1 Base model construction

1.1 Platform for infectious disease dynamics simulation

We developed a deterministic compartmental model of COVID-19 transmission using the AuTuMN platform, publicly available at https://github.com/monash-emu/AuTuMN/. Our repository allows for the rapid and robust creation and stratification of models of infectious disease epidemiology and includes pluggable modules to simulate heterogeneous population mixing, demographic processes, multiple circulating pathogen strains, repeated stratification and other dynamics relevant to infectious disease transmission. The platform was created to simulate TB dynamics, being an infectious disease whose epidemiology differs markedly by setting, such that considerable flexibility is desirable [1]. We have progressively developed the structures of our platform over recent years, and further adapted it to be sufficiently flexible to permit simulation of other infectious diseases for the purpose of this project.

1.2 Base COVID-19 model

Using the base framework of an SEIR model (susceptible, exposed, infectious, removed), we split the exposed and infectious compartments into two sequential compartments each (SEEIIR). The two sequential exposed compartments represent the non-infectious and infectious phases of the incubation period, with the latter representing the "presymptomatic" phase such that infectiousness occurs during three of the six sequential phases. For this reason, "active" is a more accurate term for the two sequential "I" compartments and is preferred henceforward. The two infectious compartments represent early and late phases of active disease, during which symptoms occur if the disease episode is symptomatic, and allow explicit representation of notification, case isolation, hospitalisation and admission to ICU. The "active" compartment also includes some persons who remain asymptomatic throughout their disease episode, such that these compartments do not map directly to either persons who are infectious or those who are symptomatic (Figure 1).
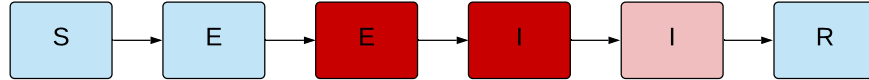

Figure 1: Unstratified compartmental model structure. S = susceptible, E = exposed, I = active, R = recovered/removed. Depth of pink/red shading indicates the infectiousness of the compartment.

The latently infected and infectious presymptomatic periods together comprise the incubation period, with the incubation period and the proportion of this period for which patients are infectious defined by input parameters described below. In general, two sequential compartments can be used to form

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a gamma-distributed profile of transition to infectiousness following exposure if the progression rates for these two compartments are equal, although in implementing this model the relative sojourn times in the two sequential compartments usually differed. Nevertheless, the profiles implemented are broadly consistent with the empirically observed log-normal distribution of individual incubation periods [2].

The transition from early active to late active represents the point at which patients are detected (for those persons for whom detection does eventually occur) and isolation then occurs from this point forward (i.e. applies during the late disease phase only. This transition point is also intended to represent the point of admission to hospital or transition from hospital ward to intensive care for patients for whom this occurs (see Section 1.3).

1.3 Clinical stratification

The age-stratified late exposed/incubation and both the early and late active disease compartments were further stratified into five "clinical" categories: *1)* asymptomatic, *2)* symptomatic ambulatory, never detected, *3)* symptomatic ambulatory, ever detected, *4)* ever hospitalised, never critical and *5)* ever critically unwell (Figure 2). The proportion of new infectious persons entering stratum 1 (asymptomatic) is age-dependent. The proportion of symptomatic patients (strata 2 to 5) ever detected (strata 3 to 5) is set through a parameter that represents the time-varying proportion of all symptomatic patients who are ever detected (the case detection rate). Of those ever symptomatic (strata 2 to 5), a time-constant but age-specific proportion is considered to be hospitalised (entering strata 4 or 5). Of those hospitalised (entering strata 4 or 5), a fixed proportion was considered to be critically unwell (entering stratum 5, Figure 3).

1.4 Hospitalisation

For COVID-19 patients who are admitted to hospital, the sojourn time in the early and late active compartments is modified, superseding the default values of the sojourn times for these compartments. The point of admission to hospital is considered to be the transition from early to late active disease, such that the sojourn time in the late disease represents the period of time admitted to hospital. For patients admitted to ICU, admission to ICU occurs at this same transition point. For this group, the period of time hospitalised prior to ICU admission is estimated as a proportion of the early active period, such that the early active period represents both the period ambulatory in the community and the period in hospital prior to ICU admission.

1.5 Infectiousness

Asymptomatic persons are assumed to be less infectious per unit time active than symptomatic persons not undergoing case isolation (typically by around 50%, although this is varied in calibration/uncertainty analysis). Infectiousness
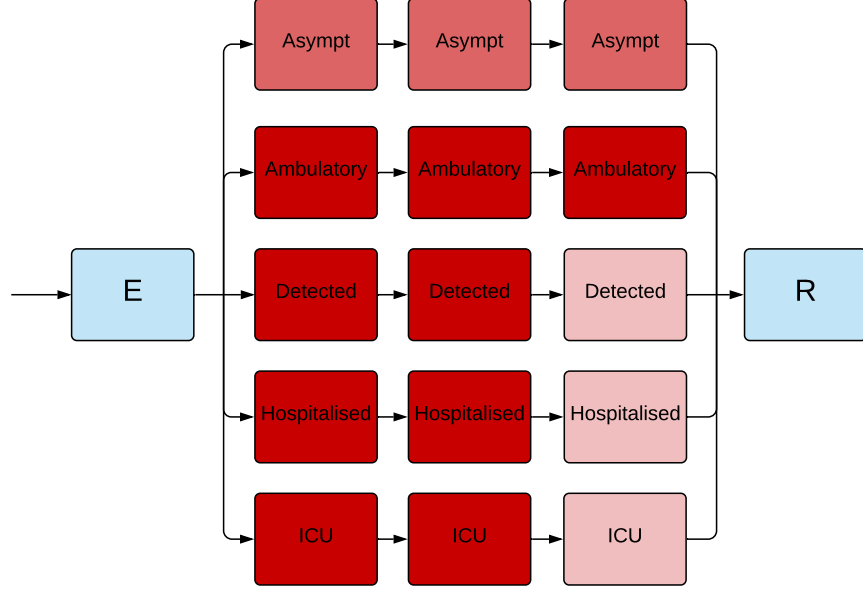
Figure 2: Illustration of the implementation of the clinical stratification. Depth of pink/red shading indicates the infectiousness of the compartment. Typical parameter values represented, although the infectiousness of asymptomatic persons is varied in calibration.

is also decreased for persons who have been detected to reflect case isolation, and for those admitted to hospital or ICU to reflect infection control procedures (by 80% for both groups). Presymptomatic individuals are presumed to have equivalent infectiousness to those with early active COVID-19.

1.6   Application of COVID-19-related death

Age-specific infection fatality rates (IFRs) were applied and distributed across strata 4 and 5, with no deaths typically applied to the first three strata. A ceiling of 50% is set on the proportion of those admitted to ICU (entering stratum 5) who die. If the infection fatality rate is greater than this ceiling, the proportion of critically unwell persons dying was set to 50%, with the remainder of the infection fatality rate then applied to the hospitalised proportion. Otherwise, if the infection fatality rate is less than half of the absolute proportion of persons critically unwell, the infection fatality rate is applied entirely through stratum 5 (such that the proportion of critically unwell persons dying in that age group becomes <50% and the proportion of stratum 4 dying is set to zero). In the event that the infection fatality rate for an age group is greater than the total proportion hospitalised (which is unusual, but could occur for the oldest
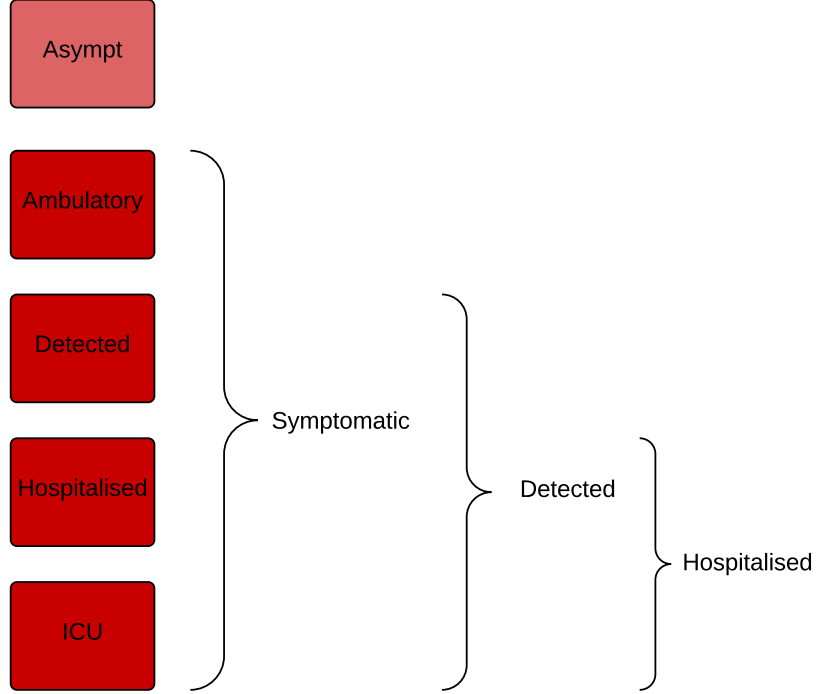
Figure 3: Illustration of the rationale for the clinical stratification.

age group under certain parameter configurations), the remaining deaths are assigned to the asymptomatic stratum. This approach was adopted for computational ease and is valid because the duration active for persons entering this stratum is the same as for the other non-hospitalised strata, such that the dynamics are identical to assigning the deaths to any of the first three strata. We used the age-specific IFRs previously estimated from age-specific death data from 45 countries and results from national-level seroprevalence surveys [3]. We allowed IFRs to vary around the previously published point estimates in order to incorporate uncertainty and to allow the IFRs to differ from the settings in which they were estimated (see Calibration section).

1.7 Age stratification

All compartments of this base compartmental structure were stratified by age into five-year bands from 0-4 years of age through to 70-74 years of age, with the final age group being those aged 75 years and older. Heterogeneous baseline contact patterns by age were incorporated using age-specific contact rates estimated by Prem et al. 2017 [4], who combined survey response data with

Clinical stratum	Stratum name	Pre-symptomatic	Early	Late
1	Asymptomatic	0.5	0.5	0.5
2	Symptomatic ambulatory never detected	1	1	1
3	Symptomatic ambulatory ever detected	1	1	0.2
4	Hospitalised never critical	1	1	0.2
5	Ever critically unwell	1	1	0.2

Table 1: Illustration of the relative infectiousness of disease compartments by clinical stratification and stage of infection. Typical parameter values displayed.

information on national demographic characteristics to produce age-structured mixing matrices with these age groupings. These are then modified by non-pharmaceutical interventions. Our modelled age groups were chosen to match these mixing matrices. The automatic demographic features of AuTuMN that can be used to simulate births, ageing and deaths were not implemented, because the issues considered pertain to the short- to medium-term and the immediate implementation of control strategies, for which population demographics are less relevant.

2 Case detection

2.1 General approach

We calculate a time-varying case detection rate, being the proportion of all symptomatic cases (clinical strata 2 to 5) that are detected (clinical strata 3 to 5). This proportion is informed by the number of tests performed using the following formula:

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

time is the time in days from the 31st December 2019 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)*. Solving for *shape* yields:

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

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 uncertainty/calibration. Given that the CDR value can be varied widely, the purpose of this is to incorporate changes in the case detection rate that reflect the empirical historical profile of changes in testing capacity over time.

3   Implementation of non-pharmaceutical interventions

A major part of the rationale for the development of this model was to capture the past impact of non-pharmaceutical interventions (NPIs) and produce future scenarios projections with the implementation or release of such interventions.

3.1   Isolation and quarantine

For persons who are identified with symptomatic disease and enter clinical stratum 3, self-isolation is assumed to occur and their infectiousness is modified as described above. The proportion of ambulatory symptomatic persons effectively identified through the public health response by any means is determined by the case detection rate as described above.

3.2   Community quarantine or "lockdown" measures

For all NPIs relating to reduction of human mobility or "lockdown" (i.e. all NPIs other than isolation and quarantine), these interventions are implemented through dynamic adjustments to the age-assortative mixing matrix. The baseline mixing matrices of Prem et al. [4] are synthetic and do not represent direct observations or reports from surveys (in the case of the 144 countries to which they were extrapolated from observations in the eight "POLYMOD" countries of Western Europe). Although synthetic, the matrices are contextualised to national demographic information, including country-specific data that include household size, workforce participation and school enrolment. Further, the matrices presented are easily machine-readable and appear to be plausible representations of contact structures within these countries.

The matrices also have the major advantage of allowing for disaggregation of total contact rates by location, i.e. home, work, school and other locations. This disaggregation allows for the simulation of various NPIs in the local context by dynamically varying the contribution of each location to reflect the historical implementation of the interventions.

The corresponding mixing matrix (denoted C_0) is presented using the standard convention that a row represents the average number of age-specific contacts per day for a contact recipient of a given age-group. In other words, the element $C_{0i,j}$ is the average number of contacts per day that an individual of age-group j makes with individuals of age-group i.

This matrix results from the summation of the four location-specific contact matrices provided by Prem et al.: $C_0 = C_H + C_S + C_W + C_L$, where C_H, C_S,

C_W and C_L are the age-specific contact matrices associated with households, schools, workplaces and other locations, respectively.

In our model, the contributions of the matrices C_S, C_W and C_L vary with time such that the input contact matrix can be written:

$$C(t) = C_H + s(t)^2 C_S + w(t)^2 C_W + l(t)^2 C_L$$

The modifying functions are each squared to capture the effect of the mobility changes on both the infector and the infectee in any given interaction that could potentially result in transmission. The modifying functions incorporate both macro-distancing and microdistancing effects, depending on the location.

3.3   School closures/re-openings

Reduced attendance at schools is represented through the function $s(t)$, which represents the proportion of all school students currently attending on-site teaching. If schools are fully closed, $s(t) = 0$ and C_S does not contribute to the overall mixing matrix $C(t)$. $s(t)$ is calculated through a series of estimates of the proportion of students attending schools, to which a smoothed step function is fitted. Note that the dramatic changes in this contribution to the mixing matrix with school closures/re-openings is a more marked change than is seen with the simulation of policy changes in workplaces and other locations (which are determined by empiric data and so do not vary so abruptly and do not fall to zero).

3.4   Workplace closures

Workplace closures are represented by quadratically reducing the contribution of workplace contacts to the total mixing matrix over time. This is achieved through the scaling term $w(t)^2$ which modifies the contribution of C_W to the overall mixing matrix $C(t)$. The profile of the function $w(t)$ is set by fitting a polynomial spline function to Google mobility data for workplace attendance (Table 2).

3.5   Community-wide movement restriction

Community-wide movement restriction (or "lockdown") measures are represented by proportionally reducing the contribution of the other locations contacts to the total mixing matrix over time. This is achieved through the scaling term $l(t)^2$ which modifies the contribution of C_L to the overall mixing matrix $C(t)$. The profile of the function $l(t)$ is set by fitting a polynomial spline function to an average of Google mobility data for various locations, as indicated in Table 2.

3.6 Household contacts

The contribution of household contacts to the overall mixing matrix $C(t)$ is fixed over time. Although Google provides mobility estimates for residential contacts, the nature of these data are different from those for each of the other Google mobility types in that they represent the time spent in that location rather than the duration. The daily frequency with which people attend their residence is likely to be close to one and we considered that household members likely have a daily opportunity for infection with each other household member. Therefore, we did not implement a function to scale the contribution of household contacts to the mixing matrix with time.

Prem "location"	Approach	Google mobility types
School	Policy response	Not applicable
Household	Constant	Not applicable
Workplace	Google mobility	Workplace
Other locations	Google mobility	Unweighted average of: • Retail and recreation • Grocery and pharmacy • Parks • Transit stations

Table 2: Mapping of Google mobility data to contact locations (as defined by Prem et al.)

3.7 Microdistancing

Interventions other than those that prevent people coming into contact with one another are thought to be important to COVID-19 transmission and epidemiology, such as maintaining interpersonal physical distance and the wearing of face coverings. We therefore implemented a "microdistancing" function to represent reductions in the rate of effective contact that is not attributable to persons visiting specific locations and so is not captured through Google mobility data. This microdistancing function reduces the values of all elements of the mixing matrices by a certain proportion. These time-varying functions multiplicatively scale the location-specific contact rate modifiers $s(t)$, $w(t)$ and $l(t)$.

References

[1] J. M. Trauer et al. Modular programming for tuberculosis control, the "autumn" platform. *BMC Infect Dis*, 17(1):546, 2017.

[2] C. McAloon et al. Incubation period of covid-19: a rapid systematic review and meta-analysis of observational research. *BMJ Open*, 10(8):e039652, 2020.

[3] M. O'Driscoll et al. Age-specific mortality and immunity patterns of sars-cov-2. *Nature*, 590(7844):140–145, 2021.

[4] K. Prem et al. Projecting social contact matrices in 152 countries using contact surveys and demographic data. *PLoS Comput Biol*, 13(9):e1005697, 2017.