Both are highly uncertain. The burden of COVID-19 during the acute phase of the pandemic, from roughly March 2020 through spring 2022, varied dramatically across countries, with morbidity and mortality varying by more than a factor of 100. Tolerance for economically and socially costly NPIs such as lockdowns, remote schooling, social distancing, and mandatory masking also differed substantially across nations. These dramatic variations cannot be explained by differences in the virus, demographics, or other biological conditions, but depend on the behavioral responses of governments, businesses, and the public (Covid-National-Preparedness-Collaborators, 2022; Lim and Rahmandad, 2022). Similarly, assessing what lies ahead requires models that integrate biological factors such as transmissibility, virulence, and the duration of immunity after infection or vaccination with social and behavioral processes such as the availability and allocation of testing and treatment resources, how people and governments assess the risk from COVID-19, how perceived risk alters individual behavior and mandatory policies including distancing, self-quarantine, mandatory lockdowns, and vaccine uptake, and how these responses may erode in the face of growing "pandemic fatigue." The task is complex, but inevitable: whether using formal or mental models, policy makers and citizens have to plan for the coming months and years. From the timing of a wedding to government budgeting, many plans require assumptions about what lies ahead. Absent more formal projections, important decisions will be based on inconsistent intuitions and politics, may diverge from biologically and behaviorally feasible options, and disappoint or mislead.

To address these issues, we first provide a simple model to develop intuition for the key factors relevant to understanding long-term COVID-19 dynamics. We then build on an existing and more detailed dynamic model of COVID-19 to project the long-term (more than a year ahead) evolution of COVID-19 for all nations for which enough data exist to estimate the parameters, a total of 93 nations covering ~5 billion people (Rahmandad *et al.*, 2021).

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The model endogenously integrates the biological, epidemiological, social, and behavioral factors above, and includes vaccination, risk perceptions and response, adherence fatigue, three distinct variants, and other factors.

Methods

To understand long-term COVID-19 trajectories we start with a very simple Susceptible-Infected-Removed-Susceptible (SIRS) model. The model yields intuition about the dynamics but is too simple to provide useful, empirically grounded projections. We then build on recent research suggesting that long-term projections for the pandemic are feasible and require mechanistic (causal) models in which community responses (e.g. adopting NPIs) respond endogenously to the evolution of the disease (Rahmandad *et al*., 2022). Specifically, we expand the model described in Rahmandad *et al*. (2021), an extension of the Susceptible-Exposed-Infectious-Removed (SEIR) model that incorporates endogenous behavioral responses and many other operational issues that condition the evolution of the pandemic.

The project is ambitious and entails grappling with many uncertainties. Some can be quantified using historical data. Specifically, we estimate the likely actual number of infections and deaths based on reported data and testing rates, infection fatality rates (IFRs), the duration of immunity acquired from vaccination and infection, the effectiveness of vaccines against transmission and severe disease, the impact of existing variants on transmission, severity, and vaccine effectiveness, and the impact of seasonal weather on transmission. We also estimate country-specific response functions quantifying risk perceptions and the responsiveness of NPIs to perceived risk, adherence fatigue, treatment capacity and effectiveness, and improvements in treatment over time.

Nevertheless, the model omits or simplifies many potentially relevant factors. Computational constraints and data limitations prompt us to keep the model aggregated (a single SEIR structure per country); we ignore sub-communities, travel, and distinct types of NPIs adopted by nations, including, among others, testing requirements, mask mandates, travel bans, remote schooling, and stay-at-home restrictions. More importantly, although the model allows us to examine the impact of new variants and differences in their impact on vaccines, and the impact of new drugs, it is impossible *ex ante* to know if and when new variants might emerge and their impacts on these factors. As such, we offer aggregate (country-level) projections based on what is known today. Nevertheless, the results offer insight into a new normal that is internally consistent and informed by more than 2 years of data across the globe.

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Intuitions from a simple model

To understand the likely dynamics of COVID-19 after it becomes endemic, we first consider a simple SIRS model in which loss of immunity returns people to the Susceptible state. The model is well-known (Murray, 2002) with the following formulations capturing the dynamics of stock variables (S, I, and R modeled as fractions of total population; extension to SEIRS is straightforward and offers no additional qualitative insights):

$$\frac{\mathrm{d}S}{\mathrm{d}t}=\frac{R}{\tau_R}-\beta SI;\ \frac{\mathrm{d}I}{\mathrm{d}t}=\beta SI-\frac{I}{\tau_I};\ \frac{\mathrm{d}R}{\mathrm{d}t}=\frac{I}{\tau_I}(1-f)-\frac{R}{\tau_R};\ 1=S+I+R. \tag{1}$$

Here β represents the transmission rate, τ_I and τ_R the average duration of disease and immunity, and f the IFR. Noting that f is very small (<0.01), the long-term dynamics can be approximated as a constant population with equal steady-state flows among the three stocks. Solving for the resulting equilibrium flows, the long-term per capita death rate in the endemic state, D, is:

$$D=\frac{fI}{\tau_I}=\frac{f(R_0-1)}{R_0(\tau_I+\tau_R)}, \tag{2}$$

where the basic reproduction number, $R_0=\beta\tau_I$. The formulation assumes the transmission rate, β, is constant. We now extend the model to account for risk-driven behavioral responses that may reduce transmission rates due to the perceived risk of death (Funk *et al.*, 2010). Specifically, assuming β responds to the perceived death rate $D^{'}$ according to $\beta=\frac{\beta_0}{1+\frac{D^{'}}{\alpha}}$, and noting that in equilibrium $D^{'}=D$, the steady-state death rate with behavioral response is:

$$D=\frac{f(R_0-1)}{R_0(\tau_I+\tau_R)+f/\alpha} \tag{3}$$

The parameter α represents the tolerable risk level (in deaths per capita per day) in the community. Smaller values of α represent communities willing to adopt NPIs at lower levels of risk.

To develop intuition into the potential outcomes, consider two distinct regimes. First, if responsiveness and death rates are both high relative to regular transmission rates, $R_0(\tau_I+\tau_R)\ll\frac{f}{\alpha}$, as was the case early in the pandemic, then the steady-state death rate is largely a function of responsiveness and the basic reproduction number, but not the IFR. The resulting death $D\sim\alpha(R_0-1)$. Consider plausible values for parameters early

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in the pandemic: $R_0 \sim 3$; $\tau_R \sim 100$; $\tau_I \sim 10$; $f = 0.01$; α should be estimated for each country but one death per million per day (α~1e−6) is plausible for modestly responsive countries. Then $R_0(\tau_I + \tau_R)\,(= 330) \ll f/\alpha (= 10000)$ and thus D ≈ 2e−6 and is independent of the IFR. The decoupling of death rates from the IFR may be surprising, and points to the importance of the behavioral response function. When communities are willing to change their behavior significantly in response to perceived risks, observed death rates reflect the level of deaths the community is willing to tolerate. Deaths will not be higher even if the disease is deadlier because people will adopt NPIs sufficient to stabilize death rates at the tolerable level; likewise, deaths will not be lower even if the disease is less deadly as people respond by relaxing the NPIs, thus increasing transmission and deaths until the tolerable level is reached. The delays in this critical negative feedback process mean fluctuations are likely (and have been observed), even without the introduction of new variants, vaccines, or new treatments.

Now consider a second regime in which low responsiveness to the risk of death (large α) or a low IFR (small f) weakens the behavioral responses. As the term f/α approaches zero, the steady-state death rate becomes a linear function of the IFR:

$$D \sim \frac{f(R_0 - 1)}{R_0(\tau_1 + \tau_R)}. \tag{4}$$

For example, with $\alpha \approx$ 1e−5 and $f \approx$ 1e−3, death rates increase to $D \approx$ 6e−6 per day, higher than before despite significantly lower IFR, because behavioral responses are not strong enough to reduce transmission rates. The second regime is more common in younger, low-income, countries as well as in the later stages of the pandemic after IFR has come down due to vaccines and treatments. This regime can also arise despite a higher IFR if pandemic fatigue causes individuals and governments to become less responsive to deaths, as appears to characterize some nations in 2022. In such settings new treatments that bring down the IFR would significantly reduce the long-term burden of the disease. Moreover, in this regime deaths drop as the duration of immunity grows, increasing the value of repeated vaccination (boosters) and vaccines designed to confer more durable immunity. The result also underscores the importance of accurately quantifying the duration of immunity after infection and vaccination (τ_R) to assess the outcomes under any new normal.

The basic reproduction number ($R_0 = \beta_0 \tau_I$ in the simple model) matters in both regimes, but less so in the second regime and especially when it grows above a value of 1. In the second regime, the death rate under higher reproduction numbers simplifies to $D \sim f/(\tau_I + \tau_R)$. Therefore, a rise in the basic reproduction number, arising for example from the emergence of new, more

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transmissible variants, may increase the long-term burden of disease, but less so at higher basic reproduction numbers when a true new normal with limited behavioral response is established.

Finally, responsiveness to risk, $1/\alpha$, directly reduces the burden of disease in the first regime. The reduction comes at some modest costs in the form of reduced contacts and social interactions relative to pre-pandemic levels, as the result of, for example, voluntary or mandated isolation, restrictions on activities, masking, and other NPIs. The reduction in these activities relative to normal is given by:

$$\frac{1}{1+D/\alpha}=\frac{\tau_I+\tau_R+f/(\alpha R_0)}{\tau_I+\tau_R+f/\alpha}. \tag{5}$$

The costs of the NPIs are nonlinear, and only notable if behavioral response is strong and the basic reproduction number high. The increased costs due to increasing R_0 with new variants may be exceedingly challenging to some countries that were initially very successful in containing the burden of disease through proactive adoption of NPIs at very low death rates (e.g. China's zero-tolerance policy, where the spread in early 2022 of the much more contagious Omicron variant led to massive mandatory lockdowns with more limited success compared to the first wave in 2020).

The simple SIRS model provides a framework to consider the determinants of outcomes under a new normal. With community-specific estimates for R_0, α, τ_R, f, one could use the results above to project long-term mortality and disruptions to life in a new normal. Estimates of these parameters, however, are not readily available for many nations, and have been changing over time as data accumulate and with the advent of vaccinations, better treatments, and new variants. Moreover, the steady-state equilibrium assumption is problematic. The pandemic has so far unfolded in distinct waves, due to the delays in risk perception and response (Rahmandad *et al.*, 2021; Lim and Rahmandad, 2022) as well as the impact of seasonality on transmission. Average outcomes in nonlinear oscillatory systems are different from the steady-state approximation. These limitations call for a more detailed model that allows for reliable estimation of relevant parameters and can endogenously capture the dynamics including potential future waves.

A detailed model

Our extended model builds on our earlier work (Rahmandad *et al.*, 2021). Here we provide a brief overview, focusing on the extensions and modifications to the model made here. Figure 1 presents an overview of the model, showing the main stock and flow structure and a high-level representation of

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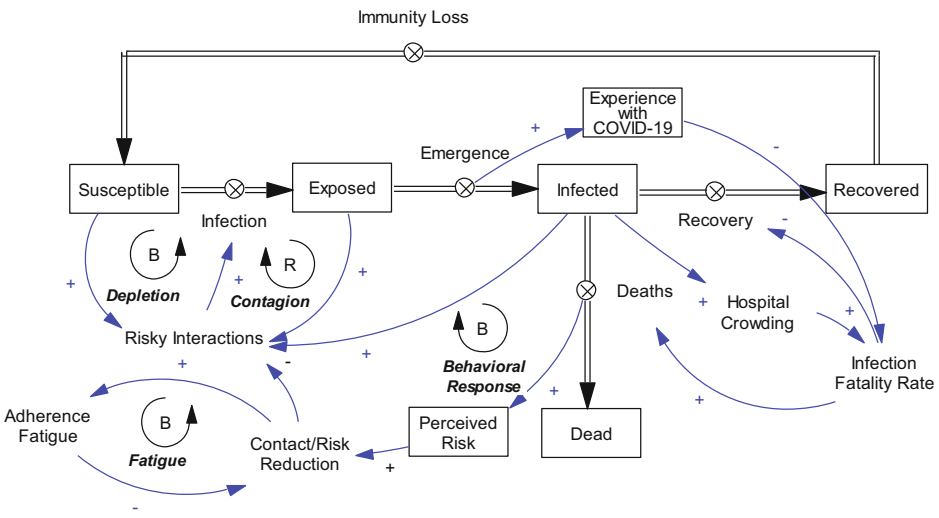

Fig. 1. Overview of model structure and key feedback loops. The actual model is more complex and distinguishes populations based on the following dimensions: vaccination/prior exposure (naïve, recently vaccinated, previously exposed/vaccinated); testing (tested, untested); hospitalization; and symptoms (asymptomatic, symptomatic) [Color figure can be viewed at wileyonlinelibrary.com]

the critical feedbacks. We refer interested readers to the previous paper and model documentation for details.

Disease states and flows

The model captures all nations that provide data sufficient to estimate the parameters. We estimate the parameters simultaneously across all countries considered to ensure consistency across country-level estimated parameters. The model backbone is the classical SEIRS model (the SEIR sequence followed by a return to the Susceptible state after an immunity period) disaggregated to distinguish the following states after exposure: pre-symptomatic, pre-detection, post-detection, and removed. We disaggregate further to account for individuals in different states capturing their (i) test status (tested or not), (ii) treatment status (hospitalized or not), and (iii) vaccination and prior immunity status (three states including naïve, recently vaccinated, or having residual protection against severe disease due to past vaccine or infection). The latter factor is new in this version of the model because the original model was completed before vaccines were available. Loss of immunity is also new in this version of the model as there were no data on immunity loss when the original model was developed. Although the model retains the classical compartment-model paradigm in the SEIR tradition, we model the distribution of disease acuity across the infected compartments using a (zero-inflated) Poisson distribution that captures the heterogeneity in disease severity and symptoms expected for individuals in each stock. We track the distribution of severity analytically (Rahmandad and Hu, 2010), which allows us to model the behavioral decision processes health care

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providers and hospitals use to allocate testing and treatment capacity to the more severe cases, quantify demand for testing based on symptom severity, reduce the underlying acuity with vaccines, and determine the IFR as a function of the state individuals are in. The analytical acuity levels also depend on the dominant variant. For example, the estimation results show that Omicron reduced acuity compared to prior variants such as Delta. A new feature in the current model is the explicit estimation of the fraction of the population covered by testing as a function of testing rates. Limited testing capacity in many nations has significantly limited the available data, often to a few affluent and urban centers, omitting large areas of some countries from official statistics. We use per capita testing rates to capture the undersampling in an empirically estimated equation and assume the infection dynamics resemble what is observed in the subset but not reflected in official case counts.

Infections and deaths

The flow of new infections depends on contacts between the susceptible population and those infected, with the possibility that individuals have different contact rates and hazard rates of infection given contact depending on the stage of the disease (e.g. pre- vs. post-symptomatic) as well as test and hospitalization status. To these we add the impacts of endogenous changes in behavior (discussed below), weather conditions based on Xu *et al.* (2021), and vaccine efficacy, which depends on the dominant variant.

Infected individuals may get tested based on the severity of their symptoms, the availability of tests, and the demand for testing from those without COVID-like symptoms. We estimate how the availability of tests (per capita) may exclude a fraction of population from testing and thus from being captured in official case counts. The demand for testing from those without the disease depends on people's perceptions of risk, which we model as an increasing function of recent official cases. Those with more severe symptoms are more likely to go to or be taken to a hospital. The burden of COVID-19 patients can overwhelm hospital and health care capacity, resulting in care rationing and delayed treatment for those with COVID-19 and those with other conditions. In the model, the greater the demand for treatment relative to capacity, the more severe COVID-19 symptoms must be to be admitted for treatment. Thus, the IFR depends endogenously on whether treatment facilities are overloaded, the age structure of the population, and the efficacy of treatments. Specifically, the IFR depends on an age-adjusted country-level baseline, the fraction of people able to receive treatment and their acuity level, and the efficacy of treatments, which itself improves following a learning curve (see below). The IFR also depends on the dominant circulating variant as well as the state of the individuals, particularly

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whether they are naïve to the virus, recently vaccinated, or have a degree of immunity from vaccines or prior infection.

Behavioral feedbacks

Three behavioral feedback processes are critical to the dynamics: behavioral responses to risk, adherence fatigue, and IFR reduction. First, regarding responses to risk, in classic SEIR models the contact frequency and probability of transmission given a contact with an infectious individual are constants. In reality, as discussed above, people alter their behavior based on the risk of harm they perceive from the disease. Prior work shows that these feedbacks have a first-order impact on the dynamics compared to, for example, the structure of the contact network among individuals (Rahmandad and Sterman, 2008). In the context of COVID-19, higher levels of perceived risk, including the likelihood of infection and the likelihood of severe disease or death given infection, lead people to adopt NPIs including self-isolation, social distancing, and improved hygiene (handwashing, masking), and to support government actions mandating such measures. Risk perception is estimated as a function of recent death rates, with an asymmetric delay time for upward versus downward adjustment of perceived risk. Second, adherence fatigue is captured as a reduction in the magnitude of the behavioral responses to risk when those responses have been actively applied in the recent months. The more people have engaged in NPIs, the stronger the pressure to reopen businesses and schools and cut back on NPIs that are economically, socially, and psychologically costly. In the model, a given level of perceived risk elicits a stronger behavioral response initially, but responses to the same level of perceived risk become weaker as the cumulative costs of NPIs rise. Finally, health care providers have learned over time how to better care for COVID-19 patients. Such learning includes drugs (e.g. Remdesivir, Dexamethasone, Paxlovid, and other anti-viral and anti-inflammatory treatments), improved non-pharmaceutical treatments (e.g. proning, better ventilator protocols, better diagnostics for patient condition), and reduced interactions among those most at risk through use of personal protective equipment and better protocols. We capture such developments using a standard learning curve in which the IFR falls by a given fraction for each doubling of cumulative deaths.

Vaccines and variants

We expanded the original model to include vaccines and new SARS-Cov-2 variants. Table 1 summarizes the most important modifications and parametric assumptions informing those changes and the estimation of their strength. During the historic period in the simulations the vaccination rate is given by the data. In the projections, vaccine adoption is modeled using a

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Table 1. New model components and key formulations

Mechanism	Equations ("*" identifies estimated parameters)	Eq no.
The fraction of the population with access to testing (and thus captured in official statistics), f_t, is a function of current per capita testing rates, T, with coefficients α^* and β^* estimated (the latter is assumed to be below 1)	$f_t = \mathrm{Min}\left(1, \alpha^* T^{\beta^*}\right)$	6
A member of the population can be in one of 3 stock and flow chains: (1) not vaccinated or infected, i.e. "Naïve" ; (2) Recently vaccinated, "Vx"; (3) Others, "NVx". Members of the Vx group eventually lose the degree of immunity conferred by vaccination with a third order delay of τ^*_{Vx}, and re-enter the susceptible NVx group. NVx individuals who are infected and recover remain fully immune for an average of τ^*_{NVx} and then flow back to the susceptible state	τ^*_{Vx} τ^*_{NVx}	7
Vaccinations are given by the historic data. Projected vaccinations continue based on historic capacity and saturate at a maximum. The maximum vaccination fraction (V_{Max}) is estimated based on data for the cumulative vaccinated fraction of the population to date (V_{Cml}) fitted to a generalized logistic curve	Estimation: $V_{\mathrm{Cml}}(t) = \frac{k^*}{(c^* + \exp^{-B^*(t-q^*)})^{\frac{1}{v^*}}}$ $V_{\mathrm{Max}} = \mathrm{Max}\left(V_{\mathrm{Cml}}(\mathrm{last}), \frac{k^*}{c^{*\frac{1}{v^*}}}\right)$	8
Acuity is modeled as a zero-inflated Poisson distribution, with average acuity, a, estimated for the naïve population with original variant a^*_0 and adjusted by vaccination status (VS; $e^*_{\mathrm{avs}} = 1$ for "Naïve") and variant impact on acuity ($e^*_{\mathrm{avt}}[\mathrm{Vrn}]$). Delta is assumed to be similar to the original variant; Omicron's impact on severity is estimated.	$a = a^*_0 e^*_{\mathrm{avs}}[VS] e^*_{\mathrm{avt}}[Vrn]$	9
The impacts of vaccination on transmission are captured as a multiplier but only affects the recently vaccinated (r_{vx}) to capture the fading efficacy of vaccination and past infection over time. The effect depends on variants through t^*_{vr} (estimated for both Delta and Omicron) capturing the potential reduction in vaccine efficacy with new variants	$r_{\mathrm{vx}} = 1 - 0.1 t^*_{\mathrm{vr}}[\mathrm{Vrn}]$	10
Variants directly affect transmission rates through a multiplicative function (r_{vr}) with each new variant potentially increasing the transmission rate over the previous one	$r_{\mathrm{vr}} = 1 + \sum_{\mathrm{Vrn}} r^*_{\mathrm{vr}}[\mathrm{Vrn}] - 1$	11

*Denotes parameters that are estimated.

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generalized logistic curve estimated separately for each nation based on the vaccination data for that nation, with an estimated saturation point constrained to be no more than 95 percent of the population. Future vaccination rates are bounded by historical vaccination capacity and allow nations to reach and maintain the estimated maximum vaccination rate. We do not distinguish between different types of vaccines and assume boosters will be administered to keep the vaccinated fraction of population freshly boosted (subject to historical maximum capacity). Relevant parameters relating to vaccine efficacy should be seen as averages across the globe rather than specific to each country.

We explicitly model the three most important variants through spring 2022: the initial strain, Delta, and Omicron, with country-specific dates for the introduction of each selected from data (from covariants.org) or, absent introduction date data, estimated with the other parameters so as to fit available data including cases. New variants gradually displace prior dominant strains, altering the parameters affecting transmissibility, vaccine effectiveness, and acuity. For example, compared to Delta, Omicron is more transmissible, less susceptible to most vaccines, and leads to lower acuity levels and more asymptomatic cases. The introduction of vaccines, and the emerging evidence on the duration of protection against severe disease conferred by infection, led to additional disaggregation of the model to distinguish between individuals who are COVID-naïve (those who have neither been vaccinated nor previously infected), the recently vaccinated, and those who have recovered from infection or were vaccinated less recently. That disaggregation enables us to estimate the extent to which protection against (re) infection dissipates as more time passes since recovery or vaccination.

Estimation

The model is estimated across all nations for which the data needed to estimate the parameters are available, a total of 93 nations spanning ~4.92 billion people. Estimation is pursued by matching model predictions against time series data on reported cases and deaths. We use a negative binomial likelihood function to account for excess dispersion and autocorrelation. Most of the data is procured from the Our World in Data (OWID) site (Ritchie *et al.*, 2020), which gets its case and death data from the John's Hopkins University Portal (Dong *et al.*, 2020). Estimation is augmented by including, for each nation, excess deaths that are not officially attributed to COVID-19 (from *The Economist* magazine's estimates; Solstad, 2022) to account for unreported deaths. Other model parameters are estimated, except for the date Omicron arrived in each nation (given by data) and the residence times in the exposed and infected compartments (the mean emergence time and duration of disease), as these are well constrained by prior

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research. The parameters that are likely to vary across nations are estimated at the country-level using a hierarchical Bayesian framework (Gelman and Hill, 2006) that ensures the country-level estimates are consistent with one another, that is, have variances that are in line with expectation. Parameters that are primarily determined by biological factors, such as the initial age-adjusted IFR, are expected to have low cross-country variance, while factors that are strongly conditioned by social and behavioral factors, such as those governing risk perceptions and responsiveness to risk, are expected to have higher cross-country variance.

The projected course of the pandemic from a deterministic simulation model is bound to diverge from observed data over the more than 2 years since COVID-19 emerged. From holidays to mass gatherings, transmission rates change as a result of many factors not captured in the model. The presence of such unobserved variations will cause the states in the model to gradually drift away from the data over time. More problematic, such drift may lead to biased estimates of parameters for important processes such as behavioral responses to risk. The basic solution to this general problem is to "reset" the state variables based on observed data to correct for the impact of unobserved process noise and other factors excluded from the model (Eberlein, 2015). Prior research shows that forecasting performance across a wide range of COVID-19 models is improved when state-resetting is included (Rahmandad *et al.*, 2022). Formal state resetting methods such as Kalman filtering and particle filtering (Cazelles and Chau, 1997) recognize that noise in a system can cause the state variables to drift away from the best empirical values for them even if the model is correctly specified (for an intuitive example, see Forrester, 1961, Appendix K). However, Kalman and particle filtering in a model of this complexity are computationally very costly and thus, as a practical matter, infeasible. We therefore adopt a heuristic approach in which we multiply transmission rates by the recent ratio of observed to expected (model-based) reported cases, effectively resetting states based on the data to account for drivers of infection not captured in the model. The adjustment aligns the model with the data and reduces the risk of biased parameter estimates.

The heuristic approach for state resetting also offers an important additional benefit: the time series for the ratio of the data on reported cases to the expected (model-based) reported cases provides an estimate of the patterns of variation in the course of the epidemic not captured in the model. These patterns, including their mean, variance, and autocorrelation structure can then be used to specify random variables that can be introduced to model projections to quantify future uncertainty in model predictions. We operationalize this approach by fitting a nonlinear auto-correlated noise formulation (the equations for $N_P(t)$ below) to the observed ratio in the primary calibration (data for $N_P(t)$ from May 2020 until March 2022). We then utilize the estimated process noise structure (the parameters $\theta_1^* - \theta_5^*$ for each

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country) to generate process noise used in projections where data are unavailable, also informing the uncertainty in projections. Specifically, the sequence is formulated as follows:

$$N_P(t) = \mathrm{e}^{N_c(t)} \tag{12}$$

$$\frac{\mathrm{d}N_C(t)}{\mathrm{d}t} = w(t)N_W(t) + \frac{\theta_1^* - N_C(t)}{\theta_2^*} \tag{13}$$

$$w(t) = \mathrm{Min}\left(\frac{1}{e^{\theta_3^* + \theta_4^* N_C(t)}}, 1\right) \tag{14}$$

$$N_W(t) \sim \mathrm{Normal}\left(0, \theta_5^*\right). \tag{15}$$

In principle Markov Chain Monte-Carlo methods could be used to estimate parameter uncertainty, as done in the original study for country-level parameters (Rahmandad *et al.*, 2021). However, the focus of the current calibration is on global parameters (i.e. those shared across countries, such as variant transmissibility and immunity loss time). Due to the high dimensionality of the parameter space and the risk of over-confidence in estimating parameter uncertainty for global parameters we do not attempt to estimate parameter uncertainty. The online supplement provides additional explanation.

Results

The parameter estimation results for the full model, summarized in Table 2, are based on data available through April 19, 2022. Table 2 lists the estimated values of the more important global parameters with country-specific parameters provided in the online documentation. Table 2 also reports the elasticities of cumulative cases and deaths with respect to each estimated parameter in simulations through the end of 2023. The elasticities inform the robustness of the results to uncertainty and potential bias in the estimated parameters: a low (high) elasticity indicates low (high) sensitivity of cumulative cases and deaths to variations in the parameter. High elasticities also suggest which parameters, and the model structure in which they are embedded, would be fruitful directions for more detailed empirical studies and modeling.

A few results are notable. First, the time constants for the loss of immunity after vaccination or infection are short, about 2–4 months. Longer immunity periods would reduce estimates for cumulative cases and deaths, with moderate elasticity values (e.g. case and death elasticities to τ_{Vx}^* are −0.20 and − 0.09, respectively). Reductions in acuity due to past exposure and especially recent vaccination are large ($e_{\mathrm{avs}}^*[\mathrm{NVx}]$=0.60; $e_{\mathrm{avs}}^*[\mathrm{Vx}]$=0.21) and

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Table 2. Estimated common parameters for new model components

Parameter	Estimate	Elasticity of cumulative cases	Elasticity of cumulative deaths	Explanation
α^*	1060 day	−0.03	−0.08	Scaling factor for test coverage
β^*	0.70	0.08	0.19	Exponent informing test coverage fraction
τ^*_{Vx}	54.0 day	−0.20	−0.09	Immunity duration for vaccinated
τ^*_{NVx}	112.0 day	−0.20	−0.11	Immunity duration after natural infection
e^*_{avs}[NVx]	0.60	−0.32	0.50	Impact of prior infection on severity
e^*_{avs}[Vx]	0.21	−0.02	0.05	Impact of recent vaccination on severity
e^*_{avt}[Omicron]	0.56	−0.35	0.52	Impact of Omicron on severity
t^*_{vr}[Delta]	−0.19	0.03	0.01	Reduction in vaccine effectiveness due to Delta
t^*_{vr}[Omicron]	−0.80	0.11	0.04	Reduction in vaccine effectiveness due to Omicron
r^*_{vr}[Delta]	2.98	0.27	0.32	Increase in transmission due to Delta
r^*_{vr}[Omicron]	1.17	0.10	0.08	Increase in transmission due to Omicron

account for significant reductions in the IFR (to 0.32 and 0.03 relative to the naïve population).

We also find a significant reduction in the severity of Omicron, with the Omicron IFR falling by as much as 73 percent compared to prior variants. The reductions in acuity significantly reduce the severity of cases and the likelihood of death. Lower acuity also increases the fraction of asymptomatic cases, which reduces the ascertainment rate (the fraction of actual cases detected). Assuming current testing rates continue, our model projects a larger fraction of cases will go undetected and unreported in official data in the coming months and years.

Results also confirm a significant increase in transmission rates for both Delta (Shiehzadegan *et al.*, 2021) and Omicron (Ito *et al.*, 2022) compared to the early variant. Interestingly, the estimated increase in the transmission rate is larger for Delta, suggesting that the major global Omicron wave has been as much due to the loss of vaccine protection and erosion of NPIs as to its innate transmissibility. NPIs in the Omicron wave fell due to lower risk of death, in turn due to improvements in treatments, the lower severity of Omicron, and the increased fraction of the population vaccinated. Overall,

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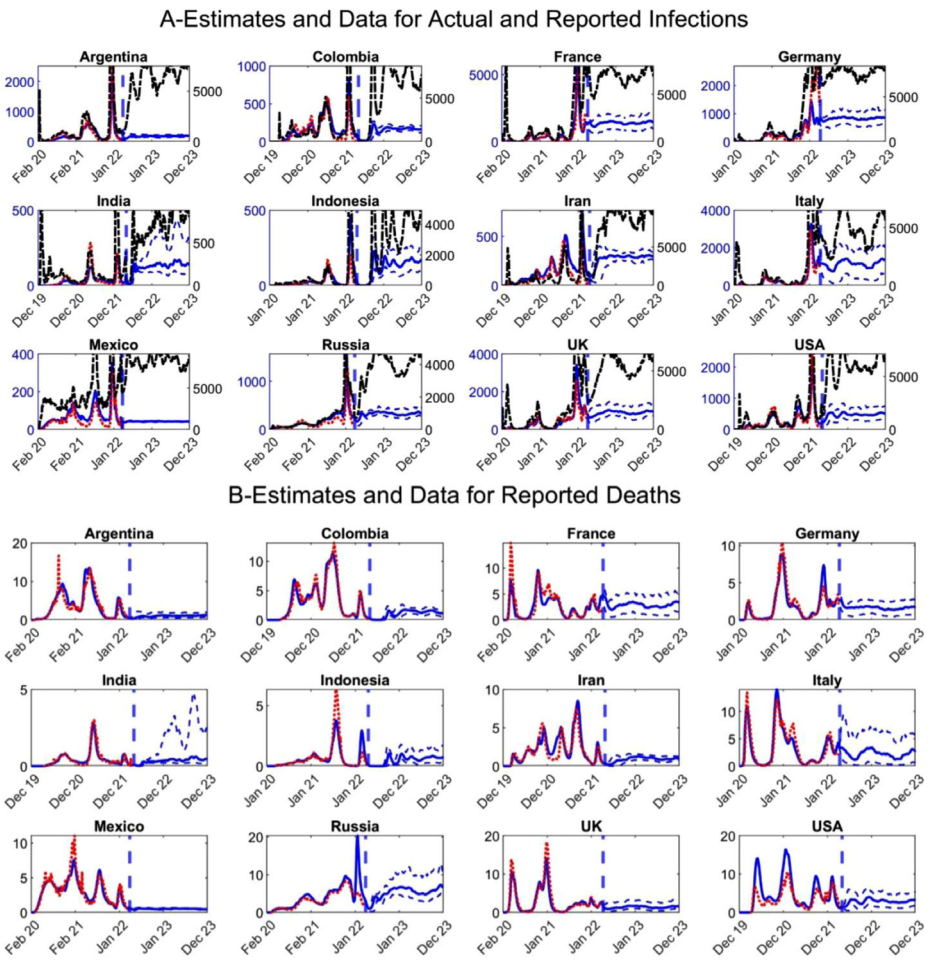

Fig. 2. Data and model results for selected countries, showing cases and deaths per million people per day. (A) Reported cases (Data: dotted red; Simulation: solid blue) with 90 percent confidence intervals for projections (dashed lines) and estimated true cases (dash-dotted black; right y-axis). (B) Reported death rates (data and simulations with 90 percent confidence intervals) [Color figure can be viewed at wileyonlinelibrary.com]

these parameters are largely consistent with the direct empirical and laboratory evidence for the relevant constructs (Shiehzadegan *et al.*, 2021; Ito *et al.*, 2022), and offer novel estimates for important factors that are hard to quantify using experimental and clinical approaches.

Figure 2 compares the model fit to the history of reported cases and deaths, with median projections through December 2023 for countries with the most cumulative COVID-19 deaths to date. The projections are based on the continuation of historical trends: no change in behavioral response, no new variants, vaccines, or treatments, and vaccination rates reaching and staying at the maximum estimated for each country. Note that the median projections hide the waves otherwise visible in single simulations (and historical data). The projections also assume current testing rates will be

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maintained. Although we could attempt to model the evolution of testing endogenously, doing so would introduce speculative assumptions and parameters and is not justified given the large uncertainty regarding government policy and individual decisions regarding testing and the growing use of at-home tests not reflected in official data. The top panel (A) also shows projections for the actual number of cases (right scale). The 90 percent confidence intervals for the projections are based on 200 simulations using the autocorrelated noise derived from the state-resetting process described above. The projections show the 50th percentile rather than any single simulation to filter out the noise in individual simulations. Note, however, the volatility, which arises from the impact of weather and the cyclicality in incidence and prevalence caused by the delays in the negative feedback involving risk perception, responsiveness, and transmission.

Figure 2 shows that projected reported cases continue to be substantial. Worse, limitations on testing and the high fraction of asymptomatic cases mean reported cases significantly undercount true incidence. Globally (across the 93 countries) we estimate cumulative actual cases by late April 2022 to be 9.8 times the reported number (this estimate is consistent with recent global estimates; Barber *et al.*, 2022), with cumulative actual deaths estimated to be 2.0 times the reported number (this estimate is on the lower end of those from the Economist magazine; Solstad, 2022). Projected actual cases may well break historical records in many nations, ranging between 6–10 thousand per million per day, implying a typical person would be reinfected every 100–150 days. Projected reported cases are lower than the peaks of major past waves but are not significantly below historical averages. The gap between the reported and actual cases will grow significantly in the coming months and years because of the reduced acuity of typical future cases, which leads to less testing and a reduction in health system surveillance accuracy. Projected reported incidence also remains above historic levels in many nations. The increase is driven by the reduction in the IFR due to vaccination, acquired immunity, the emergence of Omicron, and improved treatments. These developments reduce the risk of severe disease and death, leading to the erosion and relaxation of NPIs, including both mandatory government restrictions and voluntary individual isolation, distancing, masking, and so on. The consequence is an increase in new cases.

The resulting burden of COVID-19 will thus continue to be large for most nations. Figure 3A reports cumulative deaths per million people projected by the end of 2023 (note the logarithmic scale and that the confidence intervals only account for uncertainty in future deaths due to process noise, but not due to parameter uncertainty). We show two scenarios. Red dots denote the base case in which each nation's responsiveness to risk follows the historical level. Black dots show cumulative deaths if all NPIs are relaxed starting in mid-2022 allowing uncontrolled transmission thereafter. Many countries are expected to suffer cumulative deaths exceeding 1000 per

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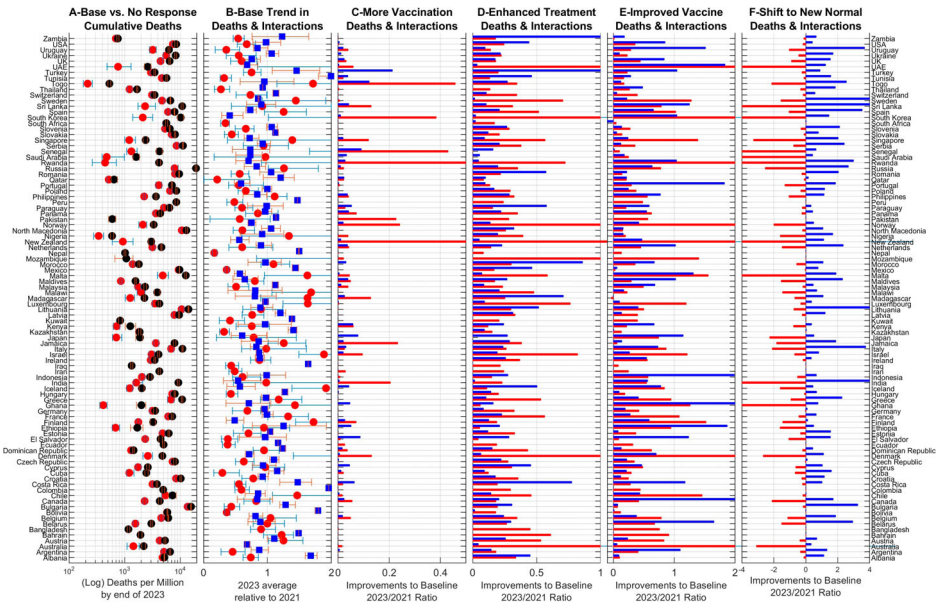

Fig. 3. Outcomes across different countries in a few scenarios. (A) Cumulative deaths (and 90 percent confidence intervals) per million by the end of 2023, assuming historical responsiveness (base case; red dots) and no NPIs (black dots). (B) Ratio of average death rates (red) and interactions (blue) in 2023 versus 2021. (C–F) Changes in the 2023/2021 ratio of deaths and interactions across four scenarios. Positive values indicate improvement (i.e. reduced death or increased interaction) [Color figure can be viewed at wileyonlinelibrary.com]

million by the end of 2023. For example in the base case we project approximately 7400 cumulative actual deaths per million for the USA, or approximately 2.45 million actual cumulative deaths by the end of 2023, more than twice the official, reported death toll by April 2022. Naturally, the biggest impact from relaxing behavioral responses comes in nations that exhibited high responsiveness in the earlier phases of the pandemic, for example New Zealand, which introduced strong measures at very low levels of incidence and mortality.

The differences across countries are also projected to be large, spanning more than one order of magnitude. Projected death rates are low for a few nations, but these results are likely artifacts of poor surveillance systems and gaps in the available data for officially reported deaths and excess mortality, e.g. Nigeria, Togo, or Ghana. However, the estimated differences in death rates for most nations, including many with excellent surveillance systems, remain significant. These differences are primarily due to differences in responsiveness to risk across nations (Lim and Rahmandad, 2022). This result is due to the critical role of the negative feedbacks captured by the endogenous treatment of risk perceptions and their impact on the willingness of individuals and governments to adopt NPIs.

The behavioral response feedback can cause the effective reproduction rate, R_e, for the disease to fluctuate around a value of 1: values of R_e above 1 lead to a growing wave of new cases and deaths, both depleting the pool of susceptible individuals and, importantly, causing perceived risk to increase,

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which leads to a reduction in transmission as people increasingly adopt NPIs and as the pool of susceptible persons falls. Consequently, R_e falls, leading to a drop in new cases, which, with a delay, causes perceived risk and the stringency of NPIs to fall, setting the stage for the next wave. At the same time, gradual loss of immunity among vaccinated and previously infected individuals increases the susceptible population, providing fuel for the next wave even in the absence of new variants. The key question is what level of risk suffices for a country to adopt the NPIs required to bring R_e down to 1. If death rates absent NPIs do not reach the intolerable risk levels for a nation (e.g. due to reduced IFR with drugs and Omicron variant), behavioral responses will not be triggered and the country transitions to a new normal. Otherwise, death rates will settle at levels required for the people and governments of a nation to adopt NPIs, voluntarily or through mandates, sufficient to reduce transmission and bring deaths to the level they are willing to accept. Those estimated tolerance levels vary significantly across nations.

The critical role of the negative feedbacks created by endogenous responses to risk leads to two important results. First, for each nation, projected death rates in 2023 tend to be similar to those experienced in 2021 despite reductions in the IFR (the red dots in Figure 3B show estimated death rates for different nations for 2023 relative to 2021 rates). Projected death rates are similar despite the reduction in the IFR because the initial drop in deaths due to vaccination, improved treatment, prior infection, and the milder nature of Omicron cause NPIs to be relaxed or abandoned, increasing incidence until deaths once again rise enough to trigger the re-imposition of NPIs. Second, death rates vary significantly across nations because different nations have different levels of responsiveness to risk (Figure 3A). Nations that are more responsive to perceived risk implement and adhere to NPIs at lower levels of risk and thus experience lower average death rates; those that are less responsive implement NPIs only when risk is much higher, causing them to endure higher average death rates.

Figure 3B shows the trends in deaths and risky interactions, comparing the 2023 projections with 2021 experience. For each country we compute the ratio of the projected death rate in 2023 to the rate in 2021, shown (with 90 percent confidence intervals) in red circles. Similarly, we calculate the average reduction in risky interactions (compared to the pre-pandemic state) for 2023 and divide that by the 2021 experience. This measure compares the drop in normal daily routines and interactions in 2023 to the 2021 experience (blue squares). A value of 1 in either measure indicates no change; higher values indicate increased deaths or interactions. Results show that values of the relative death measure below 1 are common (but not universal) across nations, indicating a reduced burden of deaths. Relative interaction measures exceed 1 in about half of the nations, indicating some degree of return to pre-pandemic levels of interactions in the population, but remain

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below 1 in the rest, suggesting a future in which the degree of voluntary actions and mandatory measures are similar to or stronger than in 2021.

The baseline results assume no change in responsiveness to risk compared to the first 2 years of the pandemic. People and governments aspire to a new normal in which people can return to pre-pandemic levels of social and economic activity while simultaneously avoiding significant rates of COVID-19 illness and death. The baseline results suggest such a state is not feasible for most countries, at least given their historical responsiveness to risk and tolerance for deaths. The large reduction in the IFR created by vaccination, prior infection, and the milder character of Omicron lead to the relaxation and abandonment of the NPIs that brought incidence down, causing renewed surges in cases until deaths rise enough to convince individuals to isolate and governments to impose restrictions again. In the baseline, the more responsive countries continue to respond to the pandemic, settling into a state with the level of NPIs needed to stabilize transmission at lower death rates than the less responsive countries. However, the results also identify a subset of countries (e.g. Columbia, Iran, South Africa) with low responsiveness that transition into a "new normal" with low levels of NPI implementation at the cost of relatively high death rates. Drawing on the analysis of the simple model, these countries effectively operate in the second regime where behavioral response is of secondary importance.

These projections assume no changes in many uncertain features. Figure 3C–F and Figure 4 compare the base case against results under a few different scenarios. In Figure 3C–F we report changes in country-level relative death rates and interaction measures (changes in 2023 to 2021 ratios) under

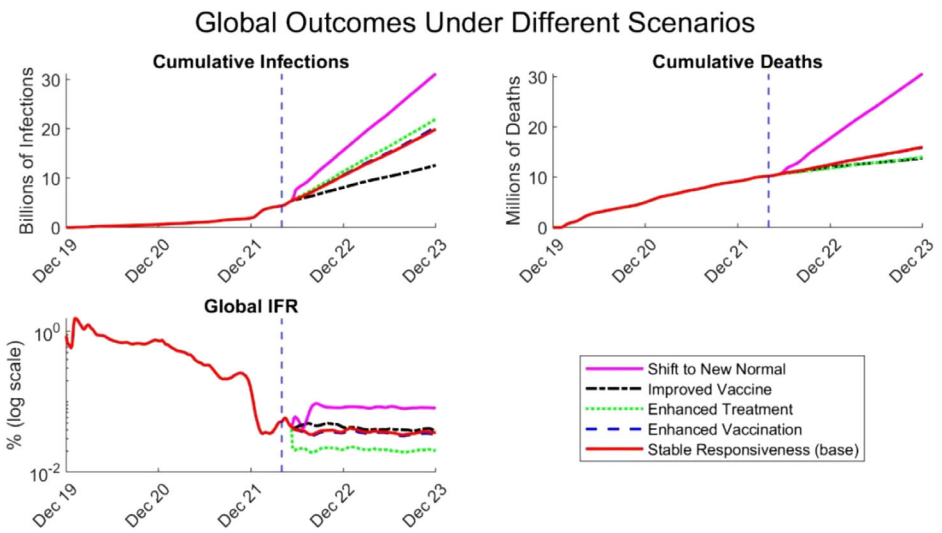

Fig. 4. Global outcomes over time in the base case and four scenarios. (A) Cumulative infections. (B) Cumulative deaths. (C) Infection fatality rates [Color figure can be viewed at wileyonlinelibrary.com]

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four scenarios (Figure 4 shows global trajectories under the same scenarios and baseline):

(C) *Enhanced vaccination*: We assume that in 2022 the uptake of current vaccines increases enough to reduce the unvaccinated population by half. For example, in the base case 23 percent of the U.S. population remains unvaccinated. In Panel C of Figure 3 that fraction falls to 11.5 percent starting in the middle of 2022. Vaccine efficacy is assumed to remain constant.
(D) *Enhanced treatment*: We assume a new treatment that cuts the IFR in half becomes globally available in the middle of 2022.
(E) *Improved vaccines*: We assume a new vaccine that restores effectiveness against transmission to 90 percent becomes globally available starting in mid-2022 and is quickly administered to all those adopting vaccines.
(F) *Shift to a new normal*: Countries adopt a new normal with reduced responsiveness, meaning perceived risk has only half the impact on interactions compared to historical responsiveness in the first 2 years of the pandemic.

The scenarios in Figure 3C–E lead to reductions in death rates, with a few notable exceptions. The reduction in deaths allows a relaxation of voluntary isolation and mandatory measures, increasing social and economic interactions. Overall, enhanced treatment and more effective vaccines have the largest beneficial impact both in avoiding deaths and improving interactions (note differences in the scales across Figure 3C–F). Enhanced vaccination rates also make a major impact in those nations with low vaccination rates to date. Figure 3F, however, shows that reduced responsiveness to risk, that is, an attempt to attain a new normal by reducing the use of and adherence to NPIs, increases deaths, often substantially, in most nations.

Variations in the results are large across nations and reveal some interesting tradeoffs. Countries with lower historical responsiveness (e.g. Bangladesh, Columbia, Iran, South Africa) may already be ready to accept a new normal in which deaths due to uncontrolled transmission are tolerated (based on the estimated historical response function for these countries). Responsiveness to risk in these nations is already low, so the additional reduction in Scenario F has little impact on them. Some others (e.g. Germany, Ireland, Mexico, USA) are close to that threshold and may gradually shift to a new normal with modest additional mortality. Others, especially those with historically stronger responsiveness, face a more acute tradeoff: new laws or regulations prohibiting NPIs or new social norms reducing individual responses to risk would lead to a (partial) return to pre-pandemic patterns of social and economic interactions, but at the cost of large increases in death rates, in many cases more than doubling deaths compared to their 2021 rates.

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Projections for actual cases and deaths summed over all countries are shown in Figure 4. We also plot IFR aggregated across all nations (log scale; Figure 4C). Again, the shift to a new normal increases death rates above past rates. Besides reduced responsiveness to risk, the significant rise in deaths is partly explained by the high load of cases that regularly overwhelms treatment capacity and increases the IFR in the new normal scenario (in our estimates this effect is most salient in a few large countries, most notably Russia and India). Also note that the number of cumulative cases is much larger than the total population of the nations we simulate. With immunity lasting on the order of a few months, the significantly increased transmission potential of Omicron, and reduced vaccine effectiveness, many people will be infected by COVID-19 multiple times, similar to the common cold or influenza, but with significantly higher morbidity and mortality. Among the scenarios we explored, a new vaccine that confers more durable protection is the only one that reduces both cases and deaths. Enhanced treatment, and even enhanced vaccination, reduce deaths and thus weaken behavioral responses, actually increasing cases.

The reduction in the IFR over time has been large, bringing death rates down by an average of 0.037 percent by the end of 2023, more than an order of magnitude compared to the first year of the pandemic. The reduction is due to multiple factors: (i) improved treatment and changes in behavior (towards protecting the most vulnerable), which directly reduce the IFR; (ii) vaccines, which reduce the IFR by a factor of more than 10; (iii) prior infections, which, like vaccines, confer some protection against severe disease (an IFR reduction factor of 0.32); and (iv) the milder disease caused by the Omicron variant (an IFR reduction factor of 0.27). Across the future scenarios, more effective treatments have the largest impact on the IFR, while enhanced vaccination also brings fatality rates down slightly. Interestingly, the IFR increases slightly with the introduction of new vaccines that are able to prevent transmission: by effectively protecting the vaccinated against infection, a larger fraction of cases occurs among the unvaccinated, who experience more severe disease if infected, increasing the IFR even as total deaths decline.

Discussion

We used a feedback-rich country-level model of the COVID-19 pandemic to consider the future of the pandemic and the feasibility and impact of shifting to a new normal in which NPIs are largely relaxed and people learn to live with some level of ongoing COVID-19 incidence, hospitalizations, and deaths. We estimated the model using a wide range of data, including historical cases and deaths across 93 nations while accounting for vaccination, variants, changes in disease acuity, and the incidence of asymptomatic cases

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arising from vaccines, variants, and prior infection, and the impact of weather and cross-national differences in demographics and hospital capacity. Importantly, and in contrast to other models (surveyed in Rahmandad *et al.*, 2022), the model includes endogenous allocation of testing and treatment capacity based on disease acuity, improvements in treatments, and especially endogenous behavioral responses to risk and the impact of pandemic fatigue. The model provides a framework to project future scenarios consistently with reasonable estimates for the many interdependent factors that influence what a new normal may look like in each country.

In these projections we find a disease that is significantly less severe than it was in 2020, yet the overall burden of disease does not drop as much as many hope and expect today. Vaccines, prior infections, improved treatment, and the milder Omicron variant have already brought down the IFR by an order of magnitude. Absent new treatments or new, milder dominant variants, further reductions in the IFR are likely to slow: the COVID-naïve population is now depleted, with new cases arising largely among vaccinated individuals and those with some prior immunity, who, given the attributes of current vaccines, cycle back into the susceptible state after a few months. The increased transmissibility of Omicron, combined with a rather short period of immunity (on the order of 2–4 months), leads to repeated reinfections and large caseloads in the future even if historical responsiveness to risk is maintained. The resulting death rates are comparable to those observed in the first 2 years of the pandemic, and large enough to elicit behavioral responses including the reimposition of various NPIs in most nations, assuming they maintain their historical responsiveness.

We identified two general regimes of behavior. In the first the behavioral response feedbacks remain potent because ongoing death rates exceed what a nation is willing to accept. In the second, the behavioral feedbacks are weak because fatality rates have fallen significantly or resistance to implementing NPIs is strong even when death rates are high. We find most countries have so far operated in the first regime. For them, reducing societal responsiveness to risk by avoiding NPIs in the hope of living with the virus imposes significant tradeoffs. Even partial relaxation of responsiveness would lead to a significant rise in cases and deaths to levels that most of these nations did not tolerate historically. In these countries the shift to a new normal without strong NPIs requires one of two conditions: further significant reductions in the IFR (e.g. with better treatments, vaccines, or the emergence and dominance of even milder variants than Omicron), or a collective decision to live with an ongoing, large toll of COVID-19 deaths that may even exceed historical levels. The smaller, second group of countries have already shifted to the second regime, moving to a new normal in which there are few restrictions on behavior, but at the cost of death rates that are significantly higher than what could be achieved with ongoing NPIs.

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Projections, using mental or formal models, are inevitable as the global community considers different options to tackle the enormous challenges created by the COVID-19 pandemic. Long-term projections are difficult and highly uncertain. Here we offer internally consistent and empirically grounded projections that account for important features regulating long-term COVID-19 trajectories, especially including the behavioral responses of individuals and governments to the state of the epidemic. Prior work (e.g. Rahmandad *et al.*, 2021, 2022) shows that these behavioral feedbacks are essential in explaining the multiple waves seen in the pandemic, orders-of-magnitude differences in death rates across nations, and for providing more reliable long-term forecasts. This study identifies the two distinct regimes a community may face depending on the strength of the behavioral response feedback, provides estimates of where each nation may stand in this continuum, and projects the likely future of the pandemic.

Nevertheless, the results should be interpreted with caution, given the many uncertainties and limitations that remain. We do not disaggregate the population by age, socioeconomic status, housing type, responsiveness to risk, or preexisting conditions. We do not capture travel, individual vaccine types, heterogeneity within countries, the attributes of different NPIs (voluntary isolation vs. mandatory lockdowns, masking, etc.), nor minor variants of SARS-Cov-2, among others. Distinguishing among different NPIs is key to identifying pathways to control transmissions with minimal disruption to daily routines (e.g. use of masks), an important bridge to establishing a new normal while minimizing deaths. The zero-inflated Poisson framework we impose on the distribution of case acuity may differ from the actual distribution. Our estimation framework does not fully quantify uncertainty in the estimated parameters and the large parameter space increases the risk of missing better alternative parameterizations. We do not capture long-COVID-19 nor the costs of different NPIs. And of course, we cannot predict whether and when new variants might emerge, nor their transmissibility and virulence. Nevertheless, we hope the work can help inform personal and policy decisions as we all face the highly uncertain and highly consequential challenge COVID-19 continues to pose.

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Supporting information

Additional supporting information may be found in the online version of this article at the publisher's website.

Appendix S1. The manuscript includes an online supplement that provides additional analysis, model documentation and replication instructions.

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