Disclaimer: The conclusions based on the analysis in this report may be used in conjunction with other data sources to inform policy but the model is not reliably predictive and should not be used as a sole source of information upon which decisions are made

Abstract

Background

A new variant of SARS-CoV-2 was detected after the health care systems of Country X were almost overwhelmed by the previous variant. This report models two variants with different characteristics and aims to describe potential scenarios based on these characteristics.

Methods

Two compartmental transmission models with parameters reflecting the known traits of each variant were used to perform sensitivity and scenario analysis based on knowledge about the evolution of previous SARS-CoV-2 variants.

Results

The initial analysis showed that there was potential for the new variant to have a greater impact on health systems than the previous variant. However, after new information emerged after one month, secondary analysis showed that, within certain conditions about natural cross-immunity, the damage may not be as significant as first estimated.

Conclusions

Country X was initially advised to implement appropriate Non-Pharmaceutical Interventions such as zonal lockdowns and hygiene practices, and to continue vaccination efforts, while continuing to monitor the transmission characteristics of the new variant. In light of the secondary analysis Country X was advised to relax these restrictions with caution but to continue to increase vaccination coverage where possible.

Background

Viruses have many characteristics that change as the virus evolves in order to maximise evolutionary fitness. Two of the most dangerous evolutionary paths a virus can take are higher transmissibility and evasion of the host immune response, either through reduced cross immunity or vaccine escape. The Delta variant of SARS-CoV-2,had a lower virulence and hence Case Fatality Rate (CFR) than previous variants [1] but a higher R0 [2]. Evolution towards higher virulence is also possible, despite commonly-held belief [3]. The Delta variant was found to be less sensitive to antibodies from immune individuals than previous variants [4]. Few studies exist on vaccine effectiveness done in Low and Middle Income Countries (LMICs) [5] however coverage is generally low due to acceptance and scarcity of resources [6]. Without knowledge on the characteristics of the emerging variant, a transmission model can help to explore possible scenarios and the effect they may have on the country and health system.

Initial Advice

During the last wave, with no Non-Pharmaceutical Interventions (NPIs), the health system was almost overwhelmed. With a new variant emerging, unless all characteristics of the virus are less dangerous, it is reasonable to assume that without action the country could be at serious risk. Before any analysis is considered, Country X is advised to take immediate action: the continuation of any and all vaccination efforts is advised where possible since the vaccine will likely offer at least some protection from the new variant. The extent of what interventions can achieve in LMICs is limited by resources, as is vaccine coverage. Hand-washing, mask-wearing and zonal lockdowns, however, have been shown to be effective at reducing burden in such settings [7, 8], hence Country X is advised to employ these practices where possible until more information is available.

Methods

Data

Little data was available on the specifics of the setting such as population, funding and access. Assumptions were made and are detailed below. The model was developed such that adjustments can be made as new data become available on the new circulating variant. The transmission parameters for V1 were based on the Delta variant of SARS-CoV-2.

Transmission Model

A Susceptible-Infected-Removed (SIR) compartmental model with a death compartment was chosen in line with those widely used throughout the pandemic to model SARS-CoV-2 transmission [9, 10, 11]. Although this framework has limitations [12], the SIR model was deemed sufficient to compare circulating strains rather than intricacies of transmission. Two models were formed: one for the previously circulating variant (V1) and one for the recently detected but unknown variant (V2). The compartment diagrams for both models are shown in Figure 1 and the associated system of differential equations can be found in appendix A. The outcomes of the model were daily and cumulative incidence and deaths. All values were given as a proportion of the population to give the model the adaptability to be used in multiple settings. The start and end of each variant's circulation is flexible in the model, but for this analysis times $t = 0$ and $t = 365$ were set to be the days of the first emergence of V1 and V2. Plots of various outcomes over time allowed for comparison between peak heights, widths and timings in order to make judgements on the new variant's impact on health systems. The model also allowed for consideration of the effect of interventions and their timing.

Figure 1: Compartment diagrams for variants V1 and V2

Parameter values

All parameter values and sources are shown in table 1. The full initial conditions for both variants can be found in appendix A. The transmission parameters for V1 were chosen to reflect the Delta variant. Relative parameters ϕ_{a-e} were incorporated into the V2 model to control for the degree to which V2 differs from V1 in terms of vaccine escape, transmissibility, recovery rate, virulence and cross-immunity. A variety of scenarios were explored to investigate the potential impact of the new variant in order to inform policy decisions about interventions and ultimately to protect the healthcare system and citizens. Sensitivity analyses were performed on ϕ parameters to investigate the effect on death and infections.

Parameter Table				
Parameter	Value	Description	Assumptions	Sources
β_1	0.152	Transmission rate of V1 (days^{-1}), calculated using $\beta = \gamma\ R0\ (1 - \mu_1)$	The value of R0 for the Delta variant is around 5 [2], however in this particular setting the variant has been circulating for a year with low incidence in recent months, so R0 was taken to be 1.52	[2]
γ_1	0.1	Recovery rate of V1 (days^{-1})	The period from infection to recovery is the same infection to death	[13]
μ_1	0.0057	Proportion of individuals that die as a result of V1 SARS-CoV-2 infection: CFR	The proportion of individuals dying as a result of infection is not uniform across demographics and is influenced by age and other comorbidities [14, 15]. The value for μ_1 was chosen as an average across all groups for one variant: the case fatality rate for SARS-CoV-2 is roughly 3% [16] but 5.7% for Delta [1].	[16, 1]
ρ_{init}	0.01	Proportion of population vaccinated before V1 wave (static value)	Vaccine coverage in LMICs is generally low due to manufacturing issues and a lack of resources and vaccine acceptance [17] and can be as low as 1% in in LICs and 14% in LMICs [18].	[18]
ρ	0.05	Proportion of population vaccinated between V1 and V2 waves (static value)	Value was chosen assuming vaccine coverage increased throughout the V1 wave: $\rho_{init} < \rho$	[18]
V2 to V1 comparison parameters				
ϕ_a	0.75-3.4	Rate multiplying factor: transmission rate of V2 compared to V1	-	Under test
ϕ_b	1	Rate multiplying factor: recovery rate of V2 compared to V1	-	Under test
ϕ_c	0.5-0.875	Proportion of fully vaccinated individuals unprotected against V2	The value of ρ then informed the initial conditions for V2: the proportion $\rho(1 - \phi_c)$ were removed from those susceptible to V2. No cross over between natural and vaccine-induced immunity exists (future adaptations could be made to the model to explore beyond this constraint)	Under test
ϕ_d	0.1-2	Virulence multiplying factor: Case Fatality Ratio of V2 compared to V1	-	Under test
ϕ_e	0.17-0.5	Proportion of individuals recovered from V1 that are immune to V2	The proportion that died as a result of V1 infection and a proportion ϕ_e with natural cross-immunity were removed from susceptible to V2. No cross over between natural and vaccine-induced immunity exists (future adaptations could be made to the model to explore beyond this constraint)	Under test
Other parameters				
$\imath_2$	0.001	Proportion of population infected with V2 when it was first reported	Individuals cannot be infected with both variants simultaneously	-

Table 1: Transmission model parameter values, descriptions and sources

App

An R-SHINY application is provided for exploration of parameter value combinations and the effect they have on model outputs. This tool can be used to aid policy decisions and allows non-experts to visualise scenarios including and beyond those discussed.
`https://github.com/student1061175/covid-variants`

Results

It was assumed that if the epidemic peaks for V2 were predicted to be higher or earlier than V1, more extreme healthcare measures may be necessary.

Scenario Analysis

Table 2 shows the scenarios considered. The differences between parameter values were compared for Delta and non-Delta variants, and the resulting ϕ values were used as a worst-case scenario due to the significant damage caused globally by the emergence of the Delta variant. The best-case scenario was imagined to be considerably dangerous characteristics.

Scenario Analysis						
Parameter	Non-Delta/ Ancestral variants	Delta Variant	Multiplication factor	Worst case	Best Case	Notes
Reproduction number R_0	2.79 [2]	5.08 [2]	-	-	-	-
Transmission rate β	0.11997	0.4064	3.339	$\phi_a = 3.4$	$\phi_a = 0.75$	Calculated using $\beta = \gamma\ R0\ (1 - \mu_1)$
Recovery rate γ	0.1 [13]	0.1 [13]	1	$\phi_b = 1$	$\phi_b = 1$	Recovery period assumed to be the same between variants. Model can be easily adapted to explore different values.
Vaccine escape	-	-	0.875	$\phi_c = 0.875$	$\phi_c = 0.5$	The Delta variant was eight times less sensitive to vaccine induced antibodies than non-Delta [4]. Best case value chosen based on discussions in [19].
CFR μ	0.57% [1]	0.2% [1]	0.351	$\phi_d = 2$	$\phi_d = 0.1$	The Delta variant evolved to become less virulent [1] hence it was considered unlikely that a new variant would evolve to be *significantly* less transmissible, although it is certainly possible that transmission rate could decrease.
Cross-immunity	-	-	0.167	$\phi_e = 0.167$	$\phi_e = 0.5$	The Delta variant was six times less sensitive to infection induced antibodies than non-Delta [4]. Cross-immunity between variants has been found to be around 0.1 [20]. Best case value chosen based on discussions in [20].

Table 2: Scenario description

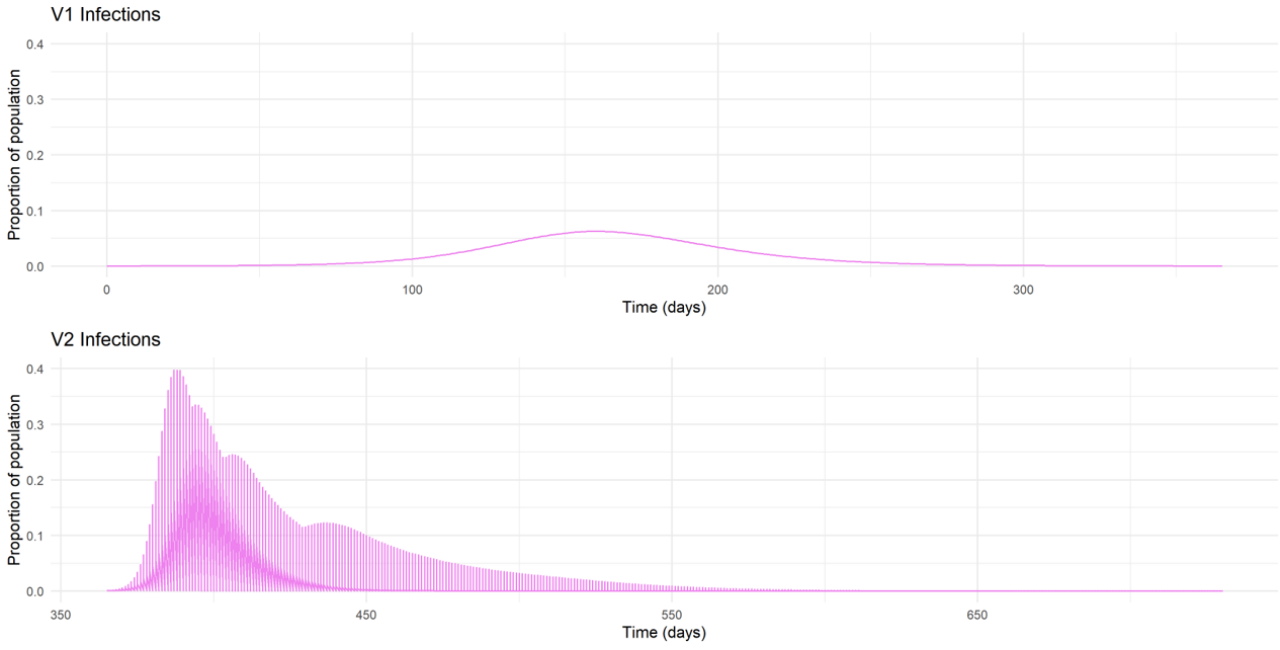

Figure 2: Sensitivity analysis on infections for all possible ϕ values between worst- and best-case scenarios

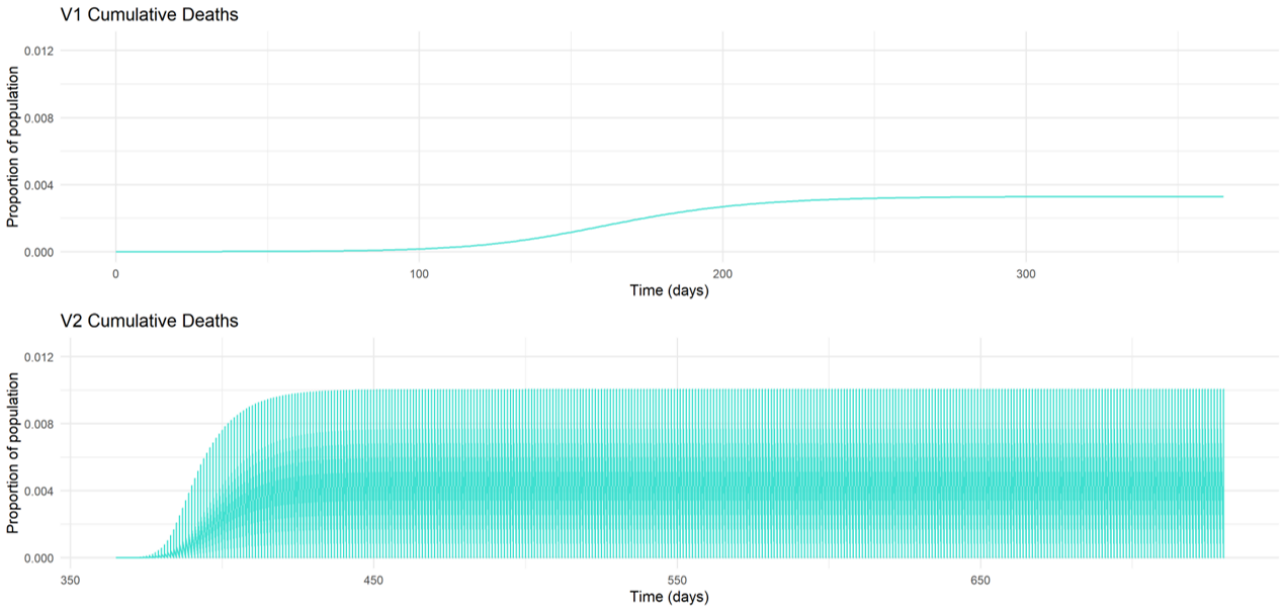

Figure 3: Sensitivity analysis on cumulative deaths for all possible ϕ values between worst- and best-case scenarios

Figures 2 and 3 show sensitivity analyses combinations of ϕ parameter with five intermediate values between the two scenarios. The model showed that if the evolutionary differences between variants are similar to those between Delta and non-Delta i.e. the worst-case scenario, without active suppression of V2 transmission the impact could be substantially higher than for V1. A significant reduction in transmission would be required to bring the peaks below those of V1, and could be achieved with a combination of public health measures [21] as discussed previously. Figure 4 shows the potential outcome if the transmission rate of V2 (β_2) was reduced, for example by the use of NPIs.

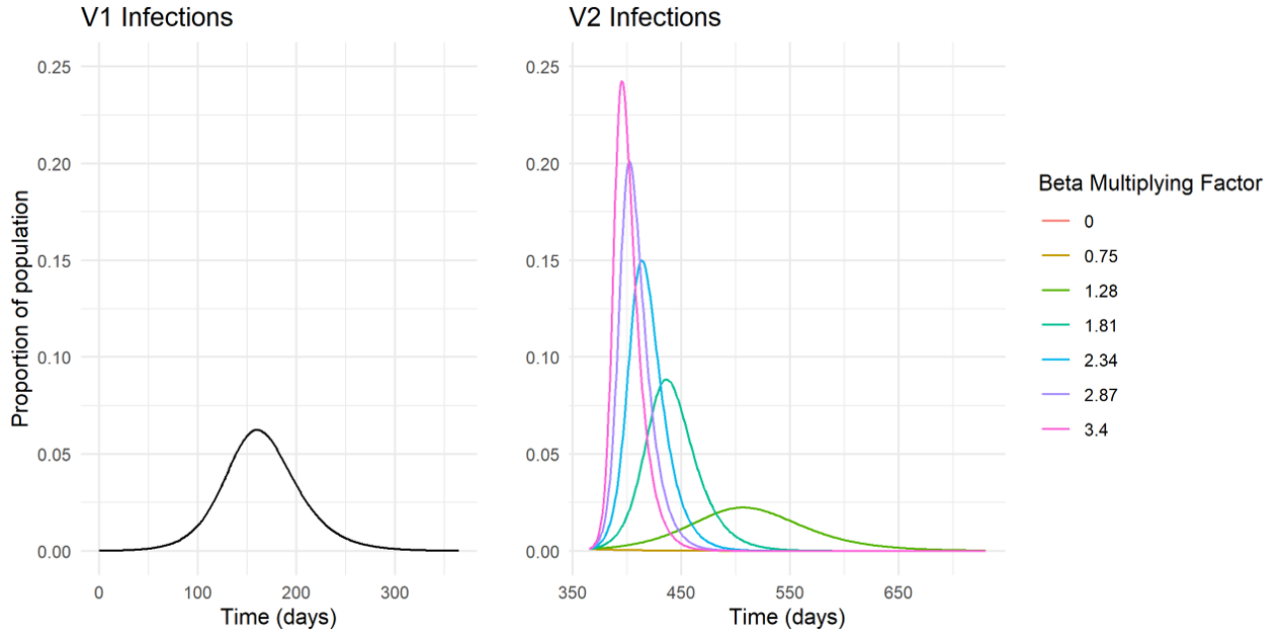

Figure 4: Sensitivity analysis on infections in worst case for six non-zero values of ϕ_a

An intermediate between the two extreme scenarios was assumed to be likely. Viruses typically evolve to gain evolutionary fitness so higher transmissibility and lower virulence was thought to be likely [3], and was in fact seen with the Delta variant [1, 2]. Values $\phi_a = 1.25$ and $\phi_d = 0.25$ were chosen and this scenario was considered with varying levels of cross immunity and vaccine escape. Figure 5 shows the value of the cumulative proportion infected for each pair of possible values of ϕ_c and ϕ_e between worst- and best-case scenarios. An intermediate value $\phi_c = 0.6$ was chosen and further sensitivity analysis was performed to observe the effect of cross-immunity on infections, shown in Figure 6. A summary of scenarios is shown in table 3.

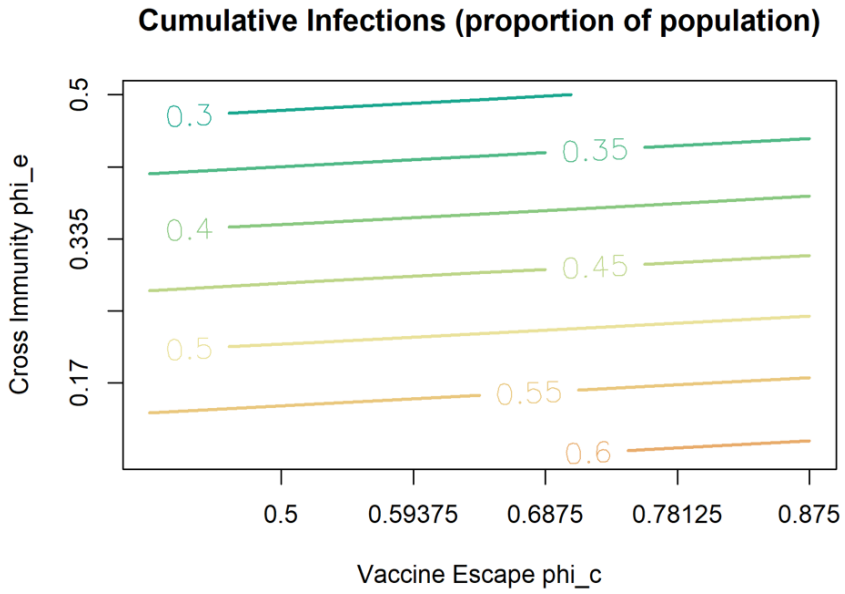

Figure 5: Sensitivity analysis on cumulative infections for five non-zero values each of ϕ_c and ϕ_e

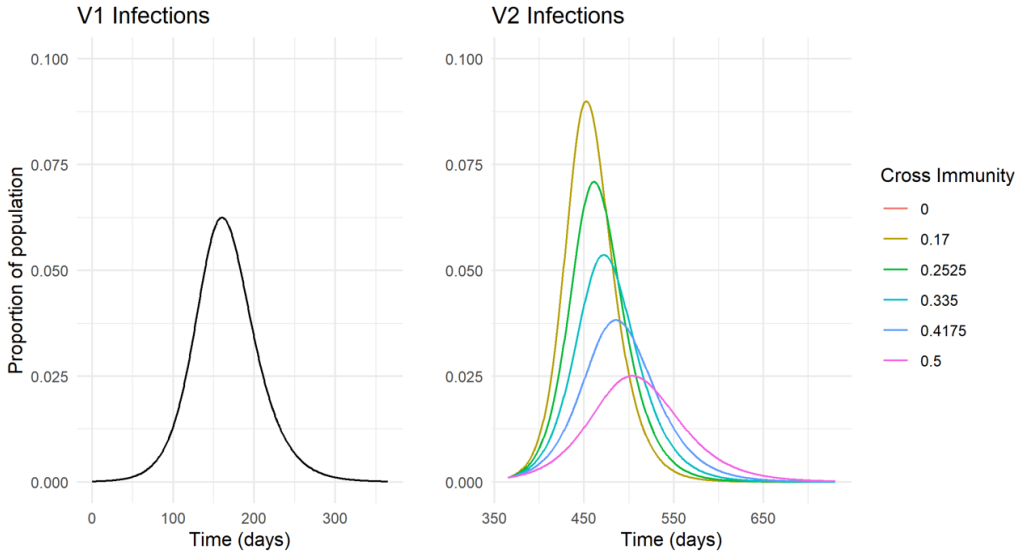

Figure 6: Sensitivity analysis on cumulative infections for five non-zero values of ϕ_e

Results Table									
Scenario	Description	Parameter values (ϕ_a, ϕ_b, ϕ_c, ϕ_d, ϕ_e)	Peak Daily Incidence Height (proportion of population)	Peak Daily Incidence Timing (approximate days since first case detected)	Peak Infections Height (proportion of population)	Peak Infections Timing (approximate days since first case detected)	Cumulative Infections (proportion of population)	Cumulative Deaths (proportion of population)	Reference Figures
V1 (baseline)	The V1 wave based on parameters given in Table 1	-	0.00655	151	0.0627	160	0.577	0.00329	Figures 2, 3
Worst-case	V2 wave based on most dangerous parameters given in Table 2	(3.4,1,0.875,2,0.167)	0.0710	18	0.400	23	0.883	0.0101	Figures 2, 3
Best-case	V2 wave based on least dangerous parameters given in Table 2	(0.75,1,0.5,0.1,0.5)	0.001	0	0.001	0	0.00334	2.47e-6	Figures 2, 3
Mid-case	V2 wave based on mean of best- and worst-case values given in Table 2	(2.08,1,0.688,1.05,0.334)	0.0225	42	0.18	48	0.698	0.00418	Figures 2, 3
Intermediate 1	Worst-case V2 scenario with reduced transmission rate	(1.28,1,0.875,2,0.167)	0.0103	77	0.095	85	0.629	0.00719	Figure 4
Intermediate 2	Lower virulence, higher transmissibility, cross-immunity below dangerous threshold	(1.25,1,0.6,0.25,0.335)	0.00493	103	0.047	112	0.445	0.000635	Figures 5, 6
Intermediate 3	Lower virulence, higher transmissibility, cross-immunity above dangerous threshold	(1.25,1,0.6,0.25,0.2525)	0.00670	91	0.0635	100	0.519	0.000741	Figures 5, 6

Table 3: Results of scenario and sensitivity analyses

Discussion

Results showed that, based on the models of V1 and V2, a variety of outcomes could be expected in terms of cases and death caused by the new variant. In particular, the new variant may have the potential to succeed the previous one in terms of overall damage to health systems. Figure 4 showed that a reduction in the transmission rate alone, even with all other characteristics more dangerous, may lead to a manageable V2 wave. However, if β_2 was just 1.81 times larger than β_1, the V2 wave appeared more disruptive than V1. According to these results, interventions targeting transmission rate could therefore be effective at reducing the impact of the new variant. The darker areas of Figures 2 and 3 show that, with many combinations of parameters, both the peak of infections and the increase in deaths will happen earlier than V1, even if the peak is not as high. The timing of NPIs is critical; early implementation of the strategies discussed at the beginning of this report could help to prevent overwhelm or collapse of healthcare systems in the event that V2 is considerably more dangerous than V1.

Figure 5 showed that, due to the low coverage of vaccinations, the evolution of V2 to escape vaccine-induced immunity may have little effect on infections. However, assuming lower virulence and higher transmissibility, if V2 evolved to evade infection-induced immunity in 66% or more cases, the impact of V2 could be larger than V1. Hence the evolution of the virus to evade the host's natural immune response appeared to be of bigger concern than vaccine escape, in particular when considering resource-limited settings. Nevertheless an increase in vaccine coverage could help to mitigate burden. Future analysis of a dynamic vaccinated proportion ρ could help to strengthen this argument.

Due to the lack of age and co-morbidity stratification in this model, an assessment of the likely scenario in terms of death was difficult. A future model featuring these intricacies could help to make a more informed judgement, but it is clear that an increase in virulence alone would lead to more deaths without intervention. Further to these suggestions of future work, the model could be easily adapted to portray different variants and can be modified as more information on the current variant of concern becomes available.

Conclusions

The analyses in this report showed that NPIs targeted to artificially reduce the transmission of V2 could help mitigate the potential damage of the new variant. The evolutionary traits of concern were found to be transmission rate, cross immunity and virulence, and continued monitoring of characteristics where possible will help to provide more information about what the future of V2 may look like and hence the timing and coverage of interventions that may be necessary. Based on the assumptions in the model and this report, Country X is advised to take steps immediately to prevent transmission while such characteristics are unknown. Widespread rapid testing, social distancing, lockdowns and isolation in the event of symptoms are recommended as solutions however in low income settings these are not always feasible. Therefore this report concludes that hand-washing, mask-wearing and some social distancing should be implemented as soon as possible in order to reduce transmission. Furthermore, zonal lockdowns should be put into effect to reduce pressure on already strained health systems as cases begin to increase.

Secondary Analysis One Month After Initial Report

Background

Since the previous report, information on the emerging variant has become available allowing for further specification of its possible impact. The transmissibility is now known to be 10% to 50% higher than V1, the virulence 2 to 10 times lower, and V2 is thought to have the capacity to infect between 25% and 40% of individuals vaccinated against V1. Information pertaining to cross immunity was not given.

Methods

The transmission model used previously was adapted to portray this information and sensitivity analyses were performed to a range of possibilities. Values at either end and in the mid-point of the given ranges were analysed.

Results

Table 4 shows a summary of the model outputs for all scenarios. Figure 7 shows the range of outcomes for V2 infections compared to V1 between the new worst- and best-case scenarios. Figure 8 shows the equivalent result for cumulative deaths.

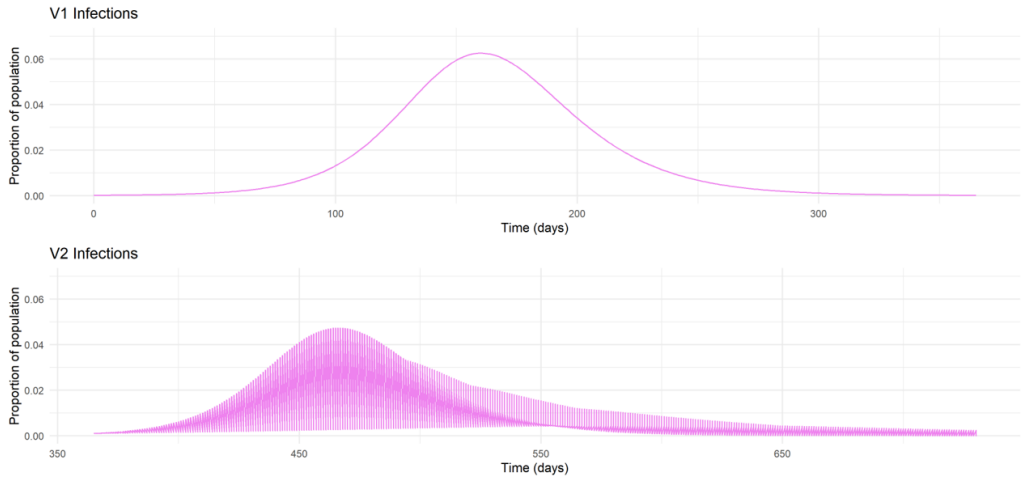

Figure 7: Sensitivity analysis on infections for all possible ϕ values in given ranges

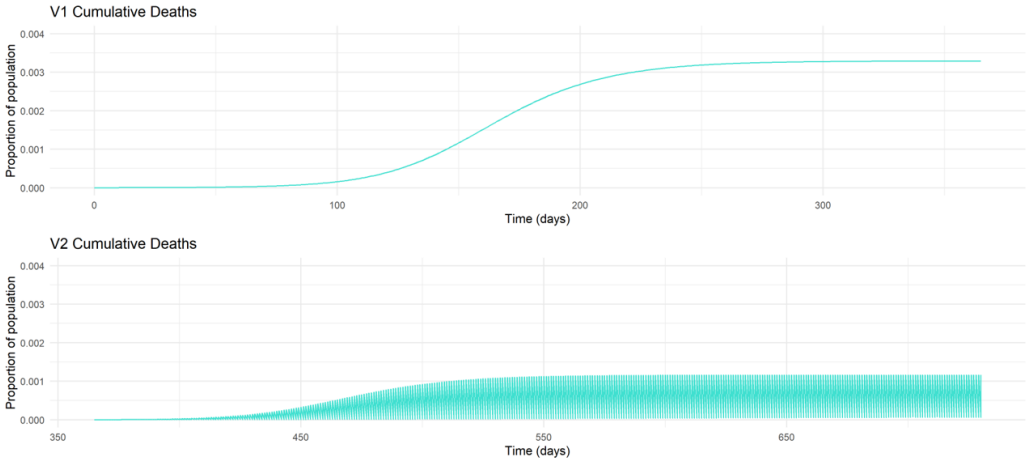

Figure 8: Sensitivity analysis on cumulative deaths for all possible ϕ values in given ranges

The value of cross immunity parameter ϕ_e was varied from 0.17 to 0.5, as in the worst- and best-case scenarios used previously. Figure 9 shows the possible infection curves for V2 based intermediate scenarios 1-3.

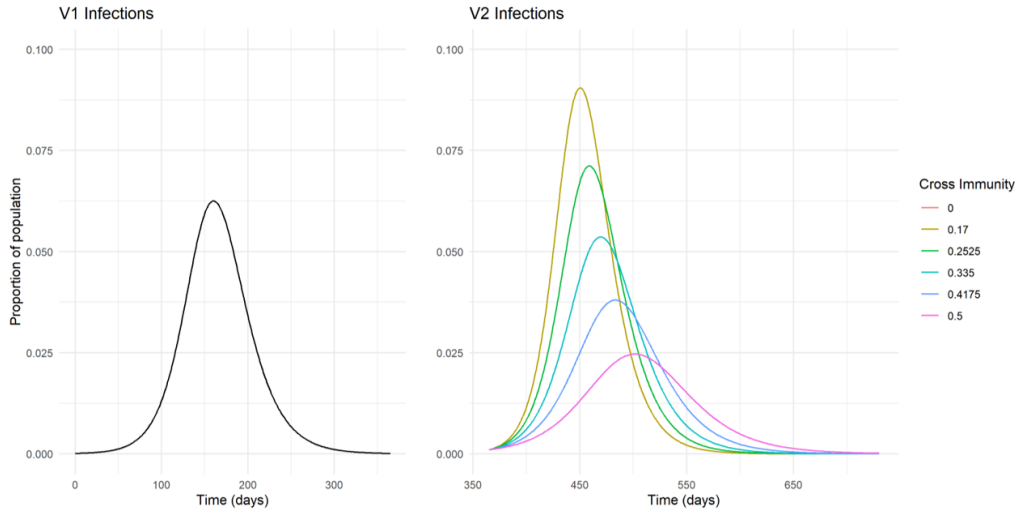

Figure 9: Sensitivity analysis on proportion infected for five non-zero values of ϕ_e with $\phi_a = 1.3,\ \phi_c = 0.325,\ \phi_d = 0.2$

Results Table									
Scenario	Description	Parameter values (ϕ_a, ϕ_b, ϕ_c, ϕ_d, ϕ_e)	Peak Daily Incidence Height (proportion of population)	Peak Daily Incidence Timing (approximate days since first case detected)	Peak Infections Height (proportion of population)	Peak Infections Timing (approximate days since first case detected)	Cumulative Infections (proportion of population)	Cumulative Deaths (proportion of population)	Reference Figures
V1 (baseline)	The V1 wave based on parameters given in Table 1	-	0.00655	151	0.0627	160	0.577	0.00329	fig
Worst-case	V2 wave based on most dangerous end of new range of values	(1.5,1,0.4,0.5,0.3)	0.0103	70	0.0094	77	0.579	0.00165	fig
Best-case	V2 wave based on least dangerous end of new range of values	(1.1,1,0.25,0.1,0.3)	0.00248	140	0.0244	150	0.337	0.000193	fig
Intermediate 1	V2 wave based on mean of highest and lowest new values	(1.3,1,0.325,0.3,0.3)	0.0061	93	0.0580	102	0.484	0.000830	fig
Intermediate 2	V2 wave based on mean of highest and lowest new values with cross-immunity above dangerous threshold	(1.3,1,0.325,0.2,0.2525)	0.00724	87	0.0680	96	0.526	0.000902	fig
Intermediate 3	V2 wave based on mean of highest and lowest new values with cross-immunity below dangerous threshold	(1.3,1,0.325,0.2,0.335)	0.00533	98	0.0507	107	0.453	0.000776	fig

Table 4: Results of scenario and sensitivity analyses

Discussion

In light of the new information, the model showed that, with the assumed value for cross-immunity, the maximum height of the infection peak would be lower than V1, even with parameters being the most dangerous, as shown in Figure 7. The peak appeared to occur earlier, however, and was only slightly lower, with an approximate maximum proportion infected of 5% compared to 6% for V2. The densest area of the shaded region appeared to show a peak at 2%-3%, implying this is a likely outcome based on the data given. Similarly, the maximum proportion of cumulative deaths output by the model given these values was lower for V2 than V1, with the maximum being approximately 0.1%, and the densest being 0.05%, as shown in Figure 8. These results imply the impact of the new variant may be manageable for Country X. With little known about the degree of natural cross-immunity between the variants however, Figure 9 showed that there was in fact a possibility of a greater V2 wave if more than approximately 75% of individuals with natural immunity from V1 are susceptible to V2.

Conclusions

The new information appeared to show that the impact may be less than initially presumed, unless natural cross-immunity between variants is particularly low. Country X is advised to relax restrictions with caution, and to continue monitoring cases as much as possible. Hand-washing and mask-wearing are advised due to their relatively low economic and practical cost, while efforts to increase vaccine coverage should be continued in order to protect as many individuals as possible from both variants.

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Supplementary information

Appendix A

V1 transmission

$$\frac{dS1}{dt} = -\beta_1\ S1\ I1$$

$$\frac{dI1}{dt} = \beta_1\ S1\ I1 - \gamma_1\ I1$$

$$\frac{dD1}{dt} = \mu_1\ \gamma_1\ I1$$

$$\frac{dR1}{dt} = (1-\mu_1)\ \gamma_1\ I1$$

$$R0_1 = \frac{\beta_1}{\gamma_1\ (1-\mu_1)}$$

Cumulative Incidence of V1

$$\frac{dCInc1}{dt} = \beta_1\ S1\ I1$$

V1 initial conditions

$$S1(0) = 1-\rho_{init} \qquad I1(0) = 0.0001 \qquad D1(0) = 0 \qquad R1(0) = \rho_{init} \qquad CInc1(0) = 0$$

V2 transmission

$$\frac{dS2}{dt} = -\beta_2\ S2\ I2$$

$$\frac{dI2}{dt} = \beta_2\ S2\ I2 - \gamma_2\ I2$$

$$\frac{dD2}{dt} = \mu_2\ \gamma_2\ I2$$

$$\frac{dR2}{dt} = (1-\mu_2)\ \gamma_2\ I2$$

Cumulative Incidence of V2

$$\frac{dCInc2}{dt} = \beta_2\ S2\ I2$$

V1 to V2 relative transmission parameters

$$\beta_2 = \phi_a\ \beta_1$$

$$\gamma_2 = \phi_b\ \gamma_1$$

$$\mu_2 = \phi_d\ \mu_1$$

V2 initial conditions

$$S2(0) = 1 - \rho\ (1-\phi_c) - i_2 - R1_{end} - \phi_e\ D1_{end}$$

$$I1(0) = i_2 \qquad D2(0) = 0 \qquad R2(0) = \rho\ (1-\phi_c) + \phi_e\ D1_{end} \qquad CInc2(0) = 0$$

Time $t = 0$ defined as the day of the first detected case of V2

Transmission model for variants V1 and V2

```
# Setup ####

library(deSolve)
library(tidyverse)
library(gridExtra)

# Parameters V1 ####
R0 <- 0.3*5.08 # Reproductive number of V1
gamma1 <- 1/10 # Latent rate of V1
mu1 <- 0.0057 # Proportion of infected individuals that die from
   ↪ V1
beta1 <- R0 * gamma1 * (1 - mu1) # Transmission rate of V1
rho_init <- 0.01 # proportion vaccinated against V1 before V1 wave
rho <- 0.05 # Proportion of population vaccinated against V1 after
   ↪  V1 wave
i2 <- 0.001 # Proportion of population infected with V2 when it is
   ↪  first detected
v2_day <-365 # Day on which V2 first detected
phia <- 1.3 # Degree to which V2 is more transmissible than V1
phib <- 1 # Degree to which latent rate of V2 is higher than V1
phic <- 0.325 # Degree to which V2 is a V1 vaccine escape
phid <- 0.3 # Degree to which V2 is more virulent than V1
phie <- 0.335 # What proportion of individuals recovered from V1
   ↪ are immune to V2
time_stop <- 730 # Total days in model

col_infections <- "violet"
col_deaths <- "turquoise"

parameters <- c(
  beta1 <- beta1,
  gamma1 <- gamma1,
  phia <- phia,
  phib <- phib,
  phic <- phic,
  phid <- phid,
  phie <- phie,
  mu1 <- mu1,
  rho_init <- rho_init,
  rho <- rho,
  i2 <- i2,
  v2_day <- v2_day,
  time_stop <- time_stop
)

# Times V1 ####

time_start1 <- 0
time_stop1 <- time_stop
```

```
deltat1 <- 1
tps1 <- seq(time_start1, time_stop1, by=deltat1)


# Times V2 ####

time_start2 <- v2_day
time_stop2 <- time_stop
deltat2 <- 1
tps2 <- seq(time_start2, time_stop2, by=deltat2)

# Initial conditions V1 ####

S1_0 <- 1 - rho_init
I1_0 <- 0.0001
D1_0 <- 0
R1_0 <- rho_init
CInc1_0 <- 0
init1 <- c(S1 = S1_0, I1 = I1_0, D1 = D1_0, R1 = R1_0, CInc1 =
   ↪ CInc1_0)

# Define model V1 ####

covid_V1 <- function(time,state,parameters){
  with(as.list(c(state,parameters)),{
    dS1 <- - beta1 * S1 * I1
    dI1 <- beta1 * S1 * I1 - gamma1 * (1 - mu1) * I1 - gamma1 *
       ↪ mu1 * I1
    dD1 <- mu1 * gamma1 * I1
    dR1 <- (1 - mu1) * gamma1 * I1
    dCInc1 <- beta1 * S1 * I1

    return(list(c(dS1,dI1,dD1,dR1,dCInc1)))
  }
  )
}



# Define model V2 ####

covid_V2 <- function(time,state,parameters){
  with(as.list(c(state,parameters)),{

    beta2 <- phia * beta1
    gamma2 <- phib * gamma1
    mu2 <- phid * mu1

    dS2 <- - beta2 * S2 * I2
    dI2 <- beta2 * S2 * I2 - gamma2 * I2
    dD2 <- mu2 * gamma2 * I2
```

```
    dR2 <- (1 - mu2) * gamma2 * I2
    dCInc2 <- beta2 * S2 * I2

    return(list(c(dS2,dI2,dD2,dR2,dCInc2)))
  }
  )
}

# Run model 1 ####

out1 <- as.data.frame(ode(y=init1, times=tps1, func = covid_V1,
   ↪ parms = parameters))

# Initial conditions V2 ####

S2_0 <- 1 - rho*(1 - phic) - i2 - out1[v2_day,4] - phie*out1[v2_
   ↪ day,5]
I2_0 <- i2
D2_0 <- 0
R2_0 <- rho*(1 - phic) + phie*out1[v2_day,5]
CInc2_0 <- 0
init2 <- c(S2 = S2_0, I2 = I2_0, D2 = D2_0, R2 = R2_0, CInc2 =
   ↪ CInc2_0)


# Run model 2 and manipulate data ####

out2_growth <- ode(y=init2, times=tps2, func = covid_V2, parms =
   ↪ parameters)

out2_initial1 <- matrix(0:(v2_day-1), nrow=v2_day, ncol=1)
colnames(out2_initial1) <- c("time")

out2_initial2 <- matrix(rep((1 - rho*(1 - phic) - i2 - out1[time_
   ↪ stop,4] - phie*out1[time_stop,5]),v2_day), nrow=v2_day, ncol
   ↪ =1)
colnames(out2_initial2) <- c("S2")

out2_initial3 <- matrix(rep(0,v2_day), nrow = v2_day, ncol=1)
colnames(out2_initial3) <- c("I2")

out2_initial4 <- matrix(rep(0,v2_day), nrow = v2_day, ncol=1)
colnames(out2_initial4) <- c("D2")

out2_initial5 <- matrix(rep((rho*(1 - phic) + i2 + phie*out1[time_
   ↪ stop,5]),v2_day), nrow=v2_day, ncol=1)
colnames(out2_initial5) <- c("R2")

out2_initial6 <- matrix(rep(0,v2_day), nrow = v2_day, ncol=1)
colnames(out2_initial6) <- c("CInc2")
```

```
out2_initial <- cbind(out2_initial1,out2_initial2,out2_initial3,
   ↪ out2_initial4,out2_initial5,out2_initial6)
tail(out2_initial)

out2_combined <- rbind(out2_initial,out2_growth)

out2 <- as.data.frame(out2_combined)

out <- merge(out1,out2,by="time")

output <- as_tibble(out) %>%
  mutate(P1 = S1+I1+D1+R1,
         P2 = S2+I2+D2+R2,
         Inc1 = c(0, diff(CInc1)),
         Inc2 = c(0, diff(CInc2)),
         Death1 = c(0, diff(D1)),
         Death2 = c(0, diff(D2))) %>%
  pivot_longer(names_to = "variable", cols = !1) %>%
  mutate(variant = ifelse(str_ends(variable, "2"), "V2", "V1")
  )

# V1 plots ####

plot1 <- output %>%
  filter(variable %in% c("Inc1"), time<v2_day,) %>%
  group_by(variable) %>%
  ggplot()+
  geom_line(aes(x = time, y=value, colour = as_factor(variable)),
     ↪ colour=col_infections)+
  theme_minimal() +
  labs(title = "Daily␣Incidence␣of␣V1␣Wave", x=('Time␣(days)'), y
     ↪ =("Proportion␣of␣population"), colour="Compartment") +
  facet_wrap(~variable)

plot2 <- output %>%
  filter(variable %in% c("Death1"), time<v2_day,) %>%
  group_by(variable) %>%
  ggplot()+
  geom_line(aes(x = time, y=value, colour = as_factor(variable)),
     ↪ colour=col_deaths)+
  theme_minimal() +
  labs(title = "Daily␣Deaths␣of␣V1␣Wave", x=('Time␣(days)'), y =("
     ↪ Proportion␣of␣population"), colour="Compartment") +
  facet_wrap(~variable)

grid.arrange(plot1, plot2, ncol=2)

# Other compartment plots ####

output %>%
```

```
  filter(variable %in% c("S1", "I1", "D1", "R1", "S2", "I2", "D2",
     ↪  "R2")) %>%
  group_by(variable) %>%
  ggplot()+
  geom_line(aes(x = time, y=value, colour = as_factor(variable)))+
  theme_minimal() +
  labs(title = "SIR Compartments", x=('Time (days)'), y =("
     ↪ Proportion of population"), colour="Compartment") +
  facet_wrap(~variant)

output %>%
  filter(variable %in% c("Inc1", "Inc2")) %>%
  group_by(variable) %>%
  ggplot()+
  geom_line(aes(x = time, y=value, colour = as_factor(variable)))+
  theme_minimal() +
  labs(title = "Daily Incidence", x=('Time (days)'), y =("
     ↪ Proportion of population"), colour="Compartment") +
  facet_wrap(~variant)

output %>%
  filter(variable %in% c("Death1", "Death2")) %>%
  group_by(variable) %>%
  ggplot()+
  geom_line(aes(x = time, y=value, colour = as_factor(variable)))+
  theme_minimal() +
  labs(title = "Daily Deaths", x=('Time (days)'), y =("Proportion
     ↪ of population"), colour="Compartment") +
  facet_wrap(~variant)

output %>%
  filter(variable %in% c("Inc1", "Inc2")) %>%
  group_by(variable) %>%
  ggplot()+
  geom_line(aes(x = time, y=value, colour = as_factor(variable)))+
  theme_minimal() +
    labs(title = "Daily Incidence", x=('Time (days)'), y =("
       ↪ Proportion of population"), colour="Compartment")# +

output %>%
  filter(variable %in% c("Death1", "Death2")) %>%
  group_by(variable) %>%
  ggplot()+
  geom_line(aes(x = time, y=value, colour = as_factor(variable)))+
  theme_minimal() +
  labs(title = "Daily Deaths", x=('Time (days)'), y =("Proportion
     ↪ of population"), colour="Compartment")


# Gathering results ####
```

```
output %>%
  filter(variable %in% c("I2")) %>%
  group_by(variable) %>%
  ggplot()+
  xlim(v2_day,time_stop) +
  geom_vline(xintercept=v2_day+107) +
  geom_hline(yintercept=0.0507) +
  geom_line(aes(x = time, y=value, colour = as_factor(variable)))+
  theme_minimal() +
  labs(title = "Infections", x=('Time␣(days)'), y =("Proportion␣of
     ↪ ␣population"), colour="Compartment")

output %>%
  filter(variable %in% c("Inc2")) %>%
  group_by(variable) %>%
  ggplot()+
  geom_vline(xintercept=v2_day+98) +
  geom_hline(yintercept=0.00533) +
  xlim(v2_day,time_stop) +
  geom_line(aes(x = time, y=value, colour = as_factor(variable)))+
  theme_minimal() +
  labs(title = "Daily␣Incidence", x=('Time␣(days)'), y =("
     ↪ Proportion␣of␣population"), colour="Compartment")

tail(out2_growth)

# *BEWARE - CAN BE LONG TO RUN* Sensitivity analysis - all five
   ↪ parameters on INFECTIONS ####

phia_vector<-seq(0.75,3.4,by=0.6625)
phib_vector<-seq(1,1,by=1)
phic_vector<-seq(0.5,0.875,by=0.09375)
phid_vector<-seq(0.1,2,by=0.475)
phie_vector<-seq(0.17,0.5,by=0.0825)

result3<-matrix(0,nrow = 1,ncol = 7)
colnames(result3)<-c("time","I","phic","phia","phid","phib","phie"
   ↪ )
result3<-as.data.frame(result3)
for (m in 1:length(phie_vector)){
  for(l in 1:length(phib_vector)){
    for (k in 1:length(phid_vector)){
      for (j in 1:length(phia_vector)){
        for (i in 1:length(phic_vector)){
          parameters["phic"]<-phic_vector[i]
          parameters["phia"]<-phia_vector[j]
          parameters["phid"]<-phid_vector[k]
          parameters["phib"]<-phib_vector[l]
          parameters["phie"]<-phie_vector[m]
```

```
          S2_0 <- 1 - rho*(1 - phic_vector[i]) - i2 - out1[v2_day
             ↪ ,4] - phie_vector[m]*out1[v2_day,5]
          I2_0 <- i2
          D2_0 <- 0
          R2_0 <- rho*(1 - phic_vector[i]) + phie_vector[m]*out1[
             ↪ v2_day,5]
          CInc2_0 <- 0
          init2 <- c(S2 = S2_0, I2 = I2_0, D2 = D2_0, R2 = R2_0,
             ↪ CInc2 = CInc2_0)

          out_aux <- ode(y = init2, times = tps2, func = covid_V2,
             ↪  parms = parameters)

          aux_mat<-cbind(out_aux[,c(1,3)],rep(phic_vector[i],
             ↪ length(tps2)), rep(phic_vector[j],length(tps2)),
             ↪ rep(phic_vector[k],length(tps2)), rep(phic_vector[
             ↪ l],length(tps2)), rep(phic_vector[m],length(tps2))
             ↪ )

          colnames(aux_mat)<-c("time","I","phic","phia","phid","
             ↪ phib","phie")
          result3<-rbind(result3,aux_mat)
        }
      }
    }
  }
}

result3 <- pivot_longer(result3, names_to="phi", cols=3:7 )



p13 <- out1 %>%
  ggplot() +
  geom_line(aes(x=time,y=I1),colour=col_infections) +
  xlim(0,v2_day) +
  ylim(0,0.4) +
  theme_minimal() +
  labs(title = "V1␣Infections", x=('Time␣(days)'), y="Proportion␣
     ↪ of␣population")

p14 <- result3 %>%
  ggplot() +
  geom_line(aes(x=time,y=I),colour=col_infections) +
  xlim(v2_day,time_stop) +
  ylim(0,0.4) +
  theme_minimal() +
  labs(title = "V2␣Infections", x=('Time␣(days)'), y =("Proportion
     ↪ ␣of␣population"))

grid.arrange(p13, p14,  nrow=2)
```

```
# *BEWARE - CAN BE LONG TO RUN* Sensitivity analysis - all five
   ↪ parameters on CUMULATIVE DEATHS ####

phia_vector<-seq(0.75,3.4,by=0.6625)
phib_vector<-seq(1,1,by=1)
phic_vector<-seq(0.5,0.875,by=0.09375)
phid_vector<-seq(0.1,2,by=0.475)
phie_vector<-seq(0.17,0.5,by=0.0825)

result4<-matrix(0,nrow = 1,ncol = 7)
colnames(result4)<-c("time","D","phic","phia","phid","phib","phie"
   ↪ )
result4<-as.data.frame(result4)
for (m in 1:length(phie_vector)){
  for(l in 1:length(phib_vector)){
    for (k in 1:length(phid_vector)){
      for (j in 1:length(phia_vector)){
        for (i in 1:length(phic_vector)){
          parameters["phic"]<-phic_vector[i]
          parameters["phia"]<-phia_vector[j]
          parameters["phid"]<-phid_vector[k]
          parameters["phib"]<-phib_vector[l]
          parameters["phie"]<-phie_vector[m]

          S2_0 <- 1 - rho*(1 - phic_vector[i]) - i2 - out1[v2_day
             ↪ ,4] - phie_vector[m]*out1[v2_day,5]
          I2_0 <- i2
          D2_0 <- 0
          R2_0 <- rho*(1 - phic_vector[i]) + phie_vector[m]*out1[
             ↪ v2_day,5]
          CInc2_0 <- 0
          init2 <- c(S2 = S2_0, I2 = I2_0, D2 = D2_0, R2 = R2_0,
             ↪ CInc2 = CInc2_0)

          out_aux <- ode(y = init2, times = tps2, func = covid_V2,
             ↪  parms = parameters)

          aux_mat<-cbind(out_aux[,c(1,4)],rep(phic_vector[i],
             ↪ length(tps2)), rep(phic_vector[j],length(tps2)),
             ↪ rep(phic_vector[k],length(tps2)), rep(phic_vector[
             ↪ l],length(tps2)), rep(phic_vector[m],length(tps2))
             ↪ )

          colnames(aux_mat)<-c("time","D","phic","phia","phid","
             ↪ phib","phie")
          result4<-rbind(result4,aux_mat)
        }
      }
    }
  }
```

```
}

result4 <- pivot_longer(result4, names_to="phi", cols=3:7 )

p15 <- out1 %>%
  ggplot() +
  geom_line(aes(x=time,y=D1),colour=col_deaths) +
  xlim(0,v2_day) +
  ylim(0,0.0125) +
  theme_minimal() +
  labs(title = "V1 Cumulative Deaths", x=('Time (days)'), y="
     ↪ Proportion of population")

p16 <- result4 %>%
  ggplot() +
  geom_line(aes(x=time,y=D),colour=col_deaths) +
  xlim(v2_day,time_stop) +
  ylim(0,0.0125) +
  theme_minimal() +
  labs(title = "V2 Cumulative Deaths", x=('Time (days)'), y =("
     ↪ Proportion of population"))

grid.arrange(p15, p16,  nrow=2)

# Sensitivity analysis  - vaccine escape and cross immunity on
   ↪ cumulative INFECTIONS ####

parameters["phia"] <- 1.25 # Transmission rate
parameters["phib"] <- 1 # Latent rate
phic_vector<-seq(0.5,0.875,by=0.09375) # Vaccine escape
parameters["phid"] <- 0.25 # Virulence
phie_vector<-seq(0.17,0.5,by=0.0825) # Cross immunity

cumulative_infections_result<-matrix(0,nrow = length(phic_vector),
   ↪ length(phie_vector))
for (i in 1:length(phic_vector)){
  for (j in 1:length(phie_vector)){
    parameters["phic"]<-phic_vector[i] # Virulence mu
    parameters["phie"]<-phie_vector[j] # Transmissibility beta

    S2_0 <- 1 - rho*(1 - phic_vector[i]) - i2 - out1[v2_day,4] -
       ↪ phie_vector[j]*out1[v2_day,5]
    I2_0 <- i2
    D2_0 <- 0
    R2_0 <- rho*(1 - phic_vector[i]) + phie_vector[j]*out1[v2_day
       ↪ ,5]
    CInc2_0 <- 0
    init2 <- c(S2 = S2_0, I2 = I2_0, D2 = D2_0, R2 = R2_0, CInc2 =
       ↪  CInc2_0)
```

```
    out <- ode(y = init2, times = tps2, func = covid_V2, parms =
      ↪ parameters)

    cumulative_infections_result[i,j]<-tail(out[,6],1)
  }
}

#contour plot of a matrix. don't want to draw the x or y axis.
  ↪ give labels. 10 levels:
contour(cumulative_infections_result,xaxt = "n", yaxt = "n",ylab="
  ↪ Cross␣Immunity␣phi_e",xlab="Vaccine␣Escape␣phi_c",nlevels =
  ↪ 10,labcex=1.3,col = hcl.colors(11, "Temps"),lwd =2)
axis(1, at=1:length(phic_vector)/length(phic_vector), labels=phic_
  ↪ vector)
axis(2, at=1:length(phie_vector)/length(phie_vector), labels=phie_
  ↪ vector)
title("Cumulative␣Infections␣(proportion␣of␣population)")


# Sensitivity analysis - worst case with beta on INFECTIONS ####

phia_vector<-seq(0.75,3.4,by=0.53)
parameters["phib"] <- 1 # Latent rate
parameters["phic"] <- 0.875 # Vaccine escape
parameters["phid"] <- 2 # Virulence
parameters["phie"] <- 0.17 # Cross immunity

result_phia<-matrix(0,nrow = 1,ncol = 3)
colnames(result_phia)<-c("time","I","phia")
result_phia<-as.data.frame(result_phia)
for (i in 1:length(phia_vector)){
  parameters["phia"]<-phia_vector[i]
  out_aux <- ode(y = init2, times = tps2, func = covid_V2, parms =
    ↪  parameters)

  aux_mat<-cbind(out_aux[,c(1,3)],rep(phia_vector[i],length(tps2))
    ↪ )
  colnames(aux_mat)<-c("time","I","phia")
  result_phia<-rbind(result_phia,aux_mat)
}

p1 <- out1 %>%
  ggplot() +
  geom_line(aes(x=time,y=I1)) +
  xlim(0,v2_day) +
  ylim(0,0.25) +
  theme_minimal() +
  labs(title = "V1␣Infections", x=('Time␣(days)'), y="Proportion␣
    ↪ of␣population")

p2 <- result_phia %>%
```

```
  ggplot() +
  geom_line(aes(x=time,y=I,colour=as.factor(phia))) +
  xlim(v2_day,time_stop) +
  ylim(0,0.25) +
  theme_minimal() +
  labs(title = "V2 Infections", x=('Time (days)'), y =(" "),
     ↪ colour="Beta Multiplying Factor")

grid.arrange(p1, p2, widths=c(0.38, 0.62), ncol=2)

# Sensitivity analysis - cross immunity on INFECTIONS ####

parameters["phia"] <- 1.25 # Transmissibility
parameters["phib"] <- 1 # Latent rate
parameters["phic"] <- 0.6 # Vaccine escape
parameters["phid"] <- 0.25 # Virulence
phie_vector<-seq(0.17,0.5,by=0.0825)

result_phie<-matrix(0,nrow = 1,ncol = 3)
colnames(result_phie)<-c("time","I","phie")
result_phie<-as.data.frame(result_phie)
for (i in 1:length(phie_vector)){
  parameters["phie"]<-phie_vector[i]

  out1 <- as.data.frame(ode(y=init1, times=tps1, func = covid_V1,
     ↪ parms = parameters))

  S2_0 <- 1 - rho*(1 - phic) - i2 - out1[v2_day,4] - phie_vector[i
     ↪ ]*out1[v2_day,5]
  I2_0 <- i2
  D2_0 <- 0
  R2_0 <- rho*(1 - phic) + phie_vector[i]*out1[v2_day,5]
  CInc2_0 <- 0
  init2 <- c(S2 = S2_0, I2 = I2_0, D2 = D2_0, R2 = R2_0, CInc2 =
     ↪ CInc2_0)

  out_aux <- ode(y = init2, times = tps2, func = covid_V2, parms =
     ↪  parameters)

  aux_mat<-cbind(out_aux[,c(1,3)],rep(phie_vector[i],length(tps2))
     ↪ )
  colnames(aux_mat)<-c("time","I","phie")
  result_phie<-rbind(result_phie,aux_mat)
}

p7 <- out1 %>%
  ggplot() +
  geom_line(aes(x=time,y=I1)) +
  xlim(0,v2_day) +
  ylim(0,0.1) +
  theme_minimal() +
```

```
  labs(title = "V1 Infections", x=('Time (days)'), y="Proportion
     ↪ of population")

p8 <- result_phie %>%
  ggplot() +
  geom_line(aes(x=time,y=I,colour=as.factor(phie))) +
  xlim(v2_day,time_stop) +
  ylim(0,0.1) +
  theme_minimal() +
  labs(title = "V2 Infections", x=('Time (days)'), y =(" "),
     ↪ colour="Cross Immunity")

grid.arrange(p7, p8, widths=c(0.4,0.6), ncol=2)


# 1 MONTH LATER - Sensitivity analysis - all three parameters on
   ↪ INFECTIONS ####

phia_vector<-seq(1.1,1.5,by=0.1) # Beta
parameters["phib"] <- 1 # Latent rate
phic_vector<-seq(0.25,0.4,by=0.05) # Vaccine escape
phid_vector<-seq(0.1,0.5,by=0.1) # Virulence
parameters["phie"] <- 0.3 # Cross immunity


result1<-matrix(0,nrow = 1,ncol = 5)
colnames(result1)<-c("time","I","phic","phia","phid")
result1<-as.data.frame(result1)
for (k in 1:length(phid_vector)){
 for (j in 1:length(phia_vector)){
  for (i in 1:length(phic_vector)){
    parameters["phic"]<-phic_vector[i]
    parameters["phia"]<-phia_vector[j]
    parameters["phid"]<-phid_vector[k]


    S2_0 <- 1 - rho*(1 - phic_vector[i]) - i2 - out1[v2_day,4] -
       ↪ phie*out1[v2_day,5]
    I2_0 <- i2
    D2_0 <- 0
    R2_0 <- rho*(1 - phic_vector[i]) + phie*out1[v2_day,5]
    CInc2_0 <- 0
    init2 <- c(S2 = S2_0, I2 = I2_0, D2 = D2_0, R2 = R2_0, CInc2 =
       ↪  CInc2_0)

    out_aux <- ode(y = init2, times = tps2, func = covid_V2, parms
       ↪  = parameters)

    aux_mat<-cbind(out_aux[,c(1,3)],rep(phic_vector[i],length(tps2
       ↪ )), rep(phic_vector[j],length(tps2)), rep(phic_vector[k
       ↪ ],length(tps2)))
```

```
    colnames(aux_mat)<-c("time","I","phic","phia","phid")
    result1<-rbind(result1,aux_mat)
  }
 }
}
result1 <- pivot_longer(result1, names_to="phi", cols=3:5 )


p9 <- out1 %>%
  ggplot() +
  geom_line(aes(x=time,y=I1),colour=col_infections) +
  xlim(0,v2_day) +
  ylim(0,0.07) +
  theme_minimal() +
  labs(title = "V1 Infections", x=('Time (days)'), y="Proportion
    ↪ of population")

p10 <- result1 %>%
  ggplot() +
  geom_line(aes(x=time,y=I),colour=col_infections) +
  xlim(v2_day,time_stop) +
  ylim(0,0.07) +
  theme_minimal() +
  labs(title = "V2 Infections", x=('Time (days)'), y =("Proportion
    ↪ of population"))

grid.arrange(p9, p10, nrow=2)


# 1 MONTH LATER - Sensitivity analysis - all three parameters on
  ↪ CUMULATIVE DEATHS ####

phia_vector<-seq(1.1,1.5,by=0.1) # Beta
parameters["phib"] <- 1 # Latent rate
phic_vector<-seq(0.25,0.4,by=0.05) # Vaccine escape
phid_vector<-seq(0.1,0.5,by=0.1) # Virulence
parameters["phie"] <- 0.3 # Cross immunity


result2<-matrix(0,nrow = 1,ncol = 5)
colnames(result2)<-c("time","D","phic","phia","phid")
result2<-as.data.frame(result2)
for (k in 1:length(phid_vector)){
  for (j in 1:length(phia_vector)){
    for (i in 1:length(phic_vector)){
      parameters["phic"]<-phic_vector[i]
      parameters["phia"]<-phia_vector[j]
      parameters["phid"]<-phid_vector[k]
```

```
      S2_0 <- 1 - rho*(1 - phic_vector[i]) - i2 - out1[v2_day,4] -
         ↪  phie*out1[v2_day,5]
      I2_0 <- i2
      D2_0 <- 0
      R2_0 <- rho*(1 - phic_vector[i]) + phie*out1[v2_day,5]
      CInc2_0 <- 0
      init2 <- c(S2 = S2_0, I2 = I2_0, D2 = D2_0, R2 = R2_0, CInc2
         ↪  = CInc2_0)

      out_aux <- ode(y = init2, times = tps2, func = covid_V2,
         ↪ parms = parameters)

      aux_mat<-cbind(out_aux[,c(1,4)],rep(phic_vector[i],length(
         ↪ tps2)), rep(phic_vector[j],length(tps2)), rep(phic_
         ↪ vector[k],length(tps2)))

      colnames(aux_mat)<-c("time","D","phic","phia","phid")
      result2<-rbind(result2,aux_mat)
    }
  }
}
result2 <- pivot_longer(result2, names_to="phi", cols=3:5 )


p11 <- out1 %>%
  ggplot() +
  geom_line(aes(x=time,y=D1),colour=col_deaths) +
  xlim(0,v2_day) +
  ylim(0,0.004) +
  theme_minimal() +
  labs(title = "V1␣Cumulative␣Deaths", x=('Time␣(days)'), y="
     ↪ Proportion␣of␣population")

p12 <- result2 %>%
  ggplot() +
  geom_line(aes(x=time,y=D),colour=col_deaths) +
  xlim(v2_day,time_stop) +
  ylim(0,0.004) +
  theme_minimal() +
  labs(title = "V2␣Cumulative␣Deaths", x=('Time␣(days)'), y =("
     ↪ Proportion␣of␣population"))

grid.arrange(p11, p12, nrow=2)

# 1 MONTH LATER - Sensitivity analysis - cross immunity on
   ↪ INFECTIONS ####

parameters["phia"] <- 1.3 # Transmissibility
parameters["phib"] <- 1 # Latent rate
parameters["phic"] <- 0.325 # Vaccine escape
parameters["phid"] <- 0.2 # Virulence
```

```
phie_vector<-seq(0.17,0.5,by=0.0825)

result_phie<-matrix(0,nrow = 1,ncol = 3)
colnames(result_phie)<-c("time","I","phie")
result_phie<-as.data.frame(result_phie)
for (i in 1:length(phie_vector)){
  parameters["phie"]<-phie_vector[i]

  out1 <- as.data.frame(ode(y=init1, times=tps1, func = covid_V1,
     ↪ parms = parameters))

  S2_0 <- 1 - rho*(1 - phic) - i2 - out1[v2_day,4] - phie_vector[i
     ↪ ]*out1[v2_day,5]
  I2_0 <- i2
  D2_0 <- 0
  R2_0 <- rho*(1 - phic) + phie_vector[i]*out1[v2_day,5]
  CInc2_0 <- 0
  init2 <- c(S2 = S2_0, I2 = I2_0, D2 = D2_0, R2 = R2_0, CInc2 =
     ↪ CInc2_0)

  out_aux <- ode(y = init2, times = tps2, func = covid_V2, parms =
     ↪  parameters)

  aux_mat<-cbind(out_aux[,c(1,3)],rep(phie_vector[i],length(tps2))
     ↪ )
  colnames(aux_mat)<-c("time","I","phie")
  result_phie<-rbind(result_phie,aux_mat)
}

p17 <- out1 %>%
  ggplot() +
  geom_line(aes(x=time,y=I1)) +
  xlim(0,v2_day) +
  ylim(0,0.1) +
  theme_minimal() +
  labs(title = "V1␣Infections", x=('Time␣(days)'), y="Proportion␣
     ↪ of␣population")

p18 <- result_phie %>%
  ggplot() +
  geom_line(aes(x=time,y=I,colour=as.factor(phie))) +
  xlim(v2_day,time_stop) +
  ylim(0,0.1) +
  theme_minimal() +
  labs(title = "V2␣Infections", x=('Time␣(days)'), y =("␣"),
     ↪ colour="Cross␣Immunity")

grid.arrange(p17, p18, widths=c(0.4,0.6), ncol=2)
```

R Shiny App

```
# Setup ####
```

```
library(pacman)
p_load(deSolve,
       readxl,
       tidyverse,
       shiny,
       shinycssloaders,
       shinyBS)

# Parameters ####
R0 <- 0.3*5.08 # Reproductive number of V1
gamma1 <- 1/10 # Latent rate of V1
mu1 <- 0.0057 # Proportion of infected individuals that die from
   ↪ V1
beta1 <- R0 * gamma1 * (1 - mu1) # Transmission rate of V1
rho_init <- 0.01 # proportion vaccinated against V1 before V1 wave
rho <- 0.05 # Proportion of population vaccinated against V1 after
   ↪  V1 wave
i2 <- 0.001 # Proportion of population infected with V2 when it is
   ↪  first detected
v2_day <-365 # Day on which V2 first detected
phia <- 1.25 # Degree to which V2 is more transmissible than V1
phib <- 1 # Degree to which latent rate of V2 is higher than V1
phic <- 0.3 # Degree to which V2 is a V1 vaccine escape
phid <- 0.25 # Degree to which V2 is more virulent than V1
phie <- 0.5 # What proportion of individuals recovered from V1 are
   ↪  immune to V2
time_stop <- 730 # Total days in model

parameters <- c(
  beta1 <- beta1,
  gamma1 <- gamma1,
  phia <- phia,
  phib <- phib,
  phic <- phic,
  phid <- phid,
  phie <- phie,
  mu1 <- mu1,
  rho_init <- rho_init,
  rho <- rho,
  i2 <- i2,
  v2_day <- v2_day,
  time_stop <- time_stop
)

# Times V1 ####

time_start1 <- 0
time_stop1 <- time_stop
deltat1 <- 1
tps1 <- seq(time_start1, time_stop1, by=deltat1)
```

```
# Times V2 ####

time_start2 <- v2_day
time_stop2 <- time_stop
deltat2 <- 1
tps2 <- seq(time_start2, time_stop2, by=deltat2)

# Define model V2 ####

covid_V2 <- function(time,state,parameters){
  with(as.list(c(state,parameters)),{

    beta2 <- phia * beta1
    gamma2 <- phib * gamma1
    mu2 <- phid * mu1

    dS2 <- - beta2 * S2 * I2
    dI2 <- beta2 * S2 * I2 - gamma2 * I2
    dD2 <- mu2 * gamma2 * I2
    dR2 <- (1 - mu2) * gamma2 * I2
    dCInc2 <- beta2 * S2 * I2

    return(list(c(dS2,dI2,dD2,dR2,dCInc2)))
  }
  )
}

# Start app ####

# Define UI for application
ui <- fluidPage(

  # Title
  titlePanel("SARS-CoV-2 new variant"),

  # Sidebar with slider inputs
  sidebarLayout(
    sidebarPanel(
      actionButton("go", "Go"),

      bsCollapse(
        bsCollapsePanel("Multiplying factors: parameters of V2
          ↪ compared to V1",
                        sliderInput(inputId="phia", label = "
                          ↪ Transmission rate", value = 1, min
                          ↪ =0.25, max=4,step=0.25),
                        sliderInput(inputId="phic", label = "
                          ↪ Vaccine escape proportion", value =
                          ↪ 0.25, min=0, max=1,step=0.05),
                        sliderInput(inputId="phid", label = "
```

```
                        ↪ Virulence/Case␣Fatality␣Rate", value
                        ↪  = 0.3, min=0.1, max=2.1,step=0.1),
                      sliderInput(inputId="phib", label = "
                        ↪ Latent␣rate", value = 1, min=0.5,
                        ↪ max=1.5,step=0.25),
                      sliderInput(inputId="phie", label = "Cross
                        ↪ ␣immunity", value = 0.1, min=0, max
                        ↪ =1,step=0.05)

      )
    ),

    bsCollapse(
      bsCollapsePanel("V1␣transmission␣parameters",
                      sliderInput(inputId="rho_init", label = "
                        ↪ Proportion␣vaccinated␣against␣V1␣
                        ↪ before␣initial␣wave", value = 0.01,
                        ↪ min=0, max=1,step=0.05),
                      sliderInput(inputId="rho", label = "
                        ↪ Proportion␣vaccinated␣against␣V1␣
                        ↪ after␣initial␣wave", value = 0.05,
                        ↪ min=0, max=1,step=0.05),
                      sliderInput(inputId="mu1", label = "Case␣
                        ↪ fatality␣rate␣of␣V1", value =
                        ↪ 0.0057, min=0.01, max=0.1,step
                        ↪ =0.001),
                      sliderInput(inputId="gamma1", label = "
                        ↪ Latent␣rate␣of␣V1", value = 0.1, min
                        ↪ =0.1, max=0.3,step=0.1),
                      sliderInput(inputId="beta1", label = "
                        ↪ Transmission␣rate␣of␣V1", value =
                        ↪ 0.152, min=0.1, max=0.8,step=0.05)

      )
    )
  ),

  # Tabs for incidence and costs
  mainPanel(
    tabsetPanel(type = "tabs",
                tabPanel("Daily␣incidence", plotOutput("incPlot"
                  ↪ ) %>% withSpinner()),
                tabPanel("Infections", plotOutput("infPlot") %>%
                  ↪  withSpinner()),
                tabPanel("Daily␣deaths", plotOutput("deathPlot")
                  ↪  %>% withSpinner())
    )
  )
 )
)
```

```
# Server
server <- function(input, output) {
  modelOut <- eventReactive(input$go, {
    parameters["phia"] <- input$phia
    parameters["phib"] <- input$phib
    parameters["phic"] <- input$phic
    parameters["phid"] <- input$phid
    parameters["phie"] <- input$phie
    parameters["rho"] <- input$rho
    parameters["beta1"] <- input$beta1
    parameters["gamma1"] <- input$gamma1
    parameters["mu1"] <- input$mu1
    parameters["rho_init"] <- input$rho_init


    # Run the model

    # Initial conditions V1

    S1_0 <- 1 - input$rho_init
    I1_0 <- 0.0001
    D1_0 <- 0
    R1_0 <- input$rho_init
    CInc1_0 <- 0
    init1 <- c(S1 = S1_0, I1 = I1_0, D1 = D1_0, R1 = R1_0, CInc1 =
       ↪  CInc1_0)

    # Define model V1

    covid_V1 <- function(time,state,parameters){
      with(as.list(c(state,parameters)),{
        dS1 <- - beta1 * S1 * I1
        dI1 <- beta1 * S1 * I1 - gamma1 * (1 - mu1) * I1 - gamma1
           ↪ * mu1 * I1
        dD1 <- mu1 * gamma1 * I1
        dR1 <- (1 - mu1) * gamma1 * I1
        dCInc1 <- beta1 * S1 * I1

        return(list(c(dS1,dI1,dD1,dR1,dCInc1)))
      }
      )
    }

    # Run model 1

    out1 <- as.data.frame(ode(y=init1, times=tps1, func = covid_V1
       ↪ , parms = parameters))

    # Initial conditions V2

    S2_0 <- 1 - input$rho*(1 - input$phic) - i2 - out1[v2_day,4] -
```

```
   ↪  input$phie*out1[v2_day,5]
I2_0 <- i2
D2_0 <- 0
R2_0 <- input$rho*(1 - input$phic) + input$phie*out1[v2_day,5]
CInc2_0 <- 0
init2 <- c(S2 = S2_0, I2 = I2_0, D2 = D2_0, R2 = R2_0, CInc2 =
   ↪  CInc2_0)

out2_growth <- ode(y=init2, times=tps2, func = covid_V2, parms
   ↪  = parameters)

out2_initial1 <- matrix(0:(v2_day-1), nrow=v2_day, ncol=1)
colnames(out2_initial1) <- c("time")

out2_initial2 <- matrix(rep((1 - rho*(1 - phic) - i2 - out1[
   ↪ time_stop,4] - phie*out1[time_stop,5]),v2_day), nrow=v2_
   ↪ day, ncol=1)
colnames(out2_initial2) <- c("S2")

out2_initial3 <- matrix(rep(0,v2_day), nrow = v2_day, ncol=1)
colnames(out2_initial3) <- c("I2")

out2_initial4 <- matrix(rep(0,v2_day), nrow = v2_day, ncol=1)
colnames(out2_initial4) <- c("D2")

out2_initial5 <- matrix(rep((rho*(1 - phic) + i2 + phie*out1[
   ↪ time_stop,5]),v2_day), nrow=v2_day, ncol=1)
colnames(out2_initial5) <- c("R2")

out2_initial6 <- matrix(rep(0,v2_day), nrow = v2_day, ncol=1)
colnames(out2_initial6) <- c("CInc2")

out2_initial <- cbind(out2_initial1,out2_initial2,out2_
   ↪ initial3,out2_initial4,out2_initial5,out2_initial6)
tail(out2_initial)

out2_combined <- rbind(out2_initial,out2_growth)

out2 <- as.data.frame(out2_combined)

out <- merge(out1,out2,by="time")

output <- as_tibble(out) %>%
  mutate(P1 = S1+I1+D1+R1,
         P2 = S2+I2+D2+R2,
         Inc1 = c(0, diff(CInc1)),
         Inc2 = c(0, diff(CInc2)),
         Death1 = c(0, diff(D1)),
         Death2 = c(0, diff(D2))) %>%
  pivot_longer(names_to = "variable", cols = !1) %>%
  mutate(variant = ifelse(str_ends(variable, "2"), "V2", "V1")
```

```
      )

  })

  #Define Plots

  output$deathPlot <- renderPlot({
    modelOut() %>%
      filter(variable %in% c("Death1", "Death2")) %>%
      group_by(variable) %>%
      ggplot()+
      geom_line(aes(x = time, y=value, colour = as_factor(variable
         ↪ )))+
      theme_minimal() +
      labs(title = "Daily␣Deaths", x=('Time␣(days)'), y =("
         ↪ Proportion␣of␣population"), colour="Compartment")
  })

  output$incPlot <- renderPlot({
    modelOut() %>%
      filter(variable %in% c("Inc1", "Inc2")) %>%
      group_by(variable) %>%
      ggplot()+
      geom_line(aes(x = time, y=value, colour = as_factor(variable
         ↪ )))+
      theme_minimal() +
      labs(title = "Daily␣Incidence", x=('Time␣(days)'), y =("
         ↪ Proportion␣of␣population"), colour="Compartment")# +
  })

  output$infPlot <- renderPlot({
    modelOut() %>%
      filter(variable %in% c("I1", "I2")) %>%
      group_by(variable) %>%
      ggplot()+
      geom_line(aes(x = time, y=value, colour = as_factor(variable
         ↪ )))+
      theme_minimal() +
      labs(title = "Infections", x=('Time␣(days)'), y =("
         ↪ Proportion␣of␣population"), colour="Compartment")# +
  })



}

# Run the application
shinyApp(ui = ui, server = server)
```