Technical Appendix:

Clinical Outcomes of a COVID-19 Vaccine:

Implementation over Efficacy

Appendix

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Model Description

We developed a dynamic, compartmental model using a modified "susceptible-exposed-infected-recovered" (or SEIR) framework. The model portrays the epidemiology and natural history of infection in a homogeneous population of at-risk individuals as a sequence of transitions, governed by difference equations, between different health states (or "compartments"). The model diagram (**Appendix Figure 1**, below) illustrates the modifications we made to the basic SEIR framework:

- Division of the "Infected" state into four distinct sub-compartments, to capture the increasing severity and hospital resource use associated with more advanced COVID-19 disease: "Asymptomatic," "Mild" (outpatient), "Severe" (hospitalized) and "Critical" (hospitalized in an intensive care unit [ICU]).
- Introduction of a vaccination program. Uninfected individuals receiving vaccine move from the "Susceptible Unvaccinated" state to the "Susceptible Vaccinated" state. From there, they may proceed through a parallel set of compartments: "Exposed Vaccinated", "Asymptomatic Vaccinated", "Mild Vaccinated", "Severe Vaccinated", and "Critical Vaccinated". Progress to Exposure, Infection, Recovery, and Death are adjusted to reflect the transmission and disease-modifying benefits of the vaccine. This modeling device also permits us to adjust the

infectiousness of persons who received an imperfect vaccine but who nevertheless became infected (i.e., "breakthrough infections").

We defined a total of 14 model states:

- U: Uninfected, susceptible
- E: Exposed, asymptomatic
- A: Infected, asymptomatic
- M: Infected, mild-moderate illness, outpatient
- S: Infected, severe illness, inpatient
- C: Infected, critical illness, inpatient
- UV: Uninfected, susceptible, vaccinated
- EV: Exposed, asymptomatic, vaccinated
- AV: Infected, asymptomatic, vaccinated
- MV: Infected, mild-moderate illness, outpatient, vaccinated
- SV: Infected, severe illness, inpatient, vaccinated
- CV: Infected, critical illness, inpatient, vaccinated
- R: Recovered, non-infectious
- D: Dead

Active transmission pool. Individuals in states U and UV are at risk of infection. Individuals in states A, M, AV, and MV are able to transmit infection. (We assumed that proper hospital infection control policies would prevent any nosocomial transmission; thus, persons in states S, C, SV, and CV do not transmit infection in the model. Persons in the recovered state R and in the exposed states E and EV remain active in the transmission pool but are neither able to transmit nor to be infected a second time.

Vaccination. Only persons in uninfected state U can be vaccinated. We make the simplifying assumption that vaccination is not available to persons in the Exposed state.

Parameters

β_i: rate at which infected individuals in state i contact susceptibles and infect them. This applies to states A, M, AV, and AM.

σ_i: susceptibility to infection for persons in state i. This is the probability that an infectious contact will result in exposure. (This applies to states U and UV.)

p_i: rate of progression from disease state i to the next stage of disease. (This applies to states E, A, M, S, EV, AV, MV, and SV.)

r_i: rate at which individuals in state i recover from disease. (This applies to states A, M, S, C, AV, MV, SV, and CV.)

m_i: mortality rate for individuals in state i. (This applies to states M, S, C, MV, SV, and CV.)

v: vaccination rate for individuals in state U.

λ: vaccine lag time. (We build in a delay between the time that a vaccine is administered and the time that the vaccine first becomes effective.)

The model uses a cycle time of 1 day. All rates are calculated per daily cycle.

Governing equations

For ease of computation, we define:

- **Weighted force of infection at time t:**

$$\beta^*(t) = \sum_i \beta_i X_i(t) = \beta_A A(t) + \beta_M M(t) + \beta_{AV} AV(t) + \beta_M MV(t)$$

- **Active population at time t:**

$$X(t) = U(t) + E(t) + A(t) + M(t) + S(t) + C(t) + UV(t) + EV(t) + AV(t) + MV(t) + SV(t) + CV(t) + R(t)$$

The equations governing transitions from one state to the next are:

- **Uninfected (t+1) = Uninfected (t) – New Transmissions to E – New Vaccinations**

$$U(t+1) = U(t) \cdot \left[1 - \frac{\beta^*(t) \cdot \sigma_U}{X(t)}\right] - U(t-\lambda) \cdot v$$

If $(t-\lambda) \leq 0$, we assume that $U(t-\lambda) = 0$. The vaccination efficacy lag λ creates the possibility of depleting uninfected state U. This equation therefore includes a logic check (not shown) that only

vaccinates as many people as are available to be vaccinated in state U. The population in state U is never permitted to fall below 0.

- **Exposed (t+1) = Exposed (t) + New Transmissions from U - New Infections to A**

$$\mathrm{E}(\mathrm{t}+1) = \mathrm{E}(\mathrm{t}) \cdot \left[1 + \frac{\beta^*(\mathrm{t}) \cdot \sigma_U}{\mathrm{X}(\mathrm{t})} - p_E\right]$$

- **Asymptomatic (t+1) = Asymptomatic (t) – Progressions to M – Recoveries + New Infections from E**

$$\mathrm{A}(\mathrm{t}+1) = \mathrm{A}(\mathrm{t}) \cdot (1 - p_A - r_A) + \mathrm{E}(\mathrm{t}) \cdot p_E$$

- **Mild/Moderate (t+1) = Mild/Moderate (t) – Progressions to S – Recoveries - Deaths + Progressions from A**

$$\mathrm{M}(\mathrm{t}+1) = \mathrm{M}(\mathrm{t}) \cdot (1 - p_M - r_M - m_M) + \mathrm{A}(\mathrm{t}) \cdot p_A$$

- **Severe (t+1) = Severe (t) – Progressions to C – Recoveries – Deaths + Progressions from M**

$$\mathrm{S}(\mathrm{t}+1) = \mathrm{S}(\mathrm{t}) \cdot (1 - p_S - r_S - m_S) + \mathrm{M}(\mathrm{t}) \cdot p_M$$

- **Critical (t+1) = Critical (t) – Recoveries – Deaths + Progressions from S**

$$\mathrm{C}(\mathrm{t}+1) = \mathrm{C}(\mathrm{t}) \cdot (1 - r_C - m_C) + \mathrm{S}(\mathrm{t}) \cdot p_S$$

- **Uninfected Vaccinated (t+1) = UV(t) – New Transmissions to EV + New Vaccinations**

$$\mathrm{UV}(\mathrm{t}+1) = \mathrm{UV}(\mathrm{t}) \cdot \left[1 - \frac{\beta^*(\mathrm{t}) \cdot \sigma_{UV}}{\mathrm{X}(\mathrm{t})}\right] + \mathrm{U}(\mathrm{t}-\lambda) \cdot \mathrm{v}$$

- **Exposed Vaccinated (t+1) = EV(t) + New Transmissions from UV - New Infections to AV**

$$\mathrm{EV}(\mathrm{t}+1) = \mathrm{EV}(\mathrm{t}) \cdot \left[1 + \frac{\beta^*(\mathrm{t}) \cdot \sigma_{UV}}{\mathrm{X}(\mathrm{t})} - p_{EV}\right]$$

- **Asymptomatic Vaccinated (t+1) = AV (t) – Progressions to MV – Recoveries + New Infections from EV**

$$\mathrm{AV}(\mathrm{t}+1) = \mathrm{AV}(\mathrm{t}) \cdot (1 - p_{AV} - r_{AV}) + \mathrm{EV}(\mathrm{t}) \cdot p_{EV}$$

- **Mild/Moderate Vaccinated (t+1) = MV (t) – Progressions to SV – Recoveries – Deaths + Progressions from AV**

$$\mathrm{MV}(\mathrm{t}+1) = \mathrm{MV}(\mathrm{t}) \cdot (1 - p_{MV} - r_{MV} - m_{MV}) + \mathrm{AV}(\mathrm{t}) \cdot p_{AV}$$

- **Severe Vaccinated (t+1) = SV(t) – Progressions to CV – Recoveries – Deaths + Progressions from MV**

$$\mathrm{SV}(\mathrm{t}+1) = \mathrm{SV}(\mathrm{t}) \cdot (1 - p_{SV} - r_{SV} - m_{SV}) + \mathrm{MV}(\mathrm{t}) \cdot p_{MV}$$

- **Critical Vaccinated (t+1) = CV (t) – Recoveries - Deaths + Progressions from AV**

$$\mathrm{CV}(\mathrm{t}+1) = \mathrm{CV}(\mathrm{t}) \cdot (1 - r_{CV} - m_{CV}) + \mathrm{SV}(\mathrm{t}) \cdot p_{SV}$$

- **Recovered (t+1) = Recovered (t) + New Recoveries**

$$\mathrm{R}(\mathrm{t}+1) = \mathrm{R}(\mathrm{t}) + r_A\mathrm{A}(\mathrm{t}) + r_M\mathrm{M}(\mathrm{t}) + r_S\mathrm{S}(\mathrm{t}) + r_C\mathrm{C}(\mathrm{t}) + r_{AV}\mathrm{AV}(\mathrm{t}) + r_{MV}\mathrm{MV}(\mathrm{t}) + r_{SV}\mathrm{SV}(\mathrm{t}) + r_{CV}\mathrm{CV}(\mathrm{t})$$

- **Deaths (t+1) = Deaths (t) + New Deaths**

$$\mathrm{D}(\mathrm{t}+1) = \mathrm{D}(\mathrm{t}) + m_M\mathrm{M}(\mathrm{t}) + m_S\mathrm{S}(\mathrm{t}) + m_C\mathrm{C}(\mathrm{t}) + m_{MV}\mathrm{MV}(\mathrm{t}) + m_{SV}\mathrm{SV}(\mathrm{t}) + m_{CV}\mathrm{CV}(\mathrm{t})$$

- **Total Population at time t =**

$$\mathrm{U}(\mathrm{t}) + +\mathrm{E}(\mathrm{t}) + \mathrm{A}(\mathrm{t}) + \mathrm{M}(\mathrm{t}) + \mathrm{S}(\mathrm{t}) + \mathrm{C}(\mathrm{t}) + \mathrm{UV}(\mathrm{t}) + \mathrm{EV}(\mathrm{t}) + \mathrm{AV}(\mathrm{t}) + \mathrm{MV}(\mathrm{t}) + \mathrm{SV}(\mathrm{t}) + \mathrm{CV}(\mathrm{t}) + \mathrm{R}(\mathrm{t}) + \mathrm{D}(\mathrm{t}) = constant$$

Initial conditions

We consider an active cohort of 100,000 individuals, 100 of whom are exposed to SARS-CoV-2 and 9,000 of whom have recovered from COVID-19. Thus,

U(0) = 90,900

E(0) = 100

R(0) = 9,000

All other state compartments are empty at time 0.

Estimating disease progression, recovery, and mortality rates

In this section, we describe how the parameters used in the governing equations are derived. Unless otherwise noted as an additional assumption, all input values contained in this section are listed and referenced in Table 1 (Inputs) in the main manuscript.

- **From Exposed state, E**

  Individuals spend an average of 3 days in the Exposed state before progressing to Asymptomatic infection. This implies $r_E = (3 \text{ days})^{-1} = 0.333$.

- **From Asymptomatic state, A**

  40% of asymptomatic individuals recover without progressing to Mild/Moderate disease. For the 60% who do progress to Mild/Moderate disease, the average time spent in the Asymptomatic state is 3 days. This permits us to solve for both progression rate pA = (3 days)^(-1) = 0.333 and recovery rate rA = (0.4/(1-0.4))*pA = 0.222.

- **From Mild-Moderate state, M**

  Individuals spend an average of 6 days in state M. This gives us $(pM + mM + rM)^{-1} = 6$.

While 60% of all exposed persons will eventually progress to Mild/Moderate illness, only 30% will progress to Severe illness. This suggests that

$pM / (pM + mM + rM) = 30/60 = 0.5$ and, hence, $pM = 0.5/6 = 0.0833$.

Finally, 1% of all persons who arrive in state M will die. This means that $mM/(pM + mM + rM) = 1\%$ and, since we know that $(pM + mM + rM)^{-1} = 6$, then $mM = 0.01/6 = 0.0167$. This also permits us to solve for rM: since $rM/(pM + mM + rM) = (1 - 50\% - 1\%) = 49\%$, $rM/(pM + mM + rM) = 0.49\%$ and, since we know that $(pM + mM + rM)^{-1} = 6$, then $rM = 0.49/6 = 0.0817$.

- **From Severe state, S**

Individuals spend an average of 4 days in state S. This gives us $(pS + mS + rS)^{-1} = 4$.

16% of all persons who arrive in state S will die. This means that $mS/(pS + mS + rS) = 0.16$ and hence $mS = 0.16/4 = 0.04$. Finally, while 30% of all exposed persons will eventually progress to Severe illness, only 6% will progress to Critical

illness. This suggests that pS / (pS + mS + rS) = 6/30 = 0.2 and, hence, pS = 0.2/4 = 0.05.

We can now solve for the proportion of persons in state S who recover: rs/(pS + mS + rS) = (1 – 16% - 20%) = 64% and since (pS + mS + rS)$^{-1}$ = 4, then rS = 0.64/4 = 0.16.

- **From Critical state, C**

  The average time spent in state C is 14 days. This gives us (mC + rC)$^{-1}$ = 14.

  Further, 25% of all persons who arrive in state C will die; the other 75% will recover. This means that mC/(mC + rC) = 0.25 and hence mC= 0.25/14 = 0.0179 while rC/(mC + rC) = 0.75 and hence rC= 0.75/14 = 0.0536.

Estimating transmission parameters

The basic reproduction number (R0) measures the transmission potential of an infectious agent. In the absence of a vaccine, the basic reproduction number associated with this model is given by:

$$R_0 = \frac{\beta_A}{p_A + r_A} + \frac{p_A}{p_A + r_A} \cdot \frac{\beta_M}{p_M + r_M + m_M}$$

We have already derived parameters pA, rA, pM, rM, and mM, above. In the absence of data to the contrary, we assumed that asymptomatic persons and persons with mild/moderate infection are equally infectious and hence β_A / β_M = 1. (Any other assumption of relative infectiousness could be applied.) We then solved for the values of β_A and β_M for a range of different reproduction numbers. In particular, for R_0 = {1.5, 1.8, 2.1}, we obtained β_A = β_M = {0.28, 0.33, 0.39}.

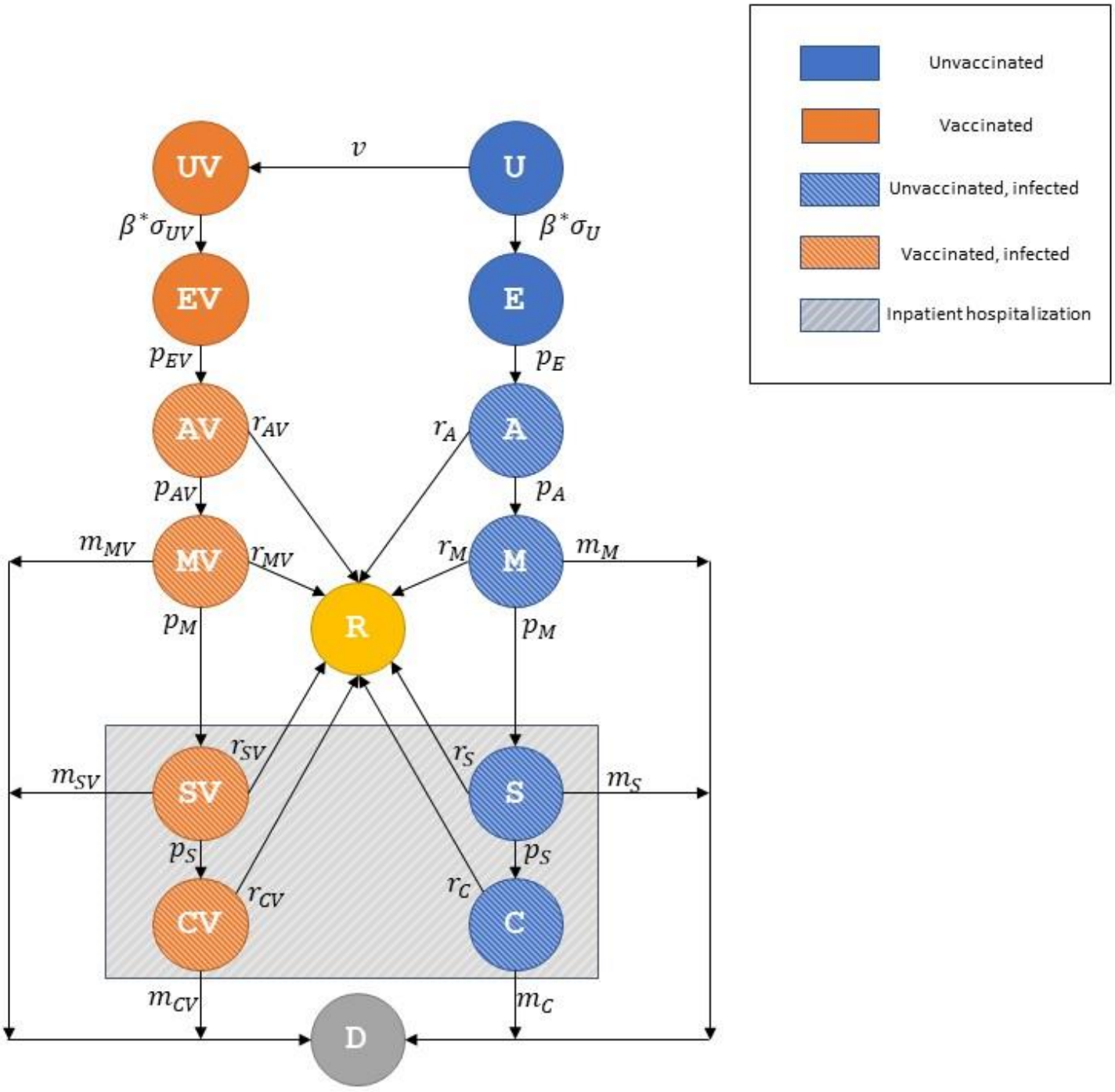
Appendix Table 1A: Base case output table (14-day delay to vaccine efficacy)

	No Vaccine	Preventive			Disease-modifying			Composite		
		Total	Unvaccinated	Vaccinated	Total	Unvaccinated	Vaccinated	Total	Unvaccinated	Vaccinated
R_t = 1.5										
Total vaccinations	0	40,900			40,900			40,900		
Total infections	34,940	11,393	8,840	2,553	8,382	5,814	2,568	5,728	4,792	937
Cumulative deaths	2,153	737	582	156	408	398	11	337	333	4
Peak hospitalizations	735	193			114			99		
R_t = 1.8										
Total vaccinations	0	40,276			40,900			40,900		
Total infections	54,701	35,196	27,123	8,073	30,438	20,636	9,802	22,169	17,862	4,307
Cumulative deaths	3,736	2,382	1,849	533	1,455	1,413	42	1,245	1,226	19
Peak hospitalizations	1,604	851			520			442		
R_t = 2.1										
Total vaccinations	0	32,591			34,813			35,743		
Total infections	63,896	51,132	40,982	10,150	49,557	35,820	13,737	41,162	33,704	7,458
Cumulative deaths	4,410	3,526	2,830	696	2,535	2,474	61	2,361	2,328	33
Peak hospitalizations	2,441	1,709			1,225			1,112		

Appendix Table 1B: Base case output table (42-day delay to vaccine efficacy)

	No Vaccine	Preventive			Disease-modifying			Composite		
		Total	Unvaccinated	Vaccinated	Total	Unvaccinated	Vaccinated	Total	Unvaccinated	Vaccinated
R_t = 1.5										
Total vaccinations	0	40,900			40,900			40,900		
Total infections	34,940	16,350	13,303	3,047	14,172	10,495	3,677	10,898	9,402	1,496
Cumulative deaths	2,153	1,070	885	185	730	714	15	652	646	6
Peak hospitalizations	735	315			229			212		
R_t = 1.8										
Total vaccinations	0	40,640			40,900			40,900		
Total infections	54,701	40,310	33,567	6,743	39,185	29,926	9,259	32,968	28,409	4,559
Cumulative deaths	3,736	2,763	2,310	453	2,104	2,064	40	1,981	1,961	20
Peak hospitalizations	1,604	1,147			921			872		
R_t = 2.1										
Total vaccinations	0	31,553			32,533			32,909		
Total infections	63,896	54,820	47,809	7,011	55,728	45,616	10,113	50,417	44,789	5,628
Cumulative deaths	4,410	3,786	3,304	482	3,198	3,153	45	3,121	3,096	25
Peak hospitalizations	2,441	2,096			1,859			1,815		

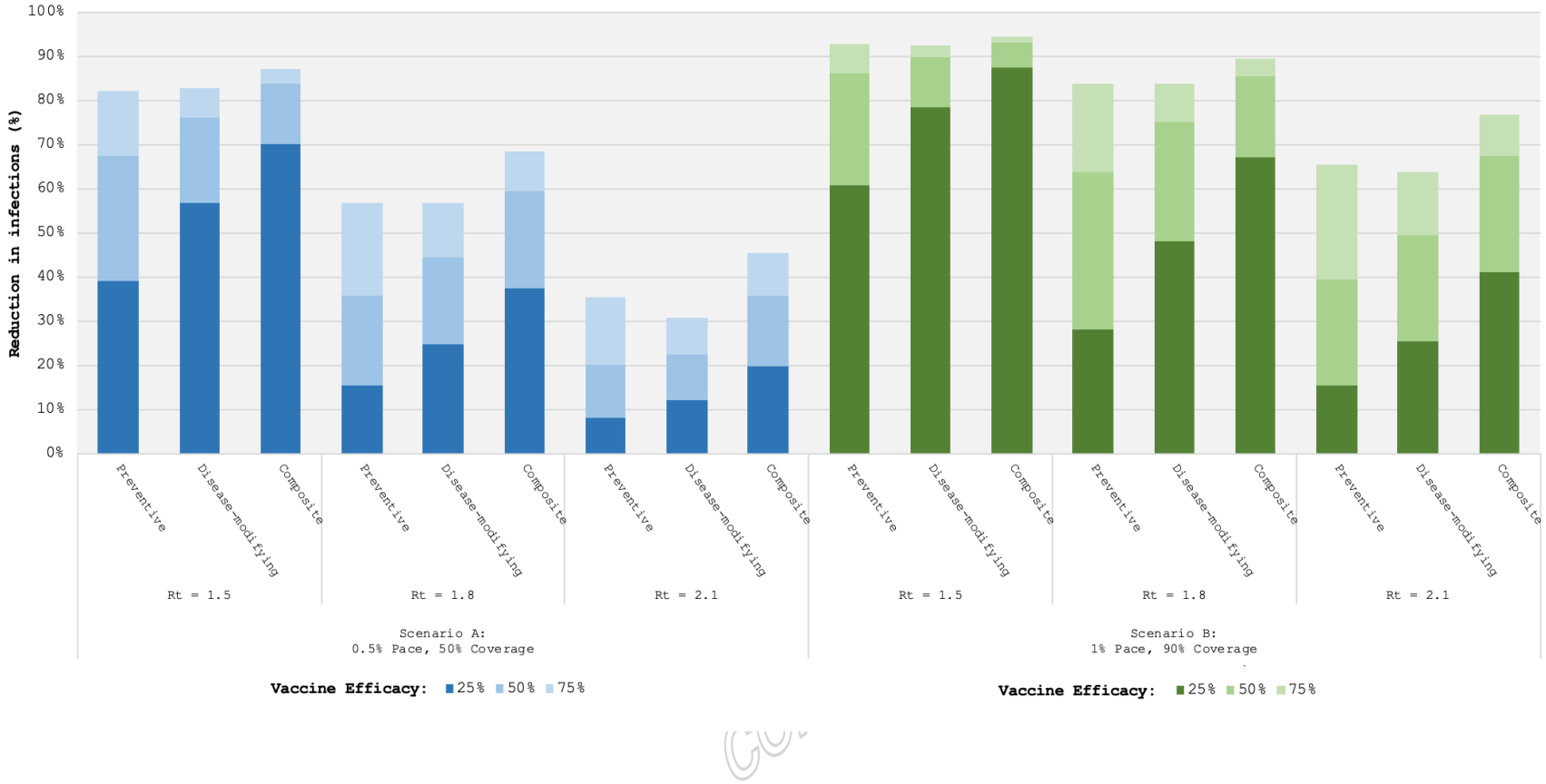
Appendix Figure 1: SEIR model diagram



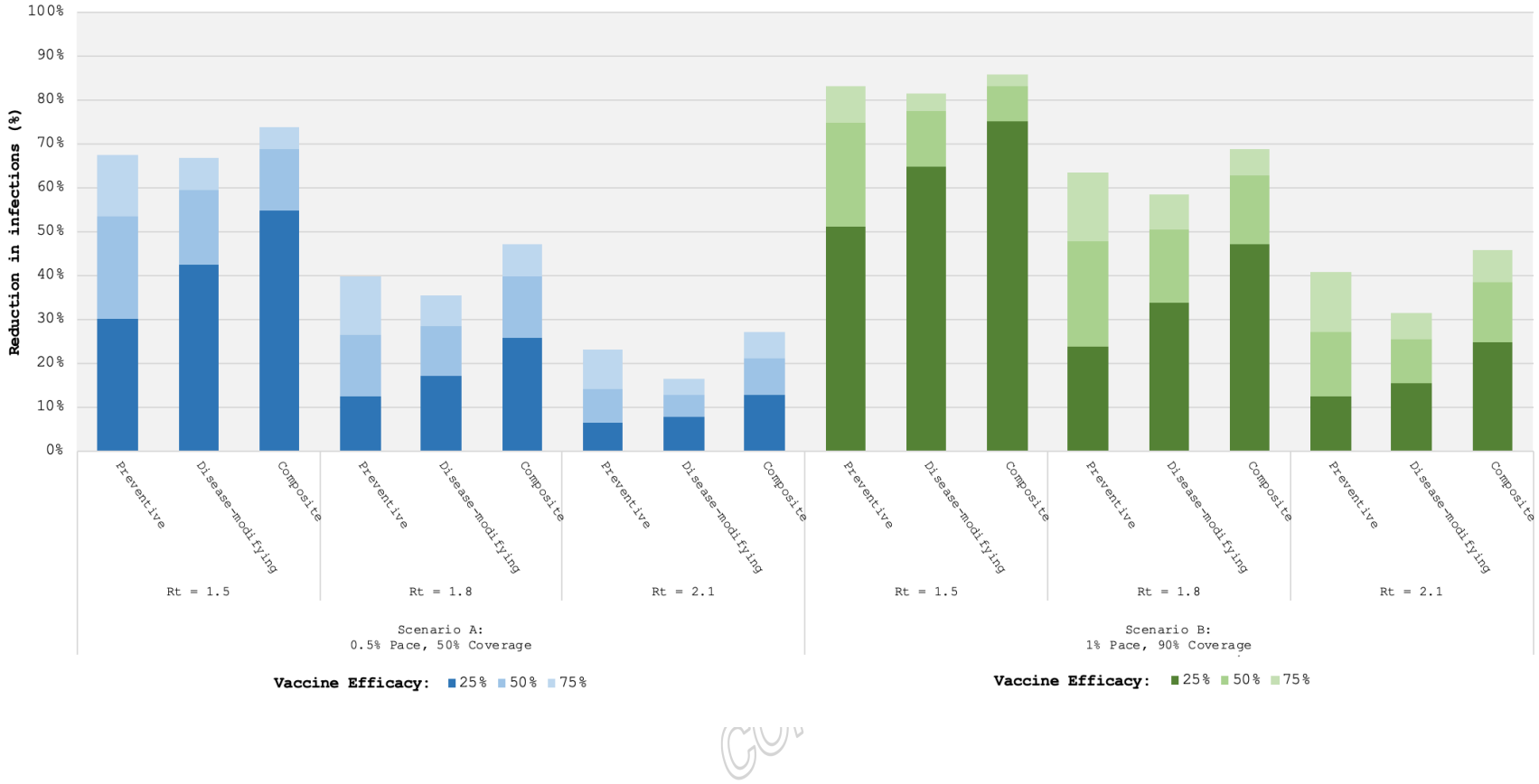
Legend for Appendix Figures 2A and 2B:

Bar graphs representing the fraction of infections averted (vertical axis) under alternative vaccine types -- preventive, disease-modifying, and composite – and at different background epidemic severities, represented by increasing R_t. The different shades of each bar represent vaccine efficacies of 25% (darkest), 50% (middle) and 75% (lightest). Blue bars on the left represent an implementation scenario where the vaccination is scaled up in the population at 0.5% per day (pace) with a maximum of 50% coverage. Green bars on the right represent an implementation scenario where the vaccination pace is 1% per day with 90% coverage. Figures 2A and 2B represent vaccine types with a 14-day and 42-day delay to efficacy, respectively.

Appendix Figure 2A: 14-day delay to vaccine efficacy; infections



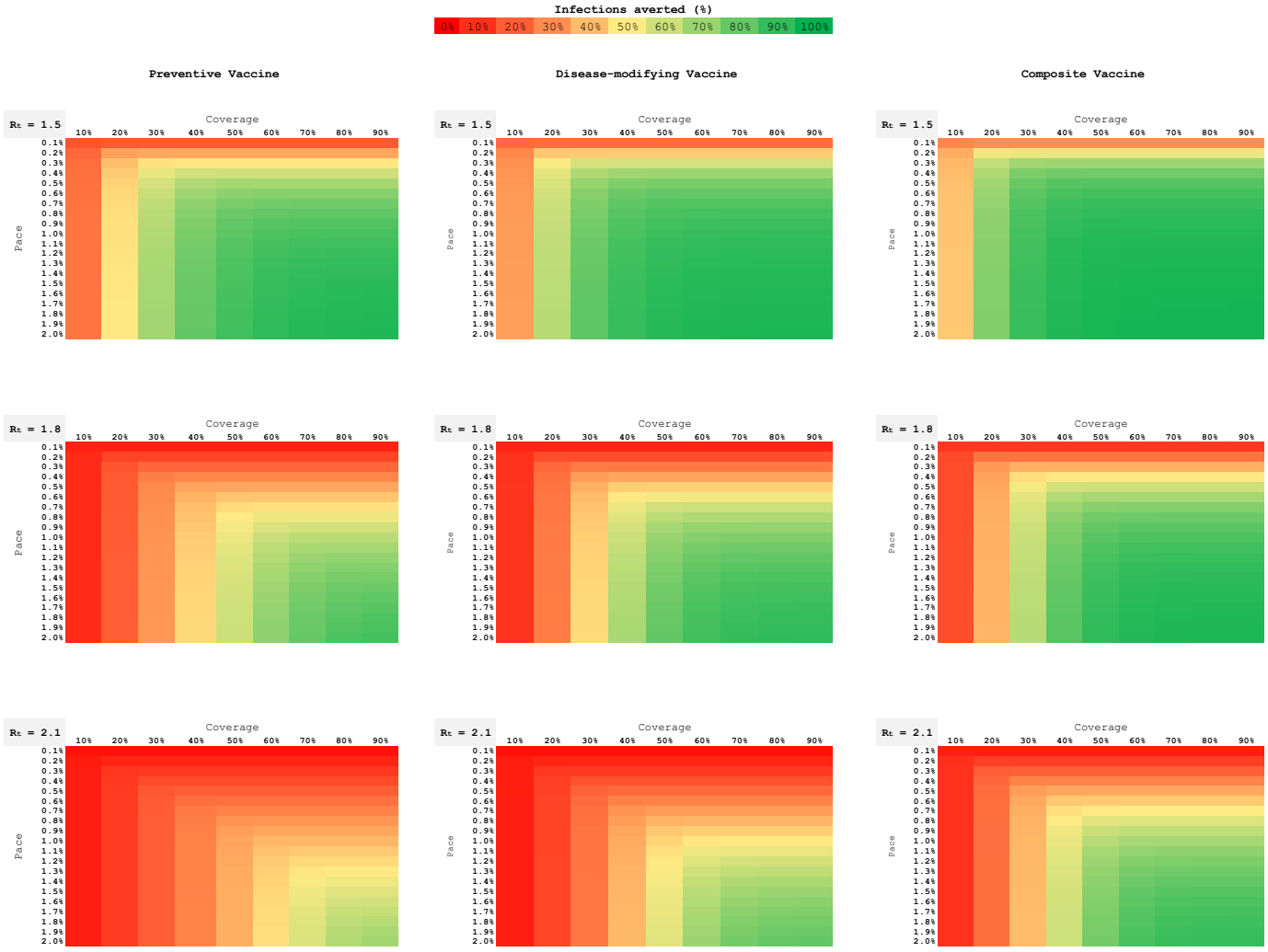
Appendix Figure 2B: 42-day delay to vaccine efficacy; infections



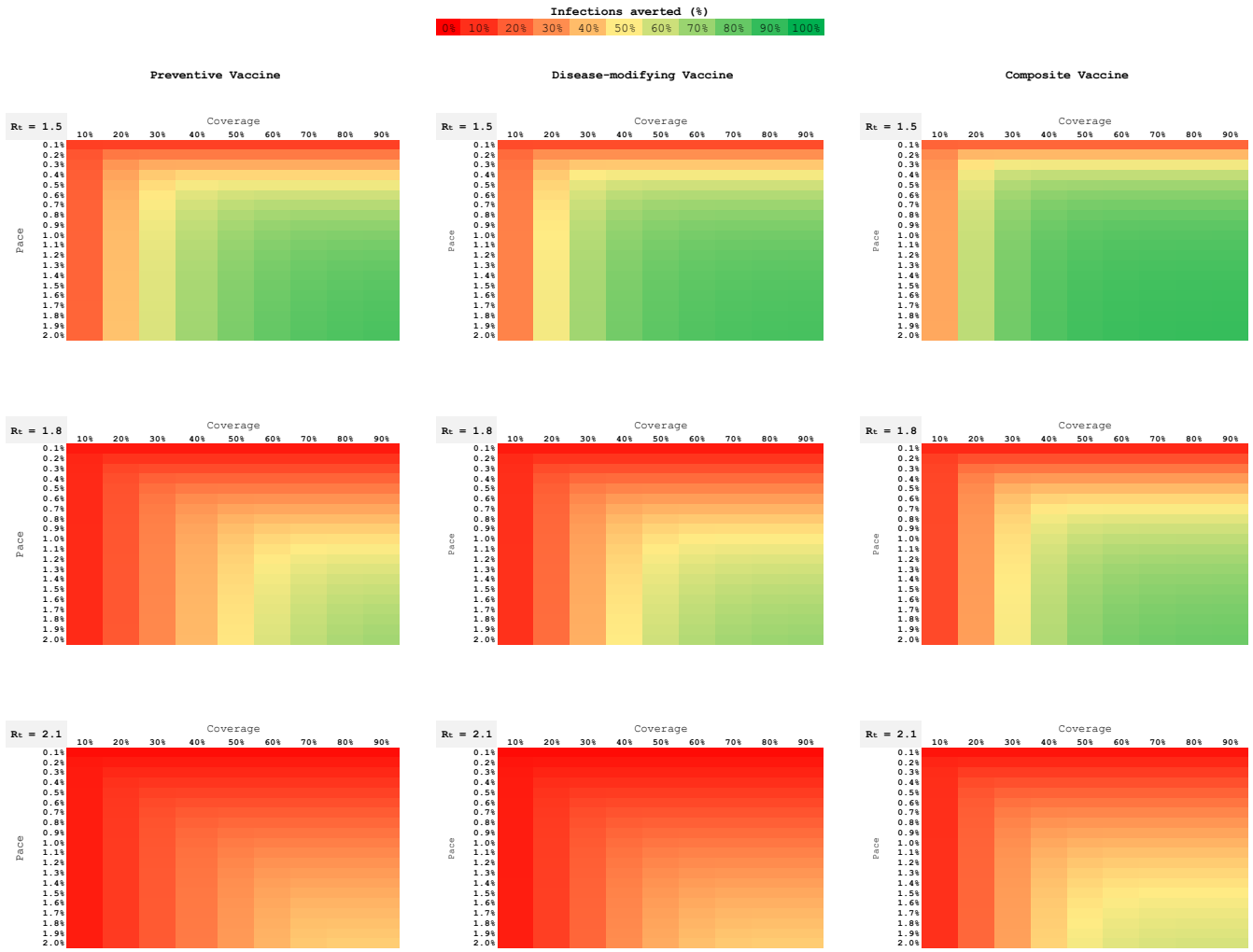
Legend for Appendix Figures 3A and 3B:

These heat maps depict an individual vaccine type (columns) at a given background epidemic severity (R_t, rows). Base case efficacies (50%) are used for the preventive, disease-modifying and composite vaccines. Individual maps demonstrate the range of vaccination coverage (horizontal axis, 10-90%) and pace of scale up (vertical axis, 0.1%-2% per day). The color spectrum represents the proportion of infections averted: green averts the largest numbers of infections, red the fewest. Figures 3A and 3B represent the heat maps for vaccine types with a 14-day and 42-day delay to efficacy, respectively.

Appendix Figure 3A: Nine heat plots for 14-day delay to vaccine efficacy



Appendix Figure 3B: Nine heat plots for 42-day delay to vaccine efficacy



Legend for Appendix Figure 4: Bar graph representing the fraction of infections averted (vertical axis) under alternative vaccine types -- preventive, disease-modifying, and composite – and at different background epidemic severities, represented by increasing R_ts. The different shades of each bar represent vaccine efficacies of 25% (darkest), 50% (middle) and 75% (lightest). Blue bars on the left represent an implementation scenario where the vaccination is scaled up in the population at 0.5% per day (pace) with a maximum of 50% coverage. Green bars on the right represent an implementation scenario where the vaccination pace is 1% per day with 90% coverage.

Appendix Figure 4: 30-day delay to vaccine efficacy; deaths