Modelling methods, Bhutan application

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Contents

1 Model Structure

1.1 General features

Our COVID-19 model is a series of compartments representing transitions between states relevant to infection with SARS-CoV-2 and onward transmission of this virus. Unlike previous iterations of this model (including our past publications on the epidemics in the Philippines [1], Malaysia [2] and Victoria, Australia [4]), our current model considers only states relevant to transmission. Hospitalisation, admission to ICU and death are no longer represented as explicit model states, but are now calculated from model outputs through a convolution process. The rationale for this approach is that the explicitly modelled states are reserved for the representation of processes relevant to epidemic transmission dynamics only. Any other relevant outcomes are then calculated from the quantities that are tracked during the process of numerically solving the dynamic system ("derived outputs"), including through convolutions. It should be noted that the process of calculating derived outputs is done after each model iteration, such that these quantities can still be compared to empirically observed outcomes and so used for calibration.

1.2 Compartments

Model compartments represent sequential progressions through the processes of infection with, progression through and recovery from the phases of SARS-CoV-2. Reinfection is permitted in our model code structure, which is represented as transition from the recovered compartments back to the first infected compartment. The following compartments are implemented:

- Susceptible
  - Persons never previously infected with SARS-CoV-2 during the model simulation period
- Latent
  - Persons recently infected with SARS-CoV-2, but not yet infectious
  - This phase is divided into two sequential compartments
- Infectious
  - Persons with active COVID-19 who are potentially infectious to others
  - This phase is divided into two sequential compartments
  - The second of these two sequential compartments includes any persons who are identified through the health system and asked to isolate
  - The infectiousness of the second compartment will be reduced to capture the effect of case isolation
- Recovered
  - Persons recovered from COVID-19 during the model simulation period
  - This phase is divided into two sequential compartments
  - Reinfection from these compartments is permitted and occurs at a different rate for the two sequential phases (if the reinfection rate is greater than zero)
  - This compartment retains the stratification by strain (or variant of concern ("VoC")), with the strain of the last infection episode used for classification

Figure 1: Unstratified compartmental model structure. S = susceptible, E = exposed, I = active, R = recovered/removed. Depth of pink/red shading indicates the infectiousness of the compartment.

2 Age stratification

All compartments of the base compartmental structure were stratified by age into the following age bands:

- Zero to 14 years
- 15 to 24 years
- 25 to 49 years
- 50 to 69 years
- 70 years and above

Demographic processes, including births, ageing and non-infection-related deaths are not simulated, given the timeframes considered in this simulation.

3 Infectious seed

The infectious seed value is assigned to the early infectious compartment. This value is subtracted from the total modelled population and assigned to the susceptible compartment, while all other compartments are assigned a starting value of zero. This process is undertaken before age stratification is applied, with the stratification process then splitting these values proportionately according to the starting age distribution of the population.

4 Clinical stratification

4.1 Stratification structure

The "clinical" stratification acts by replicating each of the two age-stratified sequential compartments representing infectious COVID-19 into three categories. The three clinical categories are:

1. Asymptomatic persons
2. Symptomatic persons who are never notified as cases
3. Symptomatic persons who are successfully detected and notified

For each age category, a proportion of new active infections are assumed to remain asymptomatic throughout their infectious period (specified in Table 3). This proportion remains fixed over time throughout a model run. It is assumed that asymptomatic persons are never detected and so do not contribute to notifications. The remaining proportion constitutes the second and third categories, comprising all persons developing symptomatic COVID-19 during their infectious period. The proportion of these symptomatic persons who progress to the third category varies with time and is described under the section on case detection (Section 5). This approach differs from that presented in our previous COVID-19 modelling publications, in that the earlier publications included additional stratification to distinguish those with detected COVID-19 according to disease severity. In this analysis, mortality and health service burden are calculated through convolutions, as described below.

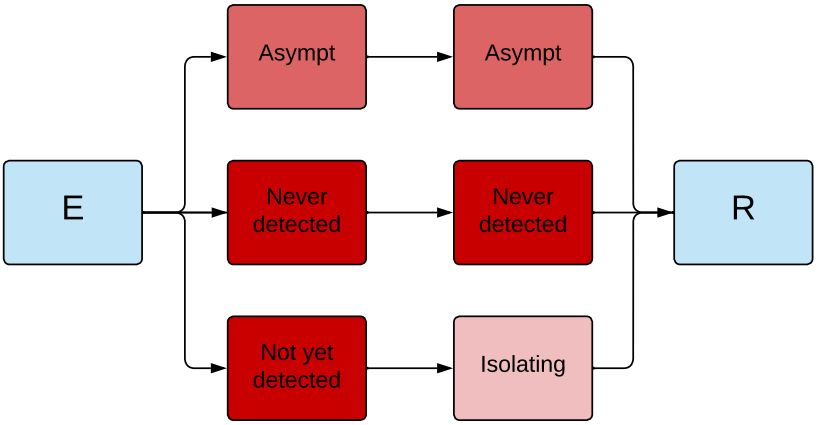

Figure 2: Illustration of the clinical stratification. Depth of red shading of compartment qualitatively indicates infectiousness.

4.2 Modification to infectiousness

Both the early and late stages of the post-stratification infectious COVID-19 compartment are assumed to have reduced infectiousness, according to the asymptomatic infectiousness parameter (in Table to be added). The late stage of the detected (third) stratum has reduced infectiousness to represent case isolation, with these persons having their infectiousness reduced according to the isolation infectiousness parameter (in Table to be added).

5 Case detection and isolation

5.1 Determining the proportion of cases detected

We calculate a time-varying case detection rate, being the proportion of all symptomatic cases (the second and third clinical strata, described in Section 4) that are detected (the third clinical stratum only). This proportion is informed by the number of tests performed using the following formula:

$$CDR(time) = 1 - (1 - floor) \times e^{-shape \times tests(time)}$$

$time$ is the calendar date and $tests(time)$ is the number of tests per capita done on that date. To determine the value of the shape parameter, we solve this equation based on the assumption that a certain daily testing rate $tests(t)$ is associated with a certain $CDR(t)$. $floor$ is the minimum case detection rate possible, which would theoretically occur when zero tests are conducted. Solving for $shape$ yields:

$$shape = \frac{-log(\frac{1-CDR(t)}{1-floor})}{tests(t)}$$

That is, if it is assumed that a certain daily per capita testing rate is associated with a certain proportion of symptomatic cases detected, we can determine $shape$. As this relationship is not well understood and unlikely to be consistent across all settings, we vary the CDR that is associated with a certain per capita testing rate during calibration. This approach allows us to both vary the $CDR(\cdot)$ relationship through calibration, while also varying the specific $CDR(time)$ to reflect historical changes in testing capacity with time.

5.2 Isolation of detected cases

As described in the clinical stratification section above, as infected persons progress from the early to the late stage of active COVID-19, infectiousness is reduced for those detected to reflect case isolation.

6 Strain stratification

The model is stratified by "strain" or Variant of Concern (VoC), adopting the summer approach to strain stratification through the `StrainStratification` object. This general approach is described in full in the summer model documentation for to represent explicitly multiple competing strains, each with a separate force of infection calculation (see `ModelRunner` object code where force of infection calculations are made and `Stratification` object code where strain stratification can be requested). This framework allows for independent calculations of the force of infection for each of the modelled strains, with the compartmental infectiousness multipliers applied identically for all of the competing strains. Additional strain features (such as differential infectiousness and duration of latency and active disease) can then be implemented with the standard features of stratification, such as adjustments to flow rates.

6.1 Seeding of new VoC

Seeding of each new strain into the model is achieved through the addition of an importation flow that introduces a small number of new infectious persons with the new VoC into the model. To achieve this, a new entry flow is added to the model with destination being the early infectious compartment. The rate of this flow is a step function that steps from zero to the requested daily rate of seeding for the requested number of days, before stepping back down to zero for the remainder of the period simulated.

7 Vaccination history stratification

History of vaccination is captured by stratifying all model compartments by vaccination status. Two vaccination strata are included to represent those who have received at least two doses of a COVID-19 vaccine, and those who have not. The following are not considered in this approach to simulating vaccination:

- Any effect of receiving a single dose of vaccine
- Waning of vaccine-induced immunity
- Any additional effect from receiving additional vaccine doses following the second dose

The effect of vaccination on transmission is to partially reduce the rate of infection for all persons at-risk of infection in the vaccinated stratum. This includes both fully susceptible (never previously infected) persons, as well as recovered persons who are at risk of reinfection. Emerging variants of concern (VoCs) may escape this immunity, as described further below.

8 Immunity-strain interaction

The strains/VoCs implemented in the model may escape both vaccine-induced and natural immunity, as follows.

8.1 Application to first infection

The first infection episode with SARS-CoV-2 is represented through the transition from the susceptible to the first latent compartment. The susceptible compartment is not stratified by strain, because these persons have no infection history. Therefore, for infection of persons never previously infected, only the vaccination-induced immunity status is relevant. The rate of infection for a particular vaccination status and infecting strain is adjusted by the factor:

$$1 - p_i \times s_j$$

Where p_i represents the protection afforded by vaccination stratum $_i$, and s_j represents the degree of immune escape against vaccine-induced immunity for strain $_j$. Note that this assumes that the extent of immune escape for a given strain is the same for all vaccination strata.

8.2 Application to re-infection

Persons who have recovered from previous infection episodes remain in a compartment that is stratified according to the last infecting strain. The recovered compartment is replicated into early and late stages, which can afford different levels of protection against re-infection. The extent of protection must be explicitly specified for each strain-stage combination. The rate of reinfection is adjusted by the factor:

$$(1 - p_i \times s_j) \times (1 - n_{i,k,l})$$

Where the additional term $n_{k,l,m}$ represents the cross protection afforded by past infection with strain $_k$ against infecting strain $_l$ in vaccination stratum $_i$.

Immunity category	Proportion of population [a]	Estimated protection [b]
No immunity, unvaccinated	0.312	0
Low immunity, vaccinated with two doses	0.302	0.5
High immunity, vaccinated with three doses	0.386	0.85

Table 1: Values used to re-weight the severity estimates provided in Nyberg et al. to separate immunity classes.

[a] Estimated population distribution as at 16th December 2021 (study mid-point), taken from Our World In Data.

[b] Estimated protection against hospitalisation or death following Omicron infection.

8.3 Adjusting age-specific severity parameters for immunity

We use inputs for the age-specific case fatality rate and the age-specific hospitalisation rate from Nyberg et al., which provides estimates of these quantities in a population that already had substantial vaccine-induced immunity. We therefore adjust these quantities for pre-existing immunity, to account for protection against death and hospitalisation. We apply the following method to ensure that after adjusting the parameters for a specific age bracket for immunity, the average parameter value would be equal to that reported by Nyberg et al. if weights were applied according to the distribution of immunity in the population that was described in this study. To do this, we estimate the proportion of the population in each of the three modelled immunity categories in the United Kingdom around the mid-point of the study, and the protection afforded by each of the immunity classes (see Table 1).

9 Scaling of contact rates

The base mixing matrix can be disaggregated into age-specific contacts that occur in the following four settings:

- Home
- Other locations
- Work
- School

The contact rates in each of these settings are scaled as indicated in Table 2. The quantity indicated in the Table is considered as a proportion relative to the baseline value of one. This quantity is then squared to consider that reductions in mobility will affect both the potential infector and infectee who will not visit the setting considered.

9.1 Estimation of microdistancing effect

In addition to the mobility considerations, we also consider that other behavioural changes independent of whether certain settings were visited may be relevant in Bhutan. This further scales the rates of contact at the work and other locations settings, with the effect squared as for the mobility considerations.

Matrix contact setting	Data used to scale contacts
Home	Not scaled
Other locations	Facebook "tiles visited" metric [a]
Work	Facebook "tiles visited" metric [a]
School	Historical timeline of school closures/re-openings in Bhutan

Table 2: **Scaling of mobility values by matrix setting.**

[a] Google mobility data not available for Bhutan.

10 Outputs

10.1 Incidence

Incidence represents the rate of onset of new disease episodes, (regardless of symptoms or detection). It is calculated as the rate of transition between the early and late active model compartments. Therefore, this indicator is slightly lagged relative to the onset of infectiousness, and occurs at the same point in the disease episode as for case isolation (for those persons for whom self-isolation occurs). Thus, this indicator can be reasonably considered as relating to the point in a disease episode at which significant symptoms would develop. However, we stress that this indicator includes all disease episodes, including asymptomatic and symptomatic undetected episodes.

10.2 Notifications

Notifications are derived from the calculation of incidence described above, but limited to the detected clinical stratum (see 4). Therefore, this considers case detection as being interchangeable with notification. A gamma distribution convolution is then applied to the detected case incidence to allow for the lag between symptom onset and case reporting. The mass of the gamma distribution between each sequential pair of time points is used in the calculation.

10.3 COVID-19-related mortality

COVID-19-related deaths are derived from the calculation of incidence described above, but limited to the two symptomatic clinical strata (both detected and undetected). Calculations are made separately for each age group, each vaccine-induced immunity stratum, and each strain, given that all these factors influence disease-induced mortality rates. A convolution is applied to each age, immunity and strain-specific symptomatic incidence rate calculation. The base case fatality rate (CFR) is first determined as a model input, which is then adjusted according to the protection afforded by vaccine-induced immunity. This may then be adjusted according to better match the local epidemic characteristics through an "adjuster" parameter. This parameter applies equally to each age group and acts to inflate or deflate the case fatality rate adjusted for vaccine-induced immunity. However, rather than directly multiplying the case fatality rate by this adjuster, we apply the adjuster to the odds of death equivalent to the risk death. That is, the adjusted case fatality rate is calculated as:

$$CFR_{adj} = \frac{CFR_{base} \times adjuster}{CFR_{base} \times (adjuster - 1) + 1}$$

Next, the adjusted CFR is again adjusted for the severity of the strain responsible for the disease episode. Having determined the age, immunity and strain-specific CFR, a gamma-distributed convolution is calculated such that the total density of the distribution is equal to the CFR determined as described above. As for notifications, the mass of the gamma distribution between each sequential pair of time points is used in the calculation.

10.4 Hospital admissions

The rate of new hospital admissions is calculated from symptomatic incidence in an exactly analogous way to that described for mortality in the previous section. Age, immunity and strain-specific risks of hospitalisation are calculated, with adjustment of all rates for local context as required, and a convolution is applied. As for notifications and deaths, the mass of the gamma distribution between each sequential pair of time points is used in the calculation.

10.5 Hospital occupancy

Having calculated the rate of hospital admissions, a second gamma-distributed convolution is applied to this output to calculate the total hospital occupancy from the admissions at every previous time point modelled. Differing from the convolution used to calculate the rates of notifications, the gamma distribution is used to determine the probability that an admitted patient would remain in hospital after the time lag from the hospital admission rate being considered. That is, the complement of the cumulative distribution function for the rate of hospital discharge is applied.

10.6 ICU admissions and occupancy

The calcuation of ICU admissions and occupancy is analogous to that of hospital admissions and occupancy.

11 Parameters

11.1 Age-specific parameters

Age-structured parameters are presented in Table 3.

Age group (years)	**Clinical fraction** [a]	**Relative susceptibility to infection**	**Case fatality rate**	**Proportion of symptomatic patients hospitalised**
0 to 9	0.533	0.36	5×10^{-5}	0.011
10 to 19	0.533	0.36	1×10^{-5}	0.0038
20 to 29	0.679	1	2×10^{-5}	0.006
30 to 39	0.679	1	5×10^{-5}	0.0066
40 to 49	0.679	1	1×10^{-4}	0.0059
50 to 59	0.679	1	5×10^{-4}	0.0077
60 to 69	0.803	1	2×10^{-3}	0.0139
70 to 79	0.803	1.41	8.3×10^{-3} [b]	0.0357 [b]
80 and above	0.803	1.41	5.12×10^{-2} [b]	0.111 [b]
Justification and source	Table 1 of systematic review and meta-analysis with appropriate accounting for testing during the pre-symptomatic period[3].	Conversion of odds ratios presented in Table S15 of Zhang et al. 2020 to relative risks using data presented in Table S14 of the same study [5].	Table S2 from Supplemental Materials to Nyberg et al. for "Hospital admission up to 14 days after positive test".	Table S2 from Supplemental Materials to Nyberg et al. for "Death within 28 days after positive test".

Table 3: **Values used to estimate age-specific parameters.** Note that these base parameter values are then adjusted for immunity considerations.

[a] Proportion of incident episodes developing symptoms.

[b] Modelled age groups are five year brackets to 75 and above. These values are used to calculated weighted value for the modelled 75 and above age bracket. The value for the 75 and above age group is calculated as the weighted average of the parameters for the 75 to 79 and the 80 and above age groups. The weights applied to each of these two groups is the size of the population in the country of application in each of these brackets.

Parameter	Value	Rationale
Probability of transmission per contact	Calibrated	Assumed
ISO3 code for source country for mixing matrix	CHN	Assumed
Starting infectious seed	Calibrated	Assumed
Relative infectiousness of asymptomatic persons	0.5	Assumed
Relative infectiousness of isolated cases	0.2	Assumed
Index testing rate ($tests(t)$)	0.0001 tests per day	Assumed
CDR reached at index testing rate ($CDR(t)$)	0.0615	Assumed
CDR floor ($floor$)	0.06	Assumed
Interval for moving average of daily tests	14 days	Assumed
Duration of booster effect	90 days	Assumed
Reduction in transmission risk for boosted	0.6	Assumed
Reduction in transmission risk for primary course	0.4	Assumed

Table 4: **Epidemiological fixed parameter values.**

References

[1] Jamie M. Caldwell et al. "Understanding COVID-19 dynamics and the effects of interventions in the Philippines: A mathematical modelling study". In: *The Lancet Regional Health – Western Pacific* 14 (2021). ISSN: 2666-6065. DOI: 10.1016/j.lanwpc.2021.100211. URL: https://doi.org/10.1016/j.lanwpc.2021.100211.

[2] P. Jayasundara et al. "Sustaining effective COVID-19 control in Malaysia through large-scale vaccination". In: *Epidemics* 37 (2021), p. 100517. ISSN: 1755-4365 (Print) 1878-0067. DOI: 10.1016/j.epidem.2021.100517. URL: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8547797/pdf/main.pdf.

[3] Pratha Sah et al. "Asymptomatic SARS-CoV-2 infection: A systematic review and meta-analysis". In: *Proceedings of the National Academy of Sciences* 118.34 (2021), e2109229118. DOI: 10.1073/pnas.2109229118. URL: http://www.pnas.org/content/118/34/e2109229118.abstract.

[4] James M. Trauer et al. "Understanding how Victoria, Australia gained control of its second COVID-19 wave". In: *Nature Communications* 12.1 (2021), p. 6266. ISSN: 2041-1723. DOI: 10.1038/s41467-021-26558-4. URL: https://doi.org/10.1038/s41467-021-26558-4.

[5] J. Zhang et al. "Changes in contact patterns shape the dynamics of the COVID-19 outbreak in China". In: *Science* 368.6498 (2020), pp. 1481–1486. ISSN: 1095-9203. DOI: 10.1126/science.abb8001. URL: https://www.ncbi.nlm.nih.gov/pubmed/32350060.

Parameter	Value	Rationale
Disease onset to notification distribution	Gamma	Assumed
Mean disease onset to notification	3.0	Assumed
Onset to notification parameter	5.0	Assumed
Disease onset to death distribution	Gamma	Assumed
Mean disease onset to death	14.0 days	Assumed
Onset to death shape parameter	5.0	Assumed
Disease onset to hospital admission distribution	Gamma	Assumed
Mean disease onset to hospital admission	5.0 days	Assumed
Onset to hospitalisation shape parameter	5.0	Assumed
Proportion of hospitalised persons admitted to ICU	0.08	Assumed
Disease onset to ICU admission distribution	Gamma	Assumed
Mean disease onset to ICU admission	2.0 days	Assumed
Onset to ICU shape parameter	5.0	Assumed
Distribution type for hospital stay	Gamma	Assumed
Mean hospital stay	3.0 days	Assumed
Shape parameter for hospital stay	5.0	Assumed
Distribution type for ICU stay	Gamma	Assumed
Mean ICU stay	4.7 days	Assumed
Shape parameter for ICU stay	5.0	Assumed

Table 5: **Output-related fixed parameter values.**

Parameter	Distribution type	Distribution parameters
Probability of transmission per contact	Uniform	Range: [0.15, 0.4]
Infection latent period	Uniform	Range: [2.0, 4.0]
Period with active disease	Uniform	Range: [1.0, 5.0]
Starting infectious seed	Uniform	Range: [50.0, 300.0]
Maximum effect of microdistancing	Uniform	Range: [0.0, 0.6]

Table 6: **Output-related fixed parameter values.**