Supplementary Material

Endemicity is not a victory: the unmitigated downside risks of widespread SARS-CoV-2 transmission

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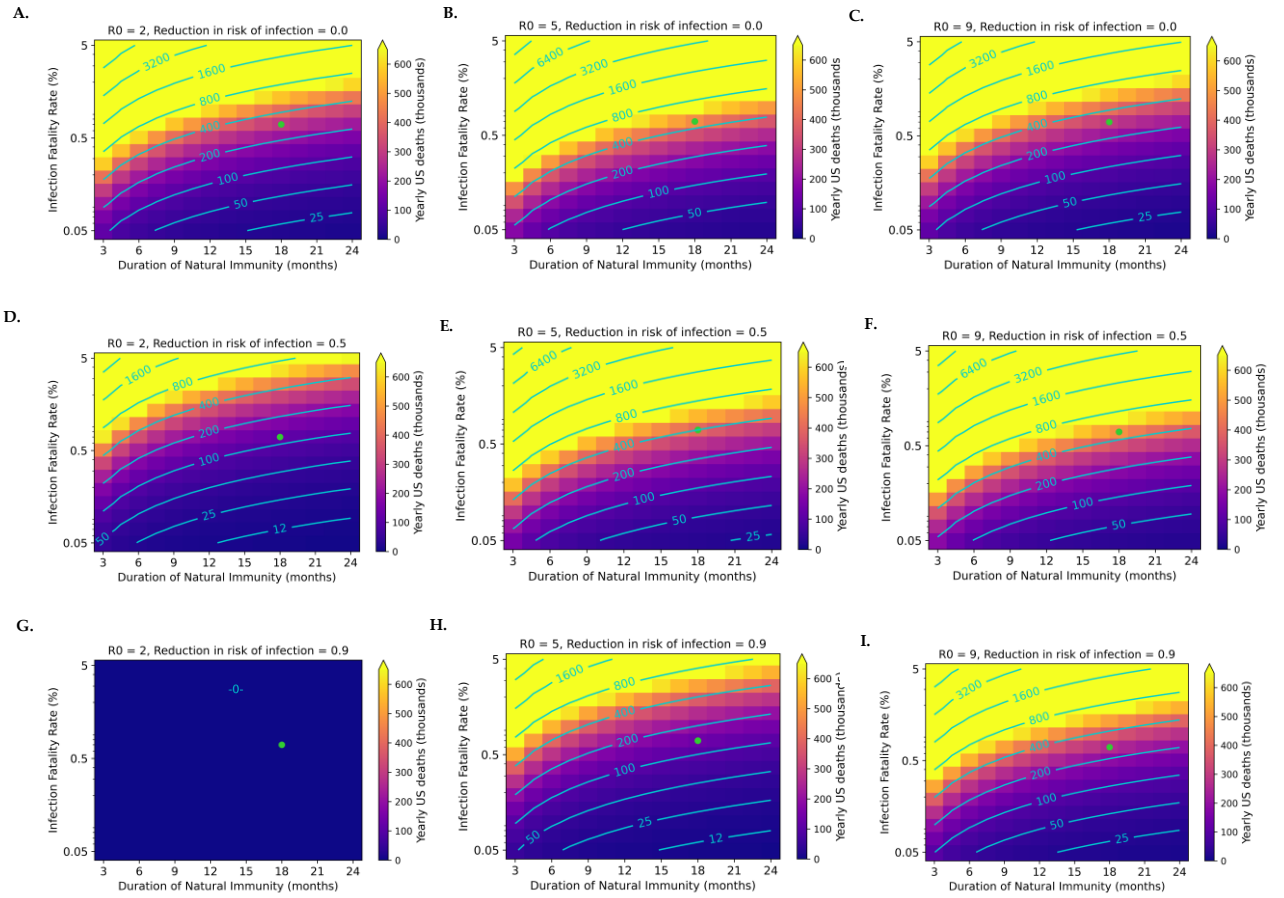

Figure S1. Death tolls are increased under poor vaccine performance. This figure mirrors Figure 3 but reduces VEm from 90% to 70%. The green point represents parameter values corresponding to the best-estimates of immunity and IFR for ancestral SARS-CoV-2. Yearly US COVID-19 deaths under the following transmissibility (R_0) and vaccine efficacy against transmission conditions: **A–C**) 0% VEi and R_0 of 2, 5, and 9; D-F) 50% VEi and R_0 of 2, 5, and 9. **G–I**) 90% VEi and R_0 of 2, 5, and 9. Vaccine compliance is 70% among the under-65 population, 90% among the over-65 population.

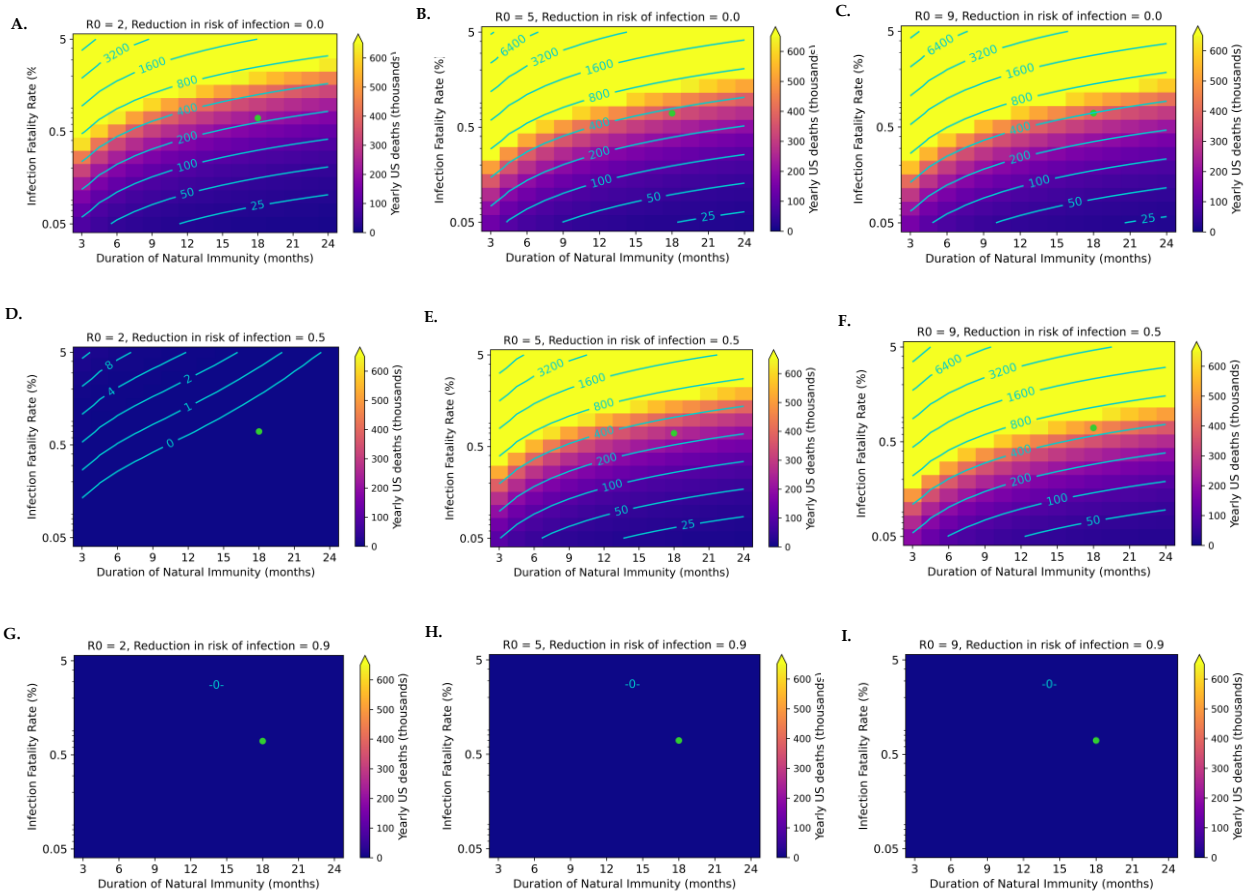

Figure S2. Suppression of SARS-CoV-2 transmission mitigates reduced vaccine effectiveness against mortality. This figure mirrors Figure 4 but reduces vaccine VEm from 90% to 70%. The green point represents parameter values corresponding to the best estimates of immunity and IFR for ancestral SARS-CoV-2. Yearly US COVID-19 deaths under the following transmissibility (R_0) and vaccine efficacy against transmission conditions: **A–C**) 0% VEi and R_0 of 2, 5, and 9; **D–F**) 50% VEi and R_0 of 2, 5, and 9; **G–I**) 90% VEi and R_0 of 2, 5, and 9. Vaccine compliance is 100%.

Table S1. Illustrative examples of the changes observed so far in the IFR and risk of hospitalization during the pandemic (Mar 2020- Jan 2021)

Change	Exemplifying scenario	Ref
Improvements based on improved ICU protocols	Reduction in inpatient mortality upon optimization of ICU protocols for ventilator use (3/2020) vs 11/2020): odds ratio 1.70 (95% CI 1.39–2.09).	[1]
	Reduction in mortality in the US, for hospitalized patients not requiring ventilation (Mar-May 2020 vs Jun-Aug 2020): 13.5% vs 4.6% ($p<0.01$)	[2]
Change in distribution of cases among population or age-IFR relationship	The observed IFR is confounded with relative risk, reflecting the behavior of vulnerable populations to reduce their relative risk of infection. We used data from the State of Massachusetts COVID tracker website to ask the question "How would the IFR change if all age groups were infected equally?" If the proportion of infected individuals in each age group reflected their proportion in the population, the intrinsic IFR so calculated is 2.46 times higher (observed IFR=0.46%, intrinsic IFR= 1.14%).	See Supplementary Table S2 for details
Increased mortality due to lack of hospital resource availability	In April 2020, in the US, regions with an increased incidence rate of death had fewer intensive care unit beds (incident rate ratio [IRR], 0.194; 95% CI, 0.076-0.491), nurses (IRR, 0.927; 95% CI, 0.888-0.967), and general medicine/surgical beds (IRR, 0.800; 95% CI, 0.696-0.920) per COVID-19 case.	[3]
	In a study of consecutive adult patients hospitalized with severe confirmed COVID-19 pneumonia (in Mexico City from Feb- Jun 2020), 45.6% (n = 110) of the patients who died did not receive full support due to lack of ICU bed availability. Mortality rate over time correlated with the availability of ICU beds, consistent with the hypothesis that overcrowding was contributing to in-patient deaths.	[4]
Intrinsic changes in virulence	Risk of death for the delta variant in Ontario, Canada (Feb- Jun 2021) estimated at 133% (95% CI 54%–231%) of that of the ancestral strain.	[5]
	Risk of death for the alpha variant in the United Kingdom (Nov 2020- Feb 2021) estimated at 161% (95% CI 142%–182%) of that of the ancestral strain.	[6]
Changes in death rate with new variant (confounding hospital	Infections with the gamma (P.1) variant in Manaus, Brazil (Feb-May 2021) were 1.2 to 1.9 times more likely (50% Bayesian	[7]

resource availability, intrinsic changes in virulence and pre-existing cross-immunity)	Confidence Interval) to result in mortality in the period after the emergence of P.1, compared with before, although posterior estimates of this relative risk are also correlated with inferred cross-immunity.	
Loss of vaccinal efficacy due to evolutionary immune evasion	In the United Kingdom (Nov- Dec 2021), three doses of the Pfizer vaccine were associated with an 81% reduction (95% CI 78-85%) in risk of hospitalization with omicron. Vaccine efficacy in risk of hospitalization after 4+ weeks of vaccination was lower for omicron (HR 0.60; 95% CI: 0.20-1.42) than for delta (HR 0.27; 95%CI 0.20-0.37).	[8]
Treatment failure due to evolutionary immune evasion	REGEN-COV demonstrated a 72% reduction in risk of hospitalization or death during its Phase 3 trial (run in the US, Sep 2020- Jan 2021). The REGEN-COV Emergency Use Authorization (EUA) was subsequently withdrawn by the FDA (Food & Drug Administration) due to lack of efficacy against the omicron variant.	[9,10]
	In a Phase 3 trial (run in the US, Dec 2020- Mar 2021), Bamlanivimab treatment was associated with a significantly reduced risk-adjusted odds of hospitalization or mortality within 28 days (odds ratio [OR], 0.40; 95% confidence interval [95% CI], 0.24–0.69; P < .001). Again, the EUA was subsequently withdrawn by the FDA due to lack of efficacy against the omicron variant.	[10,11]

Table S2: Estimation of the impact of shielding of older populations on apparent IFR using MA Covid tracker dataset (01/2021) as an example [12,13]. In this analysis, we used published data on age-dependent COVID-19 IFRs to calculate the Massachusetts population average intrinsic IFR based on the MA population age structure. The apparent MA IFR deviates from this intrinsic IFR because infections are not distributed equally by age group, with older groups having lower infection rates. We determined the apparent MA population IFR as an average of the age-dependent IFRs weighted by age-dependent case rates.

MA Age group	IFR (*)	%pop (1)	%cases (1)	relative risk	Observed IFR	Contrib. Obs. IFR	Contrib. Int. IFR	Cases (1)
0 to 4	0.0007	5.15%	5.6%	109%	0.0007	3.8E-05	3.5E-05	8,923
5 to 9	0.0012	5.30%	5.2%	98%	0.0012	6.5E-05	6.6E-05	8,268
10 to 14	0.0023	5.72%	5.9%	103%	0.0024	0.00013	0.00013	9,388
15 to 19	0.0042	6.63%	7.7%	116%	0.0048	0.00032	0.00028	12,232
20 to 29	0.0103	14.74%	22.4%	152%	0.0157	0.00232	0.00152	35,740
30 to 39	0.0345	13.13%	18.5%	141%	0.0486	0.00638	0.00453	29,453
40 to 49	0.1153	12.08%	13.0%	108%	0.1242	0.01500	0.01393	20,726
50 to 59	0.3853	13.73%	11.4%	83%	0.3199	0.04393	0.05290	18,160
60 to 69	1.2877	12.08%	6.3%	52%	0.6707	0.08102	0.15555	10,023
70 to 79	4.3033	7.20%	2.6%	36%	1.5399	0.11087	0.30984	4,104
80 +	14.3814	4.21%	1.4%	34%	4.8745	0.20522	0.60546	2,273

(1): data taken from MA covid tracker.
(2): regression formula from previously published meta-analysis [12] used to calculate IFR.

IFR= infection fatality rate
%pop= percentage of population
Contrib. Obs IFR= contribution of age group to observed IFR
Contrib. Int. IFR= contribution of age group to intrinsic IFR

Observed IFR	0.47
Intrinsic IFR	1.14
Hazard Ratio (intrinsic/true)	2.46

Table S3: IFRs and relative transmissibilities of SARS-CoV-2 ancestral strain and VoCs.

Variant	Infection fatality rate	Calculation	Transmissibility relative to ancestral strain
Ancestral	0.68%	[14]	1.00
Alpha	1.09%	1.6 x 0.68% [6] **	1.59 [15]
Beta	1.71%	1.57 x 1.6 x 0.68% [16] ***	1.50 [17]
Gamma	1.03%	1.51 x 0.68% [5] †	2.00 [7]
Delta	1.58%	2.33 x 0.68% [5] ††	1.82 [18]
Omicron	0.21%	0.13 x 2.33 x 0.68% [19] †††	2.13 (est*) [20]

* R_0 of omicron is unknown, cited study found a secondary attack rate for household transmission between unvaccinated individuals that was 1.17-fold higher than delta. (2.6-3.6 fold higher than delta, in the vaccinated population).

** estimated as 60% higher than the ancestral strain in the cited publication.

*** estimated as 57% higher than the alpha variant in the cited publication.

† estimated as 51% higher than the ancestral strain in the cited publication.

†† estimated as 133% higher than the ancestral strain in the cited publication.

††† estimated as 87% lower than the delta variant in the cited publication.

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