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RELEASE OF UPDATED VERSION OF THE ASSA COVID-19 MODEL

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The members of the group contributed to the work and also to a vigorous debate on various aspects of the assumptions, modelling and results. The result represents a broad collection of views but it should be noted that for most of the key assumptions and results there is no unanimous view within the group.

1. Introduction

The first version of the ASSA COVID-19 model was released for comment on 28 April 2020. The model and projection results were presented in various forums and published online. Wide ranging feedback was received on the model, which was very much appreciated. The ASSA COVID-19 modelling working group has also continued with its research. The model has now been updated to incorporate aspects of the feedback received and to allow for an improved understanding of the dynamics of this epidemic.

The key changes in the updated model are:

- An allowance for a factor to account for the heterogeneity of infection within a population.
- An allowance for a proportion of the population to be non-susceptible to the virus.
- An updated compartmental model structure to allow for additional types of transition.
- The ability to derive the values for parameters through calibration using a Sampling-Importance-Resampling approach[1]

There is still significant uncertainty as to the epidemic's progression in South Africa. This report provides insight into the impact of certain key assumptions on the projected outcomes. The results presented in this report therefore highlight a range of scenarios that may be possible. The updated ASSA COVID-19 model is available online for those that wish to assess their own scenarios.

At the outset we note that there remains wide ranging views within the working group on the likely trajectory of COVID-19 in South Africa. The figures here should not be taken to represent the range of possible outcomes depending on, say, how well non-pharmaceutical interventions are complied with. Rather the range of scenarios represents the range of views held by actuaries within the working

[1] This feature, described later in the report, is used to calibrate parameters to emerging data but is not part of the version made available online.

group on COVID-19 disease mechanics and the key parameters that affect progression and mortality. Individual actuaries may take more specific views.

We, again, look forward to receiving feedback from the profession.

2. Purpose

The purpose of the ASSA COVID-19 modelling working group is to:

- Develop, maintain and distribute an accessible model for projection purposes for use by actuaries who wish to assess the effect of COVID-19. The focus is on the projection of the number of cases and deaths due to COVID-19 over time, together with an estimate of the number of hospital beds required for treatment of COVID-19 patients.
- Consider the impact of the COVID-19 epidemic on the South African population by providing projections of possible outcomes.
- Present research to the actuarial community on key factors that affect the spread and modelling of the disease.

Work on other models, specifically an agent-based model, continues and may be shared in future if it is able to add value to the modelling effort.

The model will continue to evolve:

- Based on our ability to add complexity, within reason, to better model reality.
- As our understanding of the dynamics of the virus and disease improves.
- To allow for greater granularity of results by region and demographic group.

Previous versions of the model will remain available online for those that may still need to reference them.

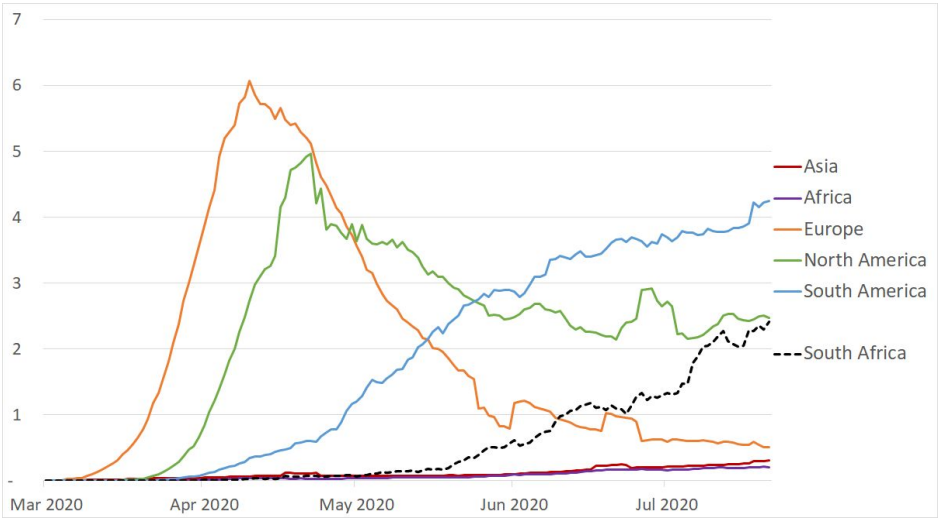
3. Brief summary of the current situation

It has been just over six months since the world first heard about the latest novel coronavirus, now given the name of SARS-CoV-2, that causes the disease COVID-19. In that short time, its impact on the world has been immense and it almost certainly will continue to impact our lives for a long while to come. At the time of writing, over 650 000 lives around the world have been confirmed to have been lost to COVID-19.

Graph 1 briefly illustrates the journey, at a high level, of the pandemic around the globe. It initially emerged in Wuhan, China, but has been successfully contained in Wuhan, the rest of China and, generally, across the rest of Asia. However, it had already spread to Europe and the USA (especially New York and New Jersey) where it seems to have spread quietly over the first three months of 2020. The rapidly escalating level of infections led to a health crisis in the affected regions where health systems were overwhelmed and a high number of COVID-19 related deaths were recorded. At this point, strict restrictions on movement and general activity were implemented in most affected countries in efforts to curb the spread further. Over this period, the number of deaths fell in both Europe and North America. Both regions are now being watched closely as they generally ease their restrictions on movement and gatherings.

Other parts of the world had forewarning of the coming pandemic but, even with the introduction of lockdowns and other non-pharmaceutical interventions (NPI's), the pandemic has progressed. South America is the current epicentre of the pandemic with the majority of the infections and deaths currently occurring across that region. With the forewarning, the impact has been relatively more

gradual but devastating nonetheless. Africa, on the whole, to date has not been as severely impacted. South Africa, however, has seen a steady increase in the number of infections and deaths over May and June, with a rapid escalation over the course of July.



Graph 1: No. of daily COVID-19 confirmed cases and deaths per million lives (by continent)
(Shows rolling 7 day average; data source: Our World In Data)

From the first confirmed case in South Africa on 5 March, and the first confirmed death on 27 March, the numbers of those confirmed to have been infected by SARS-CoV-2 have grown to over 450 000 and the confirmed deaths from COVID-19 to over 7 000 (at the time of writing). However, it is broadly acknowledged that both of these numbers are understated. In particular a large number of asymptomatic and mild cases are unlikely to have been tested. The number of confirmed cases is also heavily dependent on the testing capacity and the testing criteria used which has changed a number of times. The official number of deaths too is not considered complete as not all who die are tested. This is corroborated by SA Medical Research Council weekly excess mortality analyses[2] which show excess mortality significantly higher than official COVID-19 deaths. Their analysis indicates that there have been more than 22 000 excess natural deaths in South Africa from 6 May to 21 July, which is significantly higher than the official COVID-19 figure of 5,368 for this period (noting, however, that not all excess deaths will be due to COVID-19). On balance we are of the view that official mortality figures are understated particularly in the provinces other than the Western Cape where Case Fatality rates are lower than can be reasonably explained and differences between confirmed COVID-19 deaths and excess mortality are much wider. Future model updates will attempt to make allowance for this under reporting.

4. Current understanding of virus transmission and fatality rates

Appendix 2 contains an updated literature review providing greater detail on the research the modelling working group has done. Appendix 4 contains a clinical overview of the immunology of COVID-19.

Some aspects have become clearer while other aspects remain in mystery. With the emerging data, some scenarios seem less plausible than they may have previously, noting the considerable uncertainty of the available confirmed cases data being subject to testing protocols, constraints and backlogs, and death data almost certainly under-reporting the true extent of excess mortality caused

[2] https://www.samrc.ac.za/reports/report-weekly-deaths-south-africa

by the pandemic in many countries. There is a deluge of literature emerging on a daily basis and the urgency of the emergent pandemic has only permitted a small proportion of research to go through the usual scientific peer review process. There is much that we do not, as yet, know with certainty.

It appears that the virus is transmitted by droplets, with mixed evidence on aerosol transmission[3]. Evidence supports that non-pharmaceutical interventions (NPIs)[4] such as hand-washing, physical distancing and mask-wearing are effective at reducing the rate of transmission although debates remain as to the magnitude of the effects and compliance remains difficult to measure and monitor.

We do not know with certainty the way in which infections present symptomatically: the split between asymptomatic, mild and severe infections, with the latter driving hospitalisations and deaths. The proportion of asymptomatic infections is an important assumption in the model. For this, it is important to determine who has indeed been infected by the virus. This is a challenge because there remains uncertainty regarding the nature of the immune response and how to measure it. Seroprevalence studies are the most widely used to measure the proportion of a group infected with the virus, which can then be used to determine the proportion of those that were asymptomatic. However these studies will tend to undercount due to fading antibody counts over time and a high proportion of asymptomatic individuals becoming seronegative after infection[5]. Since the first report, the general consensus has been shifting to a lower proportion of asymptomatic infections (currently considered to be approximately 40%[6]), but considerable uncertainty still exists and a higher level remains possible. There is still the further question of whether or not the asymptomatic proportion of cases shed the virus while fighting it off successfully, and in so doing remain vectors of transmission.

We do not know what the true infection fatality curve by age looks like. We have initial evidence from research teams that studied early Chinese case data, with some further studies generally supporting their view. However, the infection fatality ratio (IFR), by definition, is dependent on the assumed proportion of asymptomatic infections so is difficult to validate. With regards to those cases severe enough to be hospitalised, early indications are that the South African mortality experience is heavier than the international baseline in the 40-70 age range.

We do not yet have a good understanding of effective treatment options, with mixed evidence, for example, on remdesivir[7] and scientific scandal tainting research into hydroxychloroquine[8]. However, the Western Cape has seen positive results from treating patients with high flow oxygen as an alternative to ventilation, allowing treatment in general wards rather than ICU beds, which is very positive news from the perspective of the risks of overburdening the healthcare system. The administration of low-dose dexamethasone to critical patients has also shown improved hospital mortality outcomes in the Western Cape. This suggests improvements in mortality may be expected. We also have no idea how long it may take to deliver an effective vaccine (if at all), nor how long immunity from previous infection lasts.

One of the criticisms of the initial ASSA model from some members is that the implied attack rates were implausibly high. The implicit assumption of homogeneous contact rates in the initial model

[3] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7293495/
[4] https://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736(20)31142-9.pdf
[5] https://www.nature.com/articles/s41591-020-0965-6?fbclid=IwAR2C_zNQA7_N_A8RV3Q5ZzWriY-Vf01rOC7Nb-nlRNbGt9W6nmIxKKem4BI
[6] https://jamanetwork.com/journals/jama/fullarticle/2768835
[7] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7129391/, https://www.sciencedirect.com/science/article/pii/S1477893920301162, https://www.sciencedirect.com/science/article/pii/S0140673620310229
[8] https://www.bmj.com/content/369/bmj.m1432/

assumes that everyone has the average level of contact frequency and is equally infective and susceptible to infection. It follows that the attack rates (the proportion of the population that will ultimately become infected) will be very high, typically over 70% for the R_0 values being used (if one also assumes full susceptibility of the population to infection).

In many cases, those critical of the initial model pointed to serology studies in countries hard-hit by the coronavirus, none of which have any seroprevalence results showing above 25% of the population having been infected so far. Sweden, for example, had a seroprevalence level below 10% as at the end of April 2020[9] despite that country not having imposed a 'hard lockdown'. Spain showed a seroprevalence of 5%[10] as at May 2020. In a more contained environment, the Diamond Princess cruise ship ended at around 20% infected[11]. These passengers would likely have been exposed to high viral loads, but on the other hand do appear to have self isolated well and been put under quarantine on board. In contrast, the Marion Correctional Institution in Ohio ended up having 78% infected in a confined, concentrated, relatively homogenous population[12]. Other examples are available, but none provide definitive guidance on the likely ultimate attack rate in any particular population.

This is an important matter to consider. There are a few potential drivers of the lower than expected national seroprevalence results published to date.

First of all, it is reasonable to assume that there is significant variation in contact patterns across a population and it would follow that those with more frequent contacts are both more likely to be infected and, once infected, to infect others even without innate biological or immunological variability. Differences in contact rates are well known to differ by age, but will also differ based on population density, community structure and general social interaction. Social interaction is affected by government intervention such as 'lockdown' but also due to natural individual and societal responses to information and risk. Studies also show that the majority of infections are caused by a minority of those infected[13], so called "super-spreaders". As such, it is important to consider the impact of heterogeneity in infectious spread in the population.

A second argument is that the lower seroprevalence levels could point to there being a level of heterogeneity in susceptibility to the virus, if not a significant portion of the population being entirely non-susceptible to SARS-CoV-2 due to the prevalence of so called memory 'T cells' responsive to SARS-CoV-2. Clinical opinion on the scientific evidence for this claim is varied in terms of the precise nature of combined immune response[14][15][16]. Should it be the case that there is indeed some level of innate immunity to the virus, this would explain the lower than expected seroprevalence results across measured populations. At this stage, without further studies shedding definitive light on the matter, it is not possible to estimate the range for the proportion of the population that may be non-susceptible. However it is a factor that warrants inclusion in the modeling effort.

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[9] https://www.folkhalsomyndigheten.se/nyheter-och-press/nyhetsarkiv/2020/maj/forsta-resultaten-fran-pagaende-undersokning-av-antikroppar-for-covid-19-virus/

[10] https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31483-5/fulltext

[11] https://www.nature.com/articles/d41586-020-00885-w

[12] https://www.medpagetoday.com/infectiousdisease/covid19/86391

[13] https://www.sciencemag.org/news/2020/05/why-do-some-covid-19-patients-infect-many-others-whereas-most-don-t-spread-virus-all

[14] https://www.medrxiv.org/content/10.1101/2020.04.17.20061440v1

[15] https://www.medicalbrief.co.za/archives/immunity-to-covid-19-may-be-higher-than-tests-have-shown-karolinska-institutet

[16] https://www.nature.com/articles/s41577-020-0389-z

Sceptics of the above two arguments argue there is a plausible alternative interpretation of serology studies in the light of significantly reduced spread of the virus following changes in behaviour and other NPIs. Given the evidence, in particular, of the effectiveness of mask-wearing and the impact of restricting mass gatherings through regulations (thereby reducing the opportunity for "super-spreader" events), it is possible that the reproduction rate was slowed down sufficiently (i.e. the R_t fell well below one) such that the number of new infections fell significantly. This argument therefore implies that there remains a large proportion of the population in such places that is still susceptible to the virus should the reproduction rate increase once more.

The dynamics of the seroprevalence results will only be better understood with time, and it may turn out to be a combination of the above. However, at this stage, it is important not to rule out any of these aspects and to examine the potential role of each in helping to explain the emerging data.

5. Details of the updated model

The model follows a modified compartmental SEIR epidemiological framework (Susceptible, Exposed, Infected, Recovered). Modifications on the standard SEIR model included adding various states of health once infected in order to produce outputs relevant to the health system. This section describes the changes that have been made to the original model.

5.1. Corrections

The previous model release used Infection Fatality Rates sourced from Verity et al. (2020). One area of critique received was that these rates had been incorrectly incorporated into the model. Specifically, that the Verity Infection Fatality Ratios (IFRs) already incorporated an allowance for asymptomatic cases, and that by overlaying our asymptomatic assumption we were essentially double counting the effect of asymptomatic cases. Upon investigation this critique was found to be valid and the correction has been made. This error understated the level of deaths in the initial model released (holding other parameters being equal). Note, however, that the hospital fatality rates are now informed by Western Cape mortality data observed thus far.

5.2. Changes in model structure and key assumptions

Model structure

The initial model only allowed for death from ICU. This was a known simplification that causes unexpected complications when calibrating to emerging data, in particular when deaths exceed ICU cases. The model structure has been updated as set out in Figure 1 below, with pathways to death through either hospital (non-iCU) or ICU, as well as the possibility of admission to ICU directly as well as indirectly via a non-ICU ward.

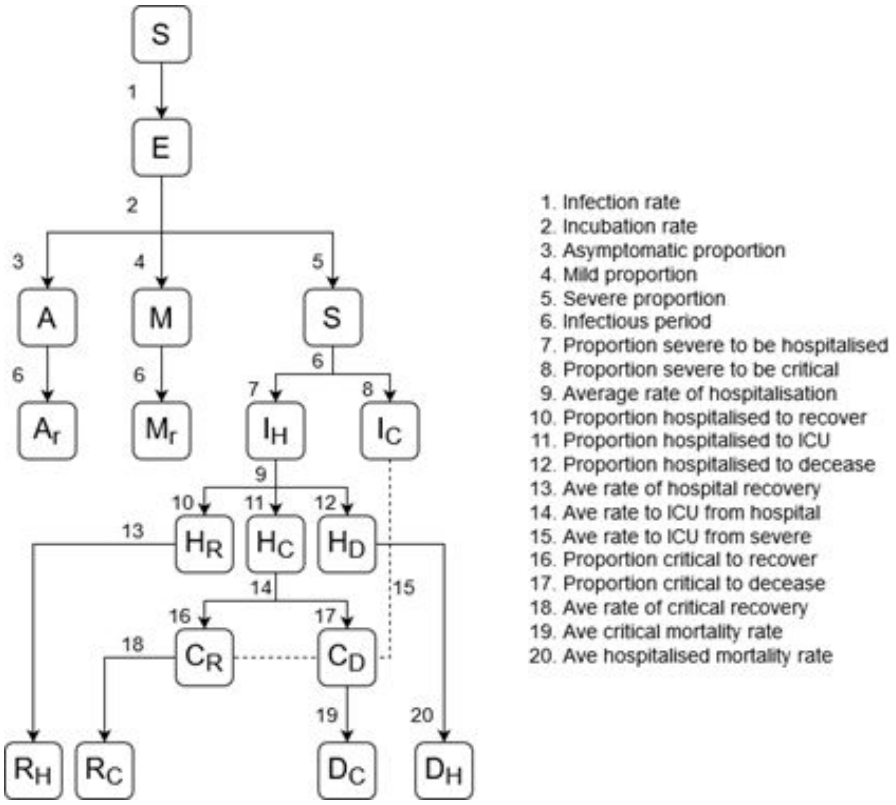


Figure 1: Revised model structure

Compartment key to Figure 1 (where Hospitalised refers to non-ICU wards):

S	Susceptible
E	Exposed
A	Infected, asymptomatic
A_r	Recovered from asymptomatic infection
M	Infected, mild
M_r	Recovered from mild infection
S	Infected, severe (will be hospitalised or in ICU)- still able to spread
I_H	Isolated, severe- will be hospitalised, no longer spreading
I_C	Isolated, severe- will go to ICU, no longer spreading
H_R	Hospitalised, will recover
H_C	Hospitalised, will go to ICU
H_D	Hospitalised, will die
C_R	In ICU, will recover
C_D	In ICU, will die
R_H	Recovered, having been hospitalised
R_C	Recovered, having been in ICU
D_H	Dead, having been hospitalised
D_C	Dead, having been in ICU

A technical write-up of the model is included as Appendix 3.

Suppression of the transmission rate due to NPIs

In the previous version we had assumed a range of possible suppression effects of lockdown on transmission. This updated model incorporates the suppression effects of level 5, 4 and 3 (so far) lockdowns in the calibration process. Lower future suppression is included in the published scenarios in this report in response to the continued de-escalation of lockdown: calibrations assume that the effective suppression in each level will vary between marginally higher and materially lower than the preceding level. The published front-end model allows for users to set the suppression parameter as they wish, including allowing for suppression to be maintained or even improved in future.

Introduction of heterogeneity in infectious spread

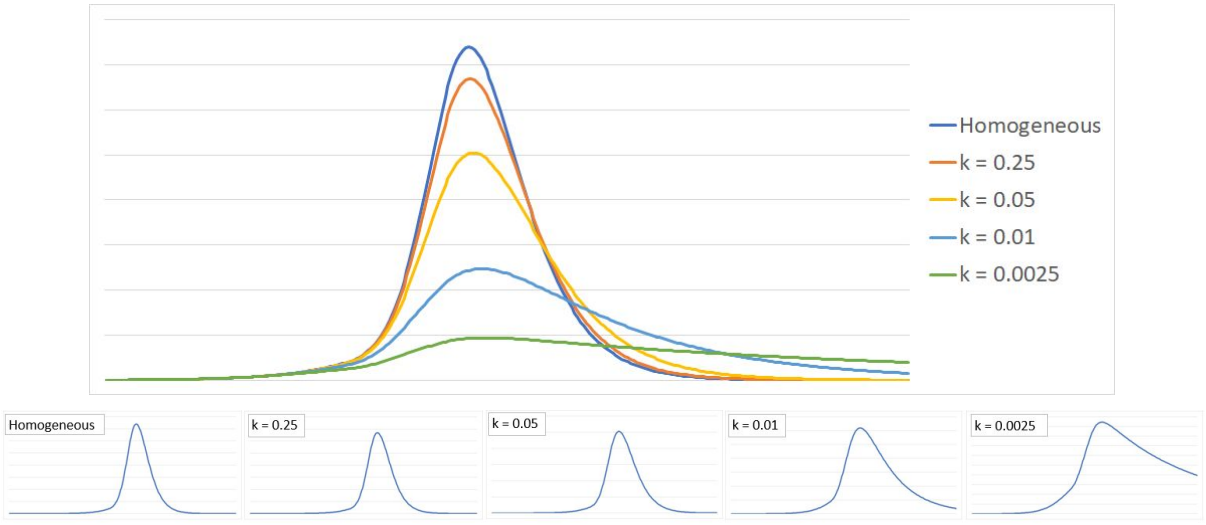
An implicit assumption in standard compartmental models is homogeneity. That is, the available reservoir of the susceptible population are all equally susceptible to being exposed and subsequently becoming infected. As discussed in the section above, there is growing evidence that this assumption is not valid.

Different approaches can be taken to allow for heterogeneity. It is possible to include further sub-groups (or compartments) within the model that then allows for different contact rates (and therefore levels of infection) between the sub-groups, although it still has an implicit assumption of homogeneity within the sub-group. An agent based modelling approach can also be used, which is a subject of ongoing work in the modelling working group. After research and discussion with other disease modellers, and some trial and error, we have opted to incorporate heterogeneity in a general way, without being specific as to the cause, and using a probability density function to modify the transmission function, rather than a static parameter or introducing additional subgroups.

This approach is described in a paper by Kong et al. (2016)[17]. It introduces heterogeneity in transmission by assuming that the number of contacts among individuals varies from person to person, and that the number of contacts that would be sufficient for transmitting the disease successfully follows a negative binomial distribution. The *k* factor in this distribution defines the shape of this distribution. Where *k* tends to infinity, the variance goes to zero which aligns with a homogenous model. As *k* decreases, it implies greater heterogeneity of the contact rates between the susceptible and infectious populations.

The impact of varying the *k* on the projection of the disease outbreak is highlighted in the graph below. As the level of heterogeneity increases, so the peak of the infections is lowered (although the timing of the peak is not significantly affected) but the tail of infections becomes greater. The ultimate attack rates decrease.

[17] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4808916/



Graph 2: Illustrative impact of increasing heterogeneity (i.e. a lower k) on the number of daily deaths

Very little if any data exists to accurately calibrate the various sources of heterogeneity, and therefore derive an estimate for *k*. An approach to do so requires detailed contact tracing data to establish the patterns of actual infection in a population, which is not available for South Africa. As such, several scenarios have been projected in this report assessing the impact of varying the level of heterogeneity, ranging from a *k* of 0.05 to 0.0025 (in addition to scenarios assuming homogeneous contact rates).

It is also likely that the level of *k* changes over time, especially after the introduction of any intervention (this would be expected to increase the level of heterogeneity). This has not been allowed for at this stage in the model. Interventions were introduced very early in the course of the epidemic in South Africa so the modelling period is essentially post-intervention. This will be reconsidered in future.

Note that a different paper by Lloyd-Smith et al. (2005)[18] describes an approach to assess the effect of individual variation on disease emergence, and specifically at the impact of "super-spreaders". Although it also finds that a negative binomial distribution is appropriate, the two approaches are different and the *k* values calculated for COVID-19 using this approach are not necessarily directly translatable into the approach described by Kong et al.(2016).

Proportion of asymptomatic infections

The proportion of asymptomatic cases was another area of critique as the baseline scenarios presented used a proportion of 75% asymptomatic cases. A wider range of scenarios is considered in this report. The separation of asymptomatic and mild cases is somewhat artificial in reality. In modelling terms making the distinction has some value in that it helps explain why many cases go undetected as asymptomatic infected patients are unlikely to be tested or seek care, although many mild cases will likely also not seek testing or treatment. It also permits an adjustment on infectivity as those showing no symptoms are less likely to cough and spread the virus. For now the split between asymptomatic and mild disease has been kept in the model.

[18] https://www.nature.com/articles/nature04153

Proportion of non-susceptible cases

Given the view in some of the recent literature regarding the possibility that a proportion of lives may not be susceptible to the virus, an additional factor has been included in the model that allows for a proportion of the population to be considered non-susceptible to the virus. The difference between asymptomatic and non-susceptible is somewhat artificial as in both cases the body has mounted a successful immune response. The distinction for modelling purposes relates to the ability to infect others. For the purposes of the model, asymptomatic cases are permitted to infect those still susceptible with an allowance for lower infectivity. Non-susceptible lives are not considered infective vectors in the model. Asymptomatic cases are included in the total infected counts and so will affect the calculation of infection fatality rates, but non-susceptible lives will not. There is no indication of the potential proportion (if any) of the population that may not be susceptible so, again, a variety of potential levels are considered.

6. Model calibration

In the initial version of the model, all parameters were set explicitly. Based on feedback received and given that we now have a longer run of data to fit to, we have altered the approach to rather calibrate certain key parameters to the emerging data. The model has been calibrated to South Africa death data using the Sampling-Importance-Resampling approach set out by Rubin (1987).[19] The approach works as follows in this application:

1. Define prior distributions for the parameters allowed to vary (we typically used uniform distributions with ranges informed by literature and other evidence).
2. Sample randomly from these prior distributions for all parameters one million times.
3. For each data point to be calibrated to, calculate the log-likelihood of the observation given the sampled set of parameters as outlined below. (In this application, we summed daily deaths in non-overlapping periods of three days in order to remove some of the reporting noise from the data.)
4. Sum the log-likelihoods to give the overall log-likelihood of the observations given the sample parameters.
5. Assign weights to each set of parameters equal to their relative likelihoods (sample likelihood divided by the sum of sample likelihoods).
6. Resample 50,000 of these samples with the probability of being drawn equal to the weights calculated above.
7. Plot 95% confidence intervals from the resulting resamples.

Likelihoods, following Johnson et al. (2017), are calculated based on the assumption that observed deaths are realisations of random variables with lognormal distributions with mean equal to the projected value given the sample parameters ψ:

$$ln\, D_t = ln\, \widehat{D}_t(\psi) + \varepsilon_t$$

where D_t is the reported number of deaths over the time interval t, $\widehat{D}_t(\psi)$ is the model estimate of deaths over that interval given parameters ψ and the error term is normally distributed with mean 0 and variance σ^2_ψ estimated as its Maximum Likelihood Estimate:

$$\widehat{\sigma}^2_\psi = \frac{1}{n}\sum_t (ln\, D_t - ln\, \widehat{D}_t(\psi))^2$$

where the sum is over all n time intervals.

[19] We are indebted to Leigh Johnson for suggesting this approach to us, as well as for generous and ever-useful input along the way.

7. Data

The death data used for the calibration is that published daily by the National Department ofHealth, sourced from the Data Science for Social Impact Research Group at the University of Pretoria[20]. It is acknowledged that this data has inaccuracies as it is provided by the date of reporting and not the date of the event. Given testing constraints and a sizeable proportion of out-of-hospital deaths, the official NDoH Covid-19 deaths counts are certainly an undercount of true Covid-19 deaths in the country; the truth is likely to lie somewhere between these figures and the SAMRC's reported excess deaths. In the absence of a robust method for estimating the true (and time-varying) extent of underreporting, we do not attempt to make any adjustment at present for this. Future work will consider the impact of using adjusted death levels on the calibration exercise and the projected results.

Detailed data on hospitalisations have been made available by the Western Cape Department of Health. However, this data is not publicly available. This data has been used to inform the transition rates and durations in each state/compartment within the model.

8. Scenarios considered

This section discusses the wide range of scenarios selected for analysis. The wide selection allows one to assess the impact of varying the key unknown parameters. In this way, it provides insight into the levels of the key parameters that may be possible when considering the projected outcomes against the emerging data.

- Proportion of asymptomatic infections

  This is a key factor that is widely debated and is difficult to determine accurately, as can be seen from the wide range of views supported in the literature review. In the first report, we included scenarios that allowed for 50% and 75% of infections being asymptomatic. In this report, to allow for the current range of views, we include scenarios with 35% of asymptomatic infections (in addition to 50% and 75%).

- Proportion of lives that are non-susceptible to the virus

  Recent literature points to the possibility that some people may not be susceptible to the virus, although there is no indication at this stage as to what proportion this may be. In addition to the base scenarios that assume that 100% of the population is susceptible, we have therefore included additional scenarios that illustrate the impact of a varying proportion of the population being non-susceptible. Levels of non-susceptibility to the virus of 15%, 30%, 45% and 60% of the population were chosen for illustrative purposes.

- Level of heterogeneity in infection rates

  As discussed, it is unlikely that the population is equally susceptible to being exposed and subsequently becoming infected. The model has been adjusted to allow for a level of heterogeneity in the transmission of the infection. However, there is no appropriate indication at this stage as to what the level of heterogeneity may be. As such, six different levels have been included in the scenarios that range from

[20] https://github.com/dsfsi/covid19za

assuming a homogeneous transmission rate to one that has a very high level of heterogeneity. This was done to illustrate the impact of the different levels on the outcomes.

As a result, 30 scenarios with different combinations of these key assumptions were run and calibrated, as follows:

- With the proportion of asymptomatic infections set at 35%, 50% and 75% respectively
    - 5 different levels of heterogeneity (*k* values from 0.0025 to 0.05) and a homogeneous scenario
    - With 100% of the population being susceptible to the virus
- With the proportion of asymptomatic infections set at 35% and 50% respectively
    - 4 different levels of non-susceptibility to the virus (15%, 30%, 45% and 60% of the population)
    - With a fixed level of heterogeneity (k of 0.025; for illustrative purposes, mid-range within our chosen range of heterogeneity)
- With the proportion of asymptomatic infections set at 50%
    - 4 different levels of non-susceptibility to the virus (15%, 30%, 45% and 60% of the population)
    - With a fixed level of heterogeneity (k of 0.01; for illustrative purposes, a higher level of heterogeneity)

Appendix 1 contains a summary table of the key outputs for all the scenarios. The detailed results of all the scenarios are provided in a separate Excel file for the profession to compare and interrogate. Commentary on key aspects is included below. The wide range of scenarios should allow actuaries to take a view based on what they consider to be a reasonable combination of parameters.

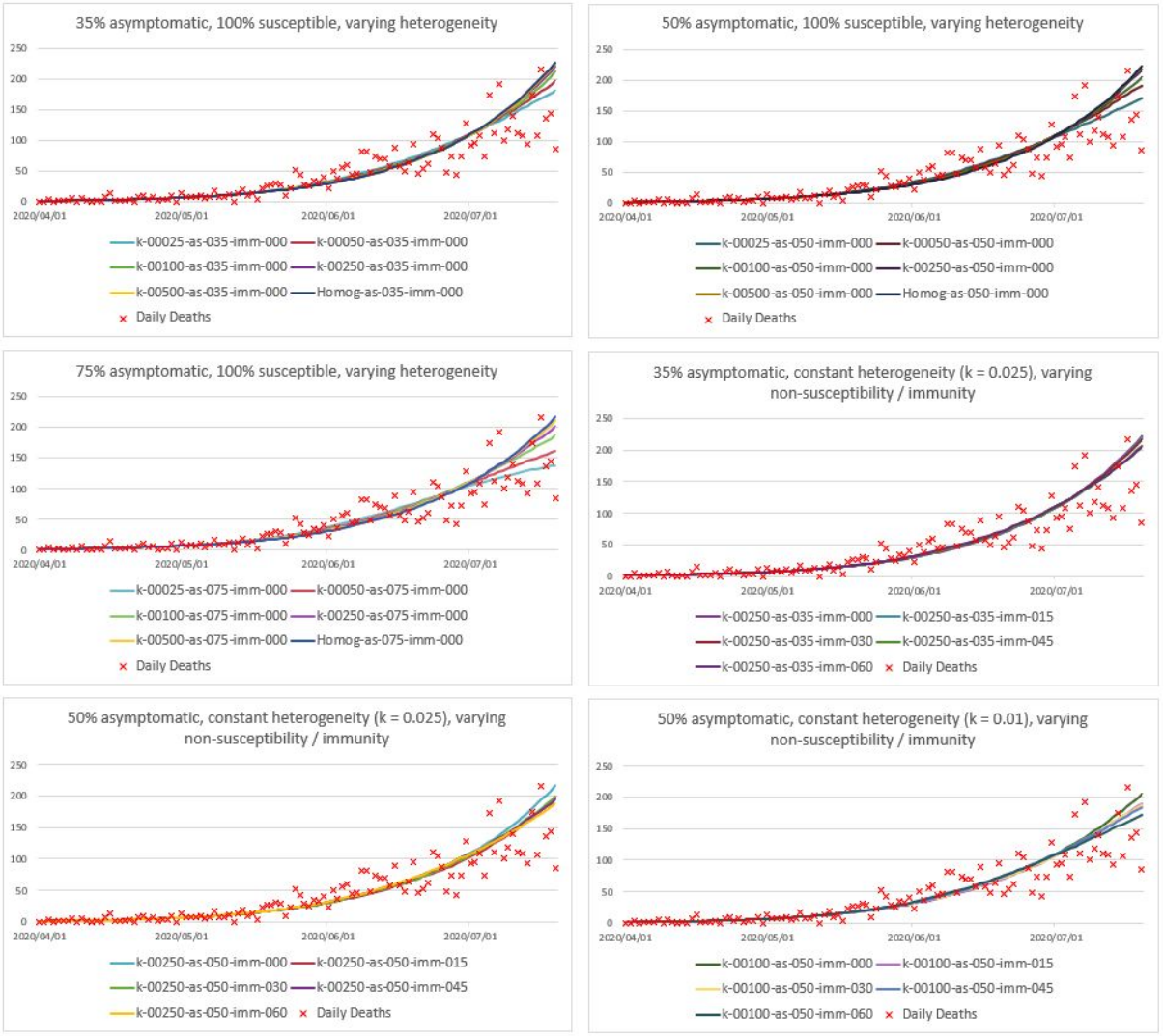
Please note that the projections have only been done to the end of this year (2020). The model available online is set up to project up to the end of 2021.

<u>Calibration of each scenario to the emerging national death data</u>

The graphs below illustrate the appropriateness of the fit for each of the calibrated scenarios to the emerging national death data. Given the number of scenarios, the graphs have been grouped as follows:

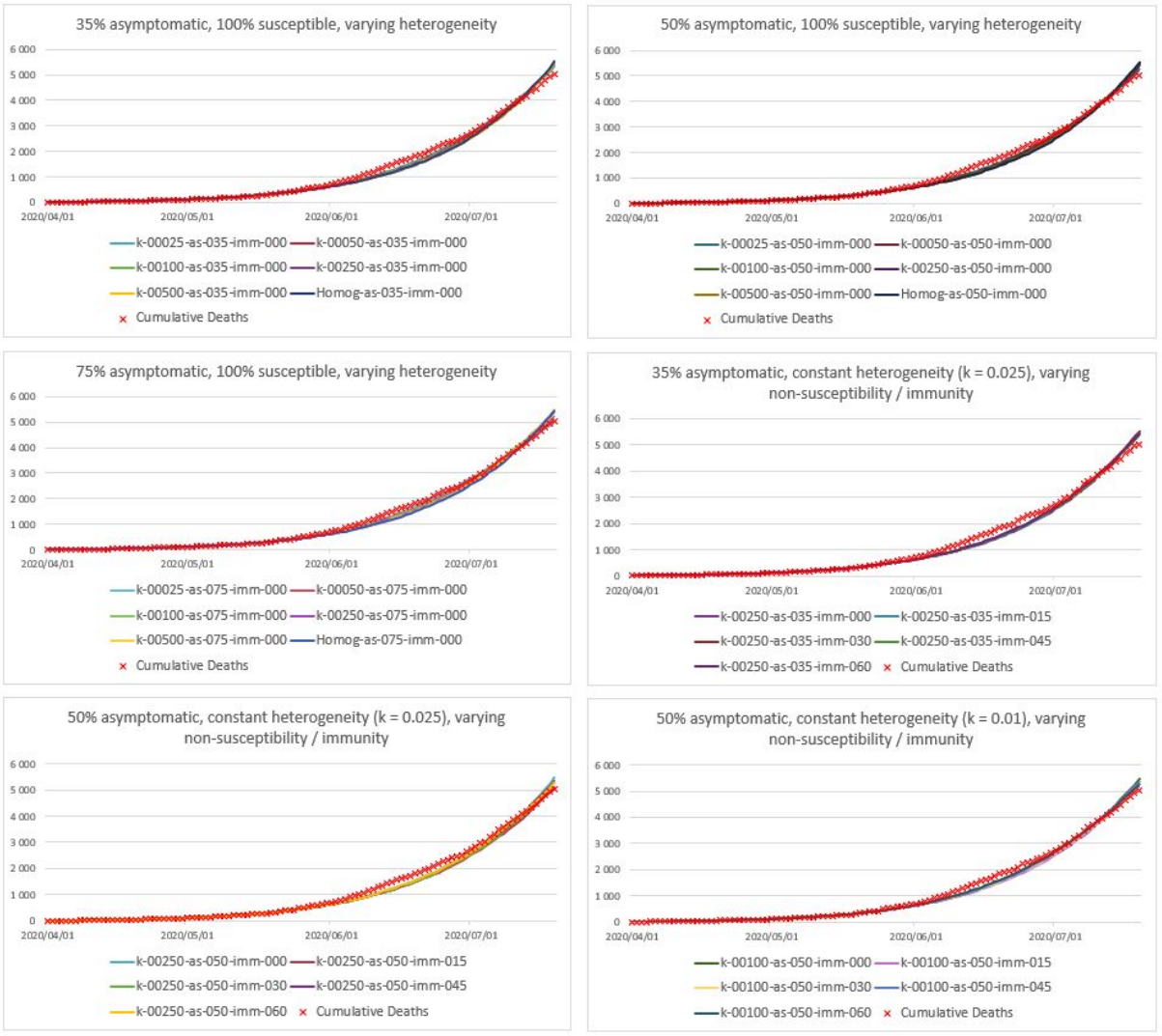
- All (6) scenarios assuming a 35% asymptomatic proportion and 100% susceptibility, varying the level of heterogeneity
- All (6) scenarios assuming a 50% asymptomatic proportion and 100% susceptibility, varying the level of heterogeneity
- All (6) scenarios assuming a 75% asymptomatic proportion and 100% susceptibility, varying the level of heterogeneity
- All (5) scenarios assuming a 35% asymptomatic proportion and a heterogeneity level of 0.025 for *k* (note this includes one scenario from the first graph), varying the proportion of the population assumed non-susceptible to the virus.
- All (5) scenarios assuming a 50% asymptomatic proportion and a heterogeneity level of 0.025 for *k* (note this includes one scenario from the first graph), varying the proportion of the population assumed non-susceptible to the virus.
- All (5) scenarios assuming a 50% asymptomatic proportion and a heterogeneity level of 0.01 for *k* (note this includes one scenario from the first graph), varying the proportion of the population assumed non-susceptible to the virus.

Due to the reporting challenges, the number of daily deaths varies significantly from day to day. All the scenarios project very similar levels of deaths at this point and provide a reasonably good fit to the emerging data.



Graph 3: Comparison of the scenario projections to the emerging data (no. of daily deaths)

The cumulative number of deaths is a lot smoother and the appropriateness of the fit is easier to identify.

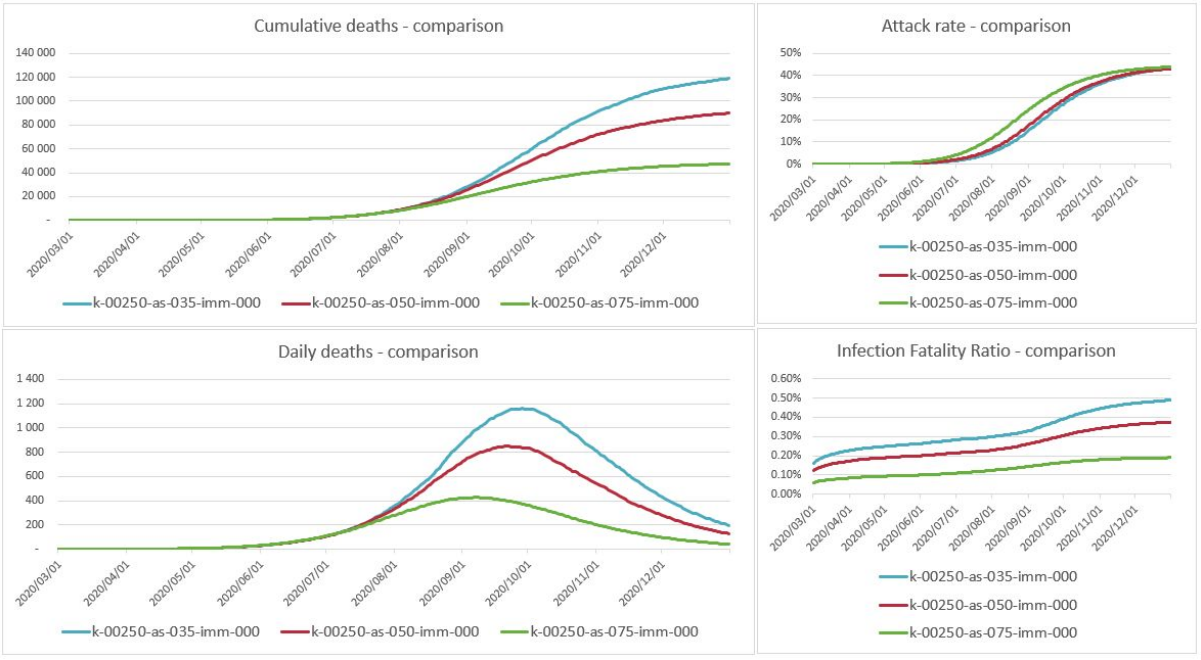


Graph 4: Comparison of the scenario projections to the emerging data (cumulative no. of deaths)

One can see that all the scenarios, even with the wide range of key assumptions, can be reasonably well calibrated to the emerging data at this point. This highlights the difficulty in doing such a modelling exercise as the emerging data can support a wide range of projected outcomes. However, in the graphs comparing the scenarios against the daily death data one can see that the projected numbers are starting to diverge over the recent period, especially as the assumed proportion of asymptomatic infections increases. As further data emerges in the coming weeks, it may be possible to start excluding certain combinations of parameters.

Illustrative impact of varying the proportion of asymptomatic infections

The graphs and table below highlight the impact of varying the assumption regarding the proportion of asymptomatic infections. 100% susceptibility to infection is assumed, and a mid-range level of heterogeneity (k = 0.025) has been used in these illustrative scenarios.

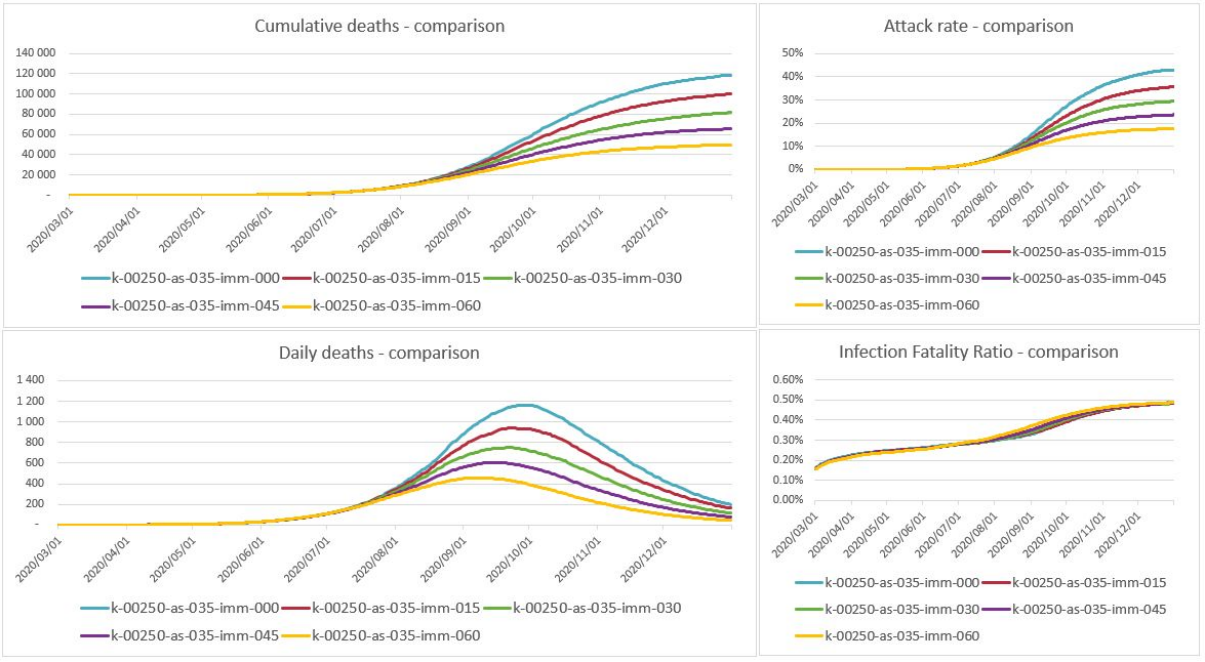


Graphs 5: Comparison of the impact of varying the proportion of asymptomatic infections

From the above, one can see that, with a constant level of heterogeneity assumed, the attack rate is the same across all three scenarios. However, the number of deaths reduces as the proportion of asymptomatic infections increases which reduces the IFR. An IFR of 0.2% is lower than that generally seen in the literature and would require a broad definition of 'asymptomatic' which could include for instance those who do become infected but remain seronegative. Allocating this group to asymptomatic infections still allows them to infect others. The higher the proportion of asymptomatic, the earlier the peak of daily deaths is. The asymptomatic assumption has a significant effect on mortality and the derived IFR since the model structure effectively alters the level of moderate and severe infections to accommodate the level of asymptomatic cases assumed. This, when one assumes a higher rate of asymptomatic infection, there are by necessity in the model structure fewer moderate and severe cases and consequently fewer deaths. Hence while the denominator of infections remains the same. The 75% assumption for asymptomatic cases included here, coupled with the resulting low IFR are among the extreme views on the modeling group.

Illustrative impact of varying the proportion of non-susceptible lives

The graphs and table below highlight the impact of varying the assumption regarding the proportion of non-susceptible lives in the population. 35% of infections are assumed to be asymptomatic and a mid-range level of heterogeneity (k = 0.025) has been used in these illustrative scenarios.



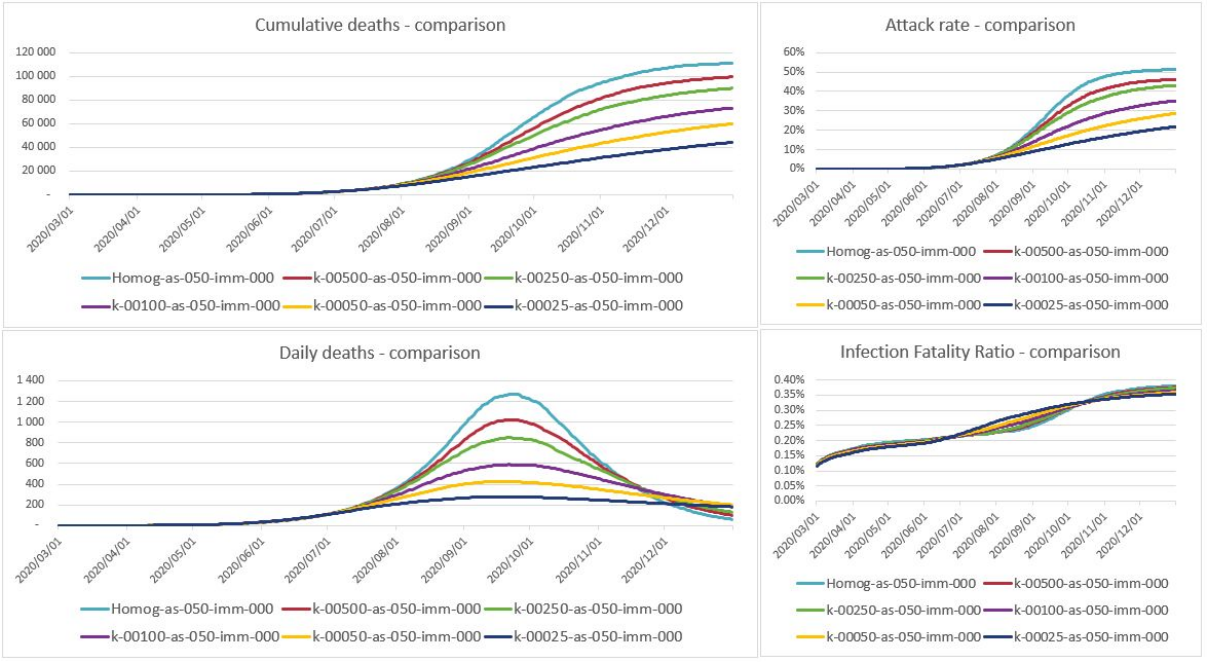
Graphs 6: Comparison of the impact of varying the level of non-susceptibility to the virus

Increasing the proportion of non-susceptible lives has a similar impact to increasing the asymptomatic proportion assumption, except that the immune lives are not ever included in the “infected” pool and do not transmit the virus to others. Increasing the proportion of non-susceptible lives results in a fall in the number of deaths. However, here the attack rate is lower as non-susceptible lives are not counted as infected. The resulting IFRs are not affected by the change in the assumption. The scenarios with higher levels of non-susceptibility peak earlier. We note here that there is insufficient research to support a narrow range for this parameter. Assuming very high levels of non-susceptibility is not supported by studies that show widespread infections for which there are some notable examples.

Actuaries making use of the model should apply what they consider to be a reasonable range and combination of the key assumptions to take a view of likely mortality projections.

Illustrative impact of varying the level of heterogeneity

The graphs and table below highlight the impact of varying the assumption regarding the level of heterogeneity from a homogeneous assumption to one with a high level of heterogeneity. 100% susceptibility to infection and a 50% asymptomatic infection level has been used in these illustrative scenarios.



Graphs 7: Comparison of the impact of varying the level of heterogeneity

As the level of heterogeneity increases (i.e. *k* decreases), fewer people get infected (i.e. lower attack rate) and the cumulative number of deaths decreases. The peak level. of daily deaths is lower, but does decrease more gradually and has a higher number of daily deaths by the end of the year. The IFR is consistent across all scenarios. All scenarios peak at a similar time.

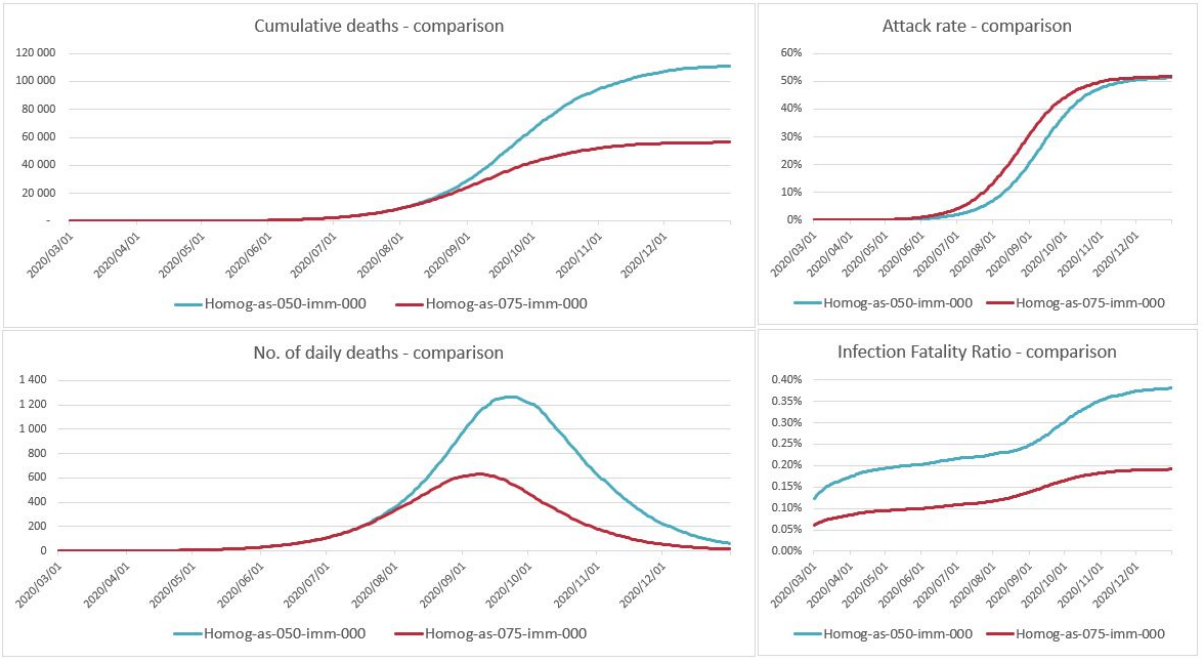
9. Sample model outputs under key variable combinations

Within the working group there is a wide range of views for plausible narratives that are consistent with our current understanding of the virus and the observed data. These have significantly different implications for the future trajectory of the epidemic in South Africa. While many in the group would lean more to particular scenarios than to others, there are robust differences of opinion as to the relative plausibility of the narratives implied in these scenarios. It will of course emerge down the line that one version that will have better described the truth than others. We feel that the acknowledgement of uncertainty, in the form of a range of possibilities is an honest reflection of the inherent uncertainties and range of views.

Revisit of the scenarios from the first report

In the first report, the core scenarios assumed either a 50% or 75% proportion of asymptomatic infections, with no allowance for possible non-susceptibility or heterogeneity in infection. Using these assumptions on the updated model (which includes the corrections regarding the handling of

mortality) and calibrated to the latest death data, the attack rate has dropped to just over 50% but the no. of projected deaths have increased considerably.



By the end of 2020	**50% asymptomatic 0% non-susceptible Homogeneous**	**75% asymptomatic 0% non-susceptible Homogeneous**
Cumulative no. of deaths	111k	56k
Max no. of daily deaths	1 269	633
Infection Fatality Ratio (IFR)	0.38%	0.19%
Attack rate	51%	52%

Consideration of four specific scenarios

Specific scenarios are considered below, with a narrative on the implied understanding and dynamics underlying each. The scenarios reflected here do not represent a consensus view of the working group or of ASSA, rather they broadly reflect the range of views held by actuaries who have contributed to the research. We note again that actuaries on the working group and others have wide ranging views on issues that affect COVID-19 progression.

SCENARIO A - HOMOGENEOUS & FULLY SUSCEPTIBLE

This model scenario is the basic compartmental model for a novel virus for which there is no innate immunity (i.e. all lives are susceptible), and assumes the population all mix in an even way. As this is a highly transmissible respiratory pathogen, the variation in contact rates will not have an impact on the spread and transmission rates can be assumed to be homogeneous. There is also increasing support for the view that the proportion of asymptomatic infections is on the lower side (i.e. closer to 35%).

With this scenario, attack rates by the end of the year will be high, around 50%. Infection fatality rates settle at 0.49%. Daily deaths peak at over 1 600 deaths per day at the end of September, but subside relatively quickly. By way of reference, Western Cape daily deaths peaked at around 55 per day

(smoothing out some of the daily volatility) which would amount to around 470 daily deaths per day for the country on a pro-rata basis (assuming all provinces peaked at the same time at the same population rate). Cumulative deaths by the end of the year will be high at over 140 000. Peak ICU bed requirement would be over 10 000.

These attack rates are notably higher than has been observed so far in other regions. The implicit assumption is that the whole population is susceptible and efforts to contain the spread fail (R_t remains above 1) so that the virus continues to spread. South Africa as a whole would be the worst performing country globally in terms of mortality per million population (2 509) based on current statistics[21]. By comparison New York and New Jersey, as individual states within the US, have amongst the highest levels of mortality currently at approximately 1 700 deaths per million[22] despite having older age profiles. Whether these benchmarks are appropriate will only be known in time as the progression of the epidemic in each country could have been limited by reducing the transmission rate (e.g. through the introduction of NPIs) which suggests that the levels may increase once more should further outbreaks occur once behaviour changes and/or restrictions are eased.

SCENARIO B - MODERATE ASYMPTOMATIC PROPORTION AND LEVEL OF HETEROGENEITY, WITH SOME LEVEL OF IMMUNITY

This scenario assumes that there is some level of non-susceptibility within the population (15%). It is also important to acknowledge the variability in contact rates by allowing for a relatively moderate level of heterogeneity (k = 0.025). The proportion of asymptomatic infections is assumed to be 50%.

With this scenario, the number of deaths by the end of the year will be approximately 75 000, with an IFR of 0.37%. However, as some of the population is not susceptible, the attack rate is lower at 35%. Daily deaths peak at over 678 deaths per day towards the end of September, and also subside relatively quickly. Peak ICU bed requirements would be just over 4 300.

The mortality per million lives would be 1 308, which would still be higher than the experience of any country to date.

SCENARIO C - HIGH LEVEL OF IMMUNITY

This scenario assumes that a large proportion (60%) of the population is not susceptible to the virus. For those that do get infected, 35% are asymptomatic. As there is heterogeneity in the rate of infection, a relatively moderate level of heterogeneity is allowed for (k of 0.025).

With this scenario, the number of deaths by the end of the year will be approximately 50 000, with a comparatively high IFR of 0.49%. However, as most of the population is not susceptible, the attack rate is much lower at 18%. Daily deaths peak at over 870 deaths per day at the beginning of September, and also subside relatively quickly. Peak ICU bed requirements would be just under 2900.

The mortality per million lives would be 876, which again would currently be amongst the highest in the world. Belgium, at the time of writing, has a level of 846 deaths per million lives which is the highest for a country with a population of over a million people.

[21] https://www.worldometers.info/coronavirus/ *Note that the circumstances and basis for counting both cases and deaths do vary per country.*
[22] https://www.worldometers.info/coronavirus/country/us/

SCENARIO D - HIGH LEVEL OF HETEROGENEITY AND HIGH ASYMPTOMATIC

This scenario assumes that the heterogeneity in contact rates is high, and has become more so due to the effects of lockdown and the other NPIs. Thus the highest level of heterogeneity (*k* of 0.0025) that fits the observed mortality data so far is assumed. The asymptomatic proportion is also high at 75% as it includes a broad definition of immunity and that all are infectious. No further allowance is made for a non-susceptible proportion.

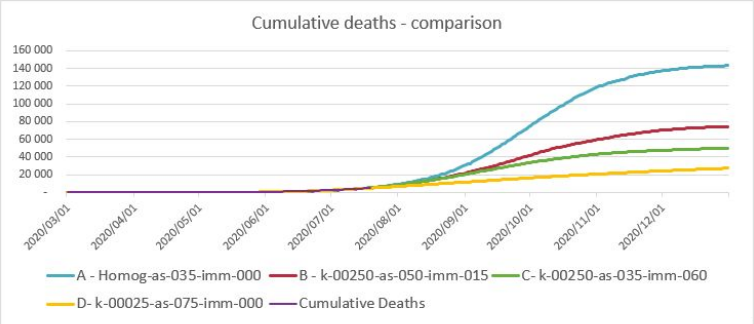
With this scenario, the number of deaths by the end of the year will be considerably lower than the other scenarios at approximately 27 000, with an IFR of 0.28%. The attack rate, by the end of the year, would be 26%. Peak ICU bed requirements would be just over 1 500. However, the daily deaths, which peak at 161 at the end of August, do not subside as quickly and are forecast to still be 92 per day at the end of the year. The peak of 161 deaths per day has been breached on several occasions already (noting that some of the daily volatility in mortality reporting is due to catch up of previous underreporting). As a result, the case for this scenario may well become weaker as more data emerges.

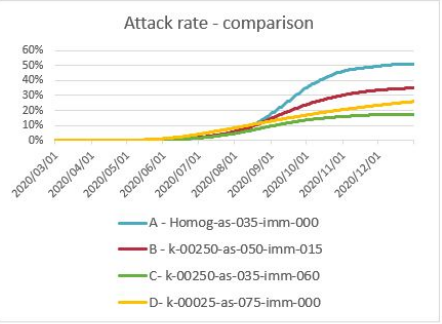
The mortality per million lives would be 481, which is lower than several European nations, but higher than most of the world currently. However, some Latin American countries are close to, or indeed over, rates higher than 400 deaths per million lives and do not appear to have peaked as yet. As at 29 July 2020 the Western Cape was at approximately 430 deaths per million[23] (counting only officially reported COVID-19 deaths).

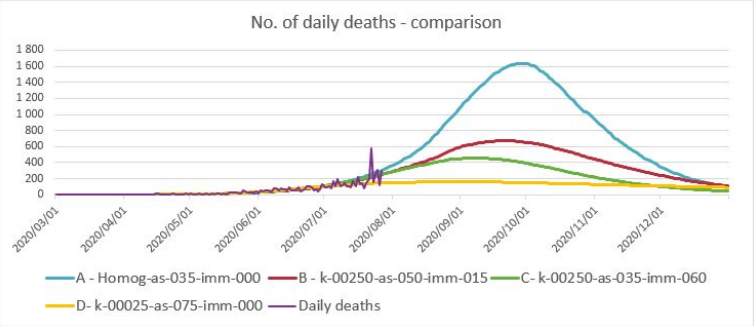
The key graphs and summary table of these four scenarios follow on the next page.

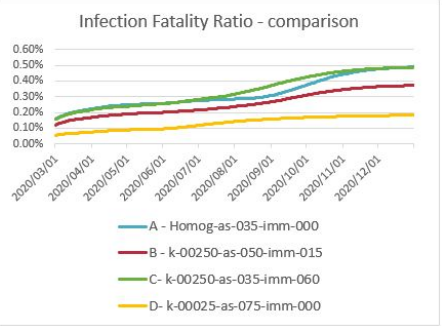
[23] https://corona-stats.mobi/en/ZA/provincial_per_million.php

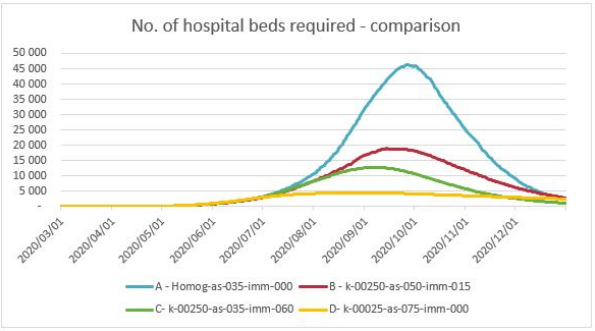
Summary graphs and metrics for the selected scenarios

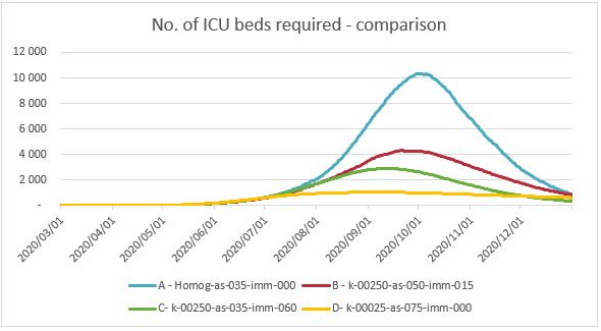












By the end of 2020	**A** **Asympt.: 35%** **Non-susc.: 0%** **Homogeneous**	**B** **Asympt.: 55%** **Non-susc.: 15%** **k = 0.025**	**C** **Asympt.: 35%** **Non-susc.: 60%** **k = 0.025**	**D** **Asympt.: 75%** **Non-susc.: 0%** **k = 0.0025**
Cumulative no. of infections	29m	20m	10m	15m
Cumulative no. of deaths	143k	75k	50k	27k
No. of deaths per million lives	2 509	1 308	876	481
Max no. of daily deaths	1 639	678	457	161
Date of peak of daily deaths	30 Sep	21 Sep	5 Sep	31 Aug
No. of daily deaths at 31 Dec	97	111	44	92
Infection Fatality Ratio (IFR)	0.49%	0.37%	0.49%	0.18%
Attack rate (at 31 Dec)	51%	35%	18%	26%
Max no. of hospital beds required	46k	19k	13k	5k
Date of max hospital beds	26 Sep	14 Sep	6 Sep	30 Aug
Max no. of ICU beds required	10k	4k	3k	1k
Date of max ICU beds	30 Sep	20 Sep	11 Sep	4 Sep
Inpatient Fatality Ratio	25.0%	25.6%	25.3%	25.2%

10. Cautions and caveats

As with all professional actuarial work, expert judgment is required when interpreting model results. Users of this ASSA COVID-19 model are urged to exercise caution when varying input parameters and when using outputs of the model. Significant contextual understanding of the disease, epidemiology and the supporting models is required to draw proper judgements.

As with all models, there is a definite model risk in that the model, as currently structured, may not reflect reality appropriately. For instance, the approach used to introduce heterogeneity in infection rates may not reflect the underlying dynamics correctly.

The current model assumes that the pandemic is a single national one when in reality it's the aggregation of a number of sub-epidemics in different regions. Thus the progression of the epidemic will differ from region to region.

There is no allowance for mortality improvements in the projections. There is early evidence that mortality outcomes may have improved with improvements in clinical management and treatment options (already high-flow oxygen and low-dose dexamethasone have proved effective).

There is no allowance for worsening mortality outcomes in the model currently if health system capacity limits are breached. It appears that this may already be occurring in certain provinces. There is currently no allowance in the model or model calibration for under reported deaths or excess deaths reported on by the SAMRC.

There is currently no allowance for heterogeneity in transmission due specifically to age.

Users may note that suppression factors on R_t during the various stages of lockdown are relatively low. This should not be interpreted to mean that NPIs had no effect during these periods, but rather that there is insufficient data before lockdown for the calibration model to settle on an R_0 figure pre-intervention. This means there is some conflation in the calibration between the initial R_0 value for infectious spread and allowance for the effect of intervention. An alternative would be to lock in a higher R_0 value (or R_0 value range) say based on literature derived figures and allow the calibration to derive suppression factors for each period based on observed deaths.

There is no endogenous allowance for responsiveness of compliance with NPIs to the severity of the epidemic; the relative suppression of infectious spread is an exogenous variable and does not respond to observed indicators of severity such as cases, hospital admissions or deaths. It is feasible that society will react to news reports of steeply climbing deaths and disease severity by improving adherence to NPIs such as physical distancing and mask wearing. This may occur whether or not the Government changes lockdown conditions.

Key hospitalisation parameters, including the split between ICU and non-ICU wards as well as the expected lengths of stay, have been derived using data from the Western Cape. This may not be applicable to the other provinces, especially those provinces that are not as well-resourced.

The calibration has been done against the official number of deaths. There is a strong likelihood that the number of deaths is underreported, which would have an impact on the appropriateness of the calibrated parameters and the resulting projection.

11. In conclusion...

Modeling the mechanics of COVID-19 is complex. Research on key parameters and factors affecting disease spread often provides mixed, wide ranging or even conflicting evidence. Even 'hard data' such as mortality can be inconsistent when comparing countries due to differing reporting standards. Nonetheless, the working group continues to try to refine the disease model in an effort to better understand it and provide actuaries with a useful tool.

Different members of the modeling working group lean towards different model scenarios and explanations of the observed data. Despite robust discussions these differences still represent a wide range. Actuaries are therefore encouraged to stay in touch with emerging evidence, engage with different viewpoints in order to learn and stay informed. Some actuaries are of the view that a runaway scenario in South Africa is possible given the timing of lockdown easing, allowance for communal gatherings and relaxation of taxi occupancy rules. Other actuaries on the working group are of the view that immunity plays a stronger role than initially thought and that there is comparatively high heterogeneity in the South African population which taken together will curtail the spread and prevent the worst case figures.

The group plans to continue working on model refinements including provincial outputs, age based heterogeneity in infectivity, and other refinements. Calibrations to the model structure will continue to be run from time to time which should narrow the plausible scenarios as time goes by. These calibration runs will be loaded onto the model site in a similar format to the accompanying spreadsheet with scenario outputs. The online version of the model is available at http://www.assacovid19.org.za/ where different parameter values can be tested and results downloaded. The old version of the model and all versions of reports and outputs will be maintained there for posterity.

Please send all comments and feedback to covid19@actuarialsociety.org.za.

Appendix 1: Key metrics for all scenarios

Table of infection and mortality related metrics for all scenarios

SCENARIOS	Level of heterogeneity (k)	Proportion asymptomatic	Proportion non-susceptible	Cumulative no. of infections	Cumulative no. of deaths	No. of deaths per million lives	Max daily deaths	Date of max daily deaths	Daily deaths at 31/12	Infection Fatality Ratio (IFR)	Attack Rate
k-00025-as-035-imm-000	0.0025	35%	0%	11 790 545	54 286	952	349	28-Sep	236	0.46%	21%
k-00050-as-035-imm-000	0.005	35%	0%	15 985 253	74 417	1 306	542	24-Sep	279	0.46%	28%
k-00100-as-035-imm-000	0.01	35%	0%	19 839 066	93 940	1 648	771	29-Sep	267	0.47%	35%
k-00250-as-035-imm-000	0.025	35%	0%	24 713 851	118 787	2 084	1 160	28-Sep	196	0.49%	43%
k-00500-as-035-imm-000	0.05	35%	0%	26 893 967	130 854	2 296	1 359	28-Sep	159	0.48%	47%
Homog-as-035-imm-000	Homogeneous	35%	0%	29 243 427	143 036	2 509	1 639	30-Sep	97	0.49%	51%
k-00025-as-050-imm-000	0.0025	50%	0%	12 574 444	44 235	776	278	18-Sep	181	0.35%	22%
k-00050-as-050-imm-000	0.005	50%	0%	16 493 174	59 844	1 050	425	19-Sep	200	0.36%	29%
k-00100-as-050-imm-000	0.01	50%	0%	20 205 342	73 288	1 286	590	21-Sep	187	0.37%	35%
k-00250-as-050-imm-000	0.025	50%	0%	24 747 270	89 935	1 578	850	21-Sep	128	0.37%	43%
k-00500-as-050-imm-000	0.05	50%	0%	26 527 620	99 455	1 745	1 024	24-Sep	101	0.38%	46%
Homog-as-050-imm-000	Homogeneous	50%	0%	29 462 500	111 020	1 948	1 269	24-Sep	62	0.38%	51%
k-00025-as-075-imm-000	0.0025	75%	0%	14 948 427	27 394	481	161	31-Aug	92	0.18%	26%
k-00050-as-075-imm-000	0.005	75%	0%	18 250 993	33 172	582	221	02-Sep	87	0.18%	32%
k-00100-as-075-imm-000	0.01	75%	0%	21 772 593	40 643	713	314	06-Sep	70	0.19%	38%
k-00250-as-075-imm-000	0.025	75%	0%	25 193 983	47 514	834	426	07-Sep	42	0.19%	44%
k-00500-as-075-imm-000	0.05	75%	0%	26 923 839	51 816	909	514	06-Sep	29	0.19%	47%
Homog-as-075-imm-000	Homogeneous	75%	0%	29 688 689	56 493	991	633	08-Sep	14	0.19%	52%
k-00250-as-035-imm-015	0.025	35%	15%	20 468 960	100 019	1 755	943	22-Sep	162	0.48%	36%
k-00250-as-035-imm-030	0.025	35%	30%	16 922 802	81 592	1 431	750	20-Sep	113	0.48%	29%
k-00250-as-035-imm-045	0.025	35%	45%	13 574 097	65 545	1 150	604	15-Sep	76	0.48%	24%
k-00250-as-035-imm-060	0.025	35%	60%	10 115 302	49 917	876	457	05-Sep	44	0.49%	18%
k-00250-as-050-imm-015	0.025	50%	15%	20 119 104	74 531	1 308	678	21-Sep	111	0.37%	35%
k-00250-as-050-imm-030	0.025	50%	30%	17 066 761	63 528	1 115	575	20-Sep	76	0.37%	30%
k-00250-as-050-imm-045	0.025	50%	45%	13 499 865	50 657	889	452	11-Sep	51	0.38%	23%
k-00250-as-050-imm-060	0.025	50%	60%	10 071 762	37 524	658	335	05-Sep	29	0.37%	18%
k-00100-as-050-imm-015	0.01	50%	15%	17 033 674	62 786	1 102	498	20-Sep	153	0.37%	30%
k-00100-as-050-imm-030	0.01	50%	30%	14 263 412	52 200	916	406	12-Sep	114	0.37%	25%
k-00100-as-050-imm-045	0.01	50%	45%	11 529 991	42 468	745	327	07-Sep	81	0.37%	20%
k-00100-as-050-imm-060	0.01	50%	60%	8 938 965	32 764	575	252	30-Aug	50	0.37%	16%

Table of hospital related metrics for all scenarios

SCENARIOS	Level of heterogeneity (k)	Proportion asymptomatic	Proportion non-susceptible	Max no. of hospital beds required	Date of max hospital beds	Max no. of ICU beds required	Date of max ICU beds	Inpatient Fatality Ratio
k-00025-as-035-imm-000	0.0025	35%	0%	9 939	25-Sep	2 310	02-Oct	25.0%
k-00050-as-035-imm-000	0.005	35%	0%	15 294	26-Sep	3 539	01-Oct	24.9%
k-00100-as-035-imm-000	0.01	35%	0%	21 962	22-Sep	5 020	03-Oct	24.8%
k-00250-as-035-imm-000	0.025	35%	0%	32 142	23-Sep	7 289	01-Oct	25.2%
k-00500-as-035-imm-000	0.05	35%	0%	38 167	27-Sep	8 613	03-Oct	25.3%
Homog-as-035-imm-000	Homogeneous	35%	0%	46 322	26-Sep	10 347	30-Sep	25.0%
k-00025-as-050-imm-000	0.0025	50%	0%	7 875	19-Sep	1 829	23-Sep	24.9%
k-00050-as-050-imm-000	0.005	50%	0%	11 985	15-Sep	2 772	24-Sep	24.9%
k-00100-as-050-imm-000	0.01	50%	0%	16 989	18-Sep	3 895	25-Sep	24.9%
k-00250-as-050-imm-000	0.025	50%	0%	24 432	22-Sep	5 525	26-Sep	25.2%
k-00500-as-050-imm-000	0.05	50%	0%	28 370	19-Sep	6 399	26-Sep	25.4%
Homog-as-050-imm-000	Homogeneous	50%	0%	36 128	20-Sep	8 088	26-Sep	25.5%
k-00025-as-075-imm-000	0.0025	75%	0%	4 527	30-Aug	1 054	04-Sep	25.2%
k-00050-as-075-imm-000	0.005	75%	0%	6 258	31-Aug	1 450	06-Sep	25.0%
k-00100-as-075-imm-000	0.01	75%	0%	8 784	03-Sep	2 016	08-Sep	25.2%
k-00250-as-075-imm-000	0.025	75%	0%	12 079	07-Sep	2 746	09-Sep	25.2%
k-00500-as-075-imm-000	0.05	75%	0%	14 319	08-Sep	3 236	10-Sep	25.5%
Homog-as-075-imm-000	Homogeneous	75%	0%	17 872	10-Sep	4 003	13-Sep	25.5%
k-00250-as-035-imm-015	0.025	35%	15%	26 136	22-Sep	5 923	27-Sep	25.4%
k-00250-as-035-imm-030	0.025	35%	30%	21 150	18-Sep	4 805	24-Sep	25.0%
k-00250-as-035-imm-045	0.025	35%	45%	16 960	14-Sep	3 851	17-Sep	25.3%
k-00250-as-035-imm-060	0.025	35%	60%	12 733	06-Sep	2 891	11-Sep	25.3%
k-00250-as-050-imm-015	0.025	50%	15%	18 937	14-Sep	4 312	20-Sep	25.6%
k-00250-as-050-imm-030	0.025	50%	30%	16 325	13-Sep	3 704	20-Sep	25.0%
k-00250-as-050-imm-045	0.025	50%	45%	12 779	09-Sep	2 899	14-Sep	25.3%
k-00250-as-050-imm-060	0.025	50%	60%	9 538	28-Aug	2 170	04-Sep	25.1%
k-00100-as-050-imm-015	0.01	50%	15%	13 662	19-Sep	3 119	24-Sep	25.2%
k-00100-as-050-imm-030	0.01	50%	30%	11 563	14-Sep	2 662	21-Sep	24.9%
k-00100-as-050-imm-045	0.01	50%	45%	9 186	08-Sep	2 106	17-Sep	25.1%
k-00100-as-050-imm-060	0.01	50%	60%	7 136	26-Aug	1 644	05-Sep	24.8%

Appendix 2: Literature review

The purpose of this appendix is to provide a review of the relevant academic publications around COVID-19 to inform the assumptions that the team is using for the model.

We note that COVID-19 research is ongoing and new papers are being published regularly, so a number of the sources cited here are likely to become obsolete as the pandemic progresses and as more information becomes available around the COVID-19 pandemic.

Transmission Rate (R0)

One of the key assumptions in respect of any SEIR model for a viral infection is the rate of transmission between members of the population. A common way of representing this is through a basic reproduction number (referred to as R0) which represents the average number of new infections generated per infectious life in the population.

Various studies have attempted to quantify this R0 figure for the populations which were infected in the initial phase of the pandemic (mostly various populations in South East Asia and the population quarantined on the Diamond Princess cruise ship). The results from those studies were as follows (a variety of different datasets and statistical methodologies were used to estimate R0 depending on the model design chosen):

- In (1), the researchers used transmission data from the Wuhan region in China for December 2019 and January 2020 to generate an estimated R0 of 2.68 (95% CI 2.47-2.86);
- In (2) the researchers used data from Wuhan and the Hubei province in China to estimate an initial R0 of 4.71 (95% CI 4.50-4.92) at the start of the outbreak on 12 December 2019, gradually declining to an estimate of 2.08 (95% CI 1.99-2.18) on 22 January 2020;
- In (3) a study of infections in the Guangdong province of China, supplemented by other regions of China and other countries estimated an R0 of 2.90 (95% CI 2.32-3.63);
- In (4) a study of all infections reported in China and other countries between 12 December 2019 and 22 January 2020 reported an R0 of 3.11 (95% CI 2.39-4.13);
- In (5) a study of infections in Italy prior to containment measures being implemented gave a range of between 2.76 and 3.25 for possible R0 values;
- In (6) and (7), using data from the Diamond Princess, R0 was estimated as 2.1 (95% CI 2.0-2.2) and 2.28 (95% CI 2.06-2.52);
- In (8) and (9), two studies of infections in Wuhan estimated R0 to be 2.2 (95% CI 1.4-3.9 for study 1 and 90% CI 1.4-3.8 for study 2);
- In (10), a study of total cases from a publicly available database estimated R0 to be 2.6 (estimated range 2.1-5.1);
- The study in (35) cites a baseline R0 of between 2 and 2.5 and uses this to model the impact of potential interventions; and
- In (17) the WHO-China joint mission report estimated an R0 of between 2.0 and 2.5 using the initial data from China, particularly Wuhan.

The results from these studies would appear to support an R0 assumption of between 2 and 3.5, although one outlier study places it higher than this. Both the Planning Scenarios of the US Centers for Disease Control and Prevention (CDC) (39) and the Society of Actuaries Research Brief (40) assume R0 to be between 2 and 4 for their planning assumptions (with the CDC using a best estimate of 2.5), noting that these are not research papers but merely documentation of assumptions for modelling purposes.

Heterogeneity of Transmission Rates

Classical SEIR models use a single transmission rate assumption, which effectively assumes homogeneous transmission of the virus through the population over time. However, in past epidemics SEIR models have seemingly over-predicted the spread of these types of viruses and as such a significant volume of research has begun into so-called heterogeneous transmission of respiratory viruses. Notably:

- The study in (46) shows the dependence of the first peak level as well as potential secondary peaks, using European countries' data, on the so-called coefficient of variation (CV) of individual transmission rates, and demonstrates lower and fewer peaks the higher this coefficient is (the study suggests that final post-peak infection rates within populations could reduce from the usual 60%-70% standard SEIR models predict to as low as 20%);
- The studies in (47) and (48) show that up to 80% of new infections are driven by small groups of infected individuals (8.9% in one study and 10% in the other) – indicating significantly heterogeneous transmission of the virus;
- The study in (49) shows similar dynamics for SARS and other infectious diseases with significant evidence of heterogeneous transmission;
- The blog post in (50) converts these 80% transmission figures into coefficients of variation (using a gamma distribution of individual transmission rates) of 3.3 and 3.1 for COVID-19 and 2.5 for SARS, indicating significant variability within transmission rates; and
- The studies in (51) and (52) outline some of the mathematics around this heterogeneity and demonstrate the potential impact of this heterogeneity on the peak of the outbreak, with the study in (51) using simpler assumptions and (52) more complex mathematical operations.

Variations in Clinical Susceptibility within Populations

Another potential explanation for the inherent over-prediction of cases by the SEIR models could be that, for some viruses, certain sectors of the population show reduced susceptibility to infection and therefore the effective transmission rate is lowered. Some studies have focused on this area in respect of the COVID-19 virus, including:

- A study from China (63) indicates that children under 15 are significantly less susceptible to being infected with the COVID-19 virus when compared to adults (an odds ratio of 0.34 with a 95% CI of 0.24 to 0.49 was estimated); and
- A number of studies, including the one in (64) discuss the prevalence of so called 'T cells' which constitute part of the immune system's response to viral infection in individuals who do not test positive for having had the virus through antibody tests.

The T cell studies do not in themselves provide evidence of any kind of 'natural immunity' of certain populations, but do provide a hint that either more infections have already occurred than the serology studies would suggest or that a larger than expected proportion of the population have had mild cases of the virus. The research does not currently form a view on whether the presence of T cells constitutes any kind of 'immunity' to the virus, so drawing conclusions based on them appears to be premature.

Proportion of Cases by levels of Severity

A key consideration in modelling COVID-19 has been to accurately determine the make-up of the cases, most notably what proportion of cases are either asymptomatic or demonstrate such minor symptoms treatment is not required, as well as the breakdown of those seeking treatment into 'mild to

moderate' (out of hospital treatment only), 'severe' (requiring hospitalisation) and 'critical' (requiring ventilation and/or critical care in hospital).

The true proportion of asymptomatic cases will by its very nature be complex to model from data (since these cases are unlikely to seek any treatment), but several studies have attempted to quantify the figure nonetheless. The results of these suggest that:

- In (12), based on data from Wuhan and other affected regions of China, researchers estimated that 86% (95% CI 82%-90%) of infections were undocumented i.e. not tested and confirmed, in China before travel restrictions and other shutdown measures were imposed – this would not match exactly to asymptomatic cases since the virus was so new but gives an indication of potentially low case detection rate early in COVID-19 outbreaks (which points either to large rates of asymptomatic or mild cases where testing is not pursued or significant under testing in the early stages of this outbreak);
- In (11), data from the Diamond Princess was used to estimate that through the stages of testing, between 16.1% and 50.5% of positive tests were in patients with no symptoms – a central estimate of 17.9% (95% CI 15.5%-20.2%) was generated for those who remained asymptomatic for the entire duration of their infection;
- An updated study based on the Diamond Princess experience (60) estimated that 33 out of 104 patients studied were retrospectively determined to have been asymptomatic for the duration of their infection i.e. just over a 30% rate of asymptomatic cases;
- In a radio interview (13), the director of the US Centres for Disease Control and Prevention suggested that up to 25% of infected patients could remain wholly asymptomatic for the period of their infection;
- Citing the study listed as (14), the Imperial College Response Team (15) estimated a proportion of 40%-50% of infections were not identified as cases based on repatriation data from Wuhan in China – this was speculated to include asymptomatic cases, mild infections not requiring care and a degree of under-reporting;
- Another study (34) in the British Medical Journal indicated that up to 80% of cases may not demonstrate symptoms at the time of testing positive for the virus;
- The study in (35) assumed that 95.6% of total cases were mild, moderate or completely asymptomatic, with only 3.08% requiring hospitalisation but not critical care and 1.32% requiring critical care – this translates to around an asymptomatic case rate of between 75% and 80% assuming the distribution of symptomatic (reported) cases is in line with the WHO/China Joint Mission (16) findings below;
- News reports from Iceland (36) where any person not in quarantine is eligible to be tested and over 5% of the total population have been tested suggest that around 50% of those testing positive report themselves as being asymptomatic at the time of testing positive, noting that once off testing may identify pre-symptomatic as opposed to asymptomatic patients;
- An American study of those seeking treatment for Influenza Like Infections (ILIs) (41) shows that the rate excess ILIs during the month of March in the US implies that the rate of detection of cases of COVID-19 could be as low as 13% - meaning that a significant proportion of cases are undetected, either by virtue of being asymptomatic or through under-testing of mildly symptomatic cases;
- The study of Wuhan data in particular and China data in general by the researchers in (42) suggested that at least 59% of cases were 'unascertained' i.e. unconfirmed and attributed this primarily to asymptomatic and mildly symptomatic cases;
- The CDC planning scenarios (39) use a best estimate of asymptomatic cases of 40%, with scenarios ranging from 10% to 70%;

- A meta-study of the rate of asymptomatic cases (53) showed that an estimated 40-45% of COVID-19 cases could be entirely asymptomatic, even after accounting for pre-symptomatic cases;
- An Italian study using data from the municipality of Vo (62) estimated that 42.5% (95% CI: 31.5% - 54.6%) of cases in this Vo region were wholly asymptomatic i.e. did not have symptoms at the time of testing and did not develop symptoms subsequently; and
- Researchers from the Oxford University's Centre for Evidence Based Medicine in (38) collated a number of studies on asymptomatic cases and concluded that anywhere between 5% and 80% could be supported by the data, that these were mostly younger people and that symptom-based screening would almost inevitably miss these people.

There is minimal consensus amongst the studies, which is understandable given the difficulty of measuring these types of cases. The Imperial College assumptions appear to be a reasonable starting point for this phenomenon, but given the inherent uncertainty a range of scenarios are likely necessary, especially in models where case severity is determined using only symptomatic cases.

Another potential avenue to explore in analysing unreported (as opposed to purely asymptomatic) cases is through retrospective serology studies. These are understandably limited by the short time which has elapsed, but some figures are starting to become available, including:

- A study of blood donors in the Italian city of Milan (56) indicated that around 7.1% of the population could have been exposed to the virus, 20.2 times the official case rate reported by the Italian Ministry of Health for the Milan region;
- A study of households in Geneva, Switzerland (57) indicated the prevalence of antibodies in about 9.7% of the populations, roughly 10 times the cumulative number of detected case; and
- A study of the Iranian province of Guilan funded by the Iranian Ministry of Health (58) indicated that up to 21% of the population could have contracted the virus; and
- A study in the Kobe region of Japan (59) using blood samples collected in an outpatient clinic setting indicated that up to 2.7% of the population could have contracted the virus, which would constitute between 396 and 858 times the detected cases in the region (noting that the estimate is likely to be biased upward because those seeking care in an outpatient setting are more likely to have symptoms).

The serology studies, although not conclusive, would also appear to support the statement that a large number of COVID-19 cases remain undetected in the population. The magnitude of this is likely to encompass a broad range of potential assumptions however, given how sparse the data currently is.

A secondary issue to this is whether asymptomatic cases are able to transmit the virus, and to what extent this occurs. Given the difficulty of identifying these cases, very little research exists. The study in (37) using data from Tianjin, China and Singapore suggests that between 48% (95% CI 32%-67%) and 62% (95% CI 50% - 76%) of cases were generated by those with no symptoms i.e. presymptomatic or asymptomatic people. The CDC planning scenarios use a best estimate scenario showing 75% relative infectiousness for asymptomatic cases, but their other scenarios include both 25% and 100% infectiousness.

The researchers in (12) have applied a reduced infectiousness factor to adjust transmission rates for undocumented cases as defined in their model (the paper uses a daily rate as opposed to an R0) to 0.55 (95% CI 0.46-0.62) of the transmission rate used for reported cases i.e. a reduction of 45% (95% CI 38%-54%).

Level of Symptom Severity

In terms of the severity of disease within the reported cases set, some studies have investigated this, with most splitting cases into mild to moderate, severe and critical as outlined above. Most, including (15) from Imperial College as well as (14), cite a WHO/China Joint Mission Report (16) which states that, of laboratory confirmed cases in China:

- 80% display only mild to moderate symptoms;
- 14% are classified as 'severe'; and
- The remaining 6% are classified as 'critical'.

In addition to this the Imperial College paper gives age band specific hospitalisation and critical care utilisation rates as per the table pasted below. Their overall figures align closely to the WHO prevalence, assuming 'severe' cases are admitted and 'critical' cases require critical care. These figures have also been presented by the South African National Institute for Communicable Diseases (NICD) at some medical scheme forums.

Age-group (years)	% symptomatic cases requiring hospitalisation	% hospitalised cases requiring critical care	Infection Fatality Ratio
0 to 9	0.1%	5.0%	0.002%
10 to 19	0.3%	5.0%	0.006%
20 to 29	1.2%	5.0%	0.03%
30 to 39	3.2%	5.0%	0.08%
40 to 49	4.9%	6.3%	0.15%
50 to 59	10.2%	12.2%	0.60%
60 to 69	16.6%	27.4%	2.2%
70 to 79	24.3%	43.2%	5.1%
80+	27.3%	70.9%	9.3%

Subsequent to the publication of the Imperial College study, other studies have attempted to quantify age-specific hospitalisation rates. The CDC planning scenarios (39) use hospitalisation rates of between 1.3% and 2.6% for those under 50, between 3.6% and 5.7% for those between 50 and 64 and between 5.2% and 10.0% for those over 65. These are lower than the Imperial College figures, but appear to be calculated using the same denominator i.e. symptomatic cases.

Another study (43) using data from France uses an infection hospitalisation ratio of 3.6% overall, varying by age and sex as shown in the table below.

Age group	Percent infections hospitalized			Percent of hospitalized cases that go to ICU		
	Male	Female	Mean	Male	Female	Mean
<20	0.2 (0.1-0.3)	0.2 (0.1-0.3)	0.2 (0.1-0.3)	26.9(23.2-31.0)	16.7 (14.4-19.2)	22.2 (19.2-25.5)
20-29	0.7 (0.4- 1.1)	0.6 (0.3-0.9)	0.6 (0.4-1.0)	14.0 (12.2-15.9)	8.6 (7.5-9.9)	11.5 (10.1-13.2)
30-39	1.4 (0.9-2.2)	1.1 (0.7-1.8)	1.3 (0.8-2.0)	19.2 (17.6-20.9)	11.9 (10.9-13.0)	15.9 (14.6-17.3)
40-49	1.9 (1.1-3.0)	1.6 (0.9-2.4)	1.7 (1.0-2.7)	26.9 (25.3-28.5)	16.6 (15.6-17.7)	22.2 (21.0-23.5)
50-59	3.9 (2.3-6.1)	3.2 (1.9-4.9)	3.5 (2.1-5.4)	33.4 (32.0-34.8)	20.7 (19.8-21.7)	27.6 (26.5-28.7)
60-69	8.1 (4.8-12.6)	6.2 (3.7-9.6)	7.1 (4.2-11.0)	37.3 (36.0-38.6)	23.1 (22.2-24.0)	30.8 (29.8-31.8)
70-79	13.4 (8.0-20.7)	9.6 (5.7-14.8)	11.3 (6.7-17.5)	30.2 (29.2-31.3)	18.7 (18.0-19.5)	24.9 (24.1-25.8)
80+	45.9 (27.3-70.9)	23.6 (14.0-36.4)	32.0 (19.0-49.4)	6.8 (6.5-7.2)	4.2 (4.0-4.5)	5.6 (5.3-5.9)
Mean	4.0 (2.4-6.2)	3.2 (1.9-5.0)	3.6 (2.1-5.6)	23.1 (22.6-23.6)	14.3 (13.9-14.7)	19.0 (18.7-19.44)

A third study into symptom severity (61) was performed by age band and gender on data from the Lombardy region of Italy. The study showed that 31% of patients developed respiratory symptoms or a fever above 37.5 degrees, and 2.66% were deemed to be critically ill (either admitted to an intensive care unit or deceased during the period of infection). The rates by age band and gender along with the relevant confidence levels are shown in the table below.

	Subjects	Positive to SARS-CoV-2 infection	Symptomatic infections*		Critical patients	
			mean	95% CI	Mean	95% CI
Gender						
Male	2,398	1,220	371/1,220 (30.41%)	27.84-33.08%	42/1,220 (3.44%)	2.49-4.63%
Female	3,086	1,604	505/1,604 (31.48%)	29.22-33.82%	33/1,604 (2.06%)	1.42-2.88%
Age						
0-19y	692	304	55/304 (18.09%)	13.93-22.89%	0/304 (0%)	0-1.21%
20-39y	1,177	531	119/531 (22.41%)	18.93-26.2%	2/531 (0.38%)	0.05-1.35%
40-59y	2,015	1,002	306/1,002 (30.54%)	27.7-33.49%	8/1,002 (0.8%)	0.35-1.57%
60-79y	1,352	829	294/829 (35.46%)	32.2-38.83%	36/829 (4.34%)	3.06-5.96%
80+	248	158	102/158 (64.56%)	56.56-71.99%	29/158 (18.35%)	12.65-25.28%
Total	5,484	2,824	876/2,824 (31.02%)	29.32-32.76%	75/2,824 (2.66%)	2.09-3.32%

* respiratory or fever ≥37.5 °C

A final consideration within the severity construct is the proportion of infected lives who ultimately die. This can only be estimated as the actual fatality rate will only be known for sure once the pandemic

has ended. Various reports, including the WHO China joint mission report, state that the fatality rate depends on a variety of factors, including but not limited to:

- Age (individuals over 60 years at highest risk (as per table above));
- Underlying conditions (rates 5-10 times higher for individuals with than those without), (16);
- Gender (death rate is higher among males compared to females (4.7% vs. 2.8% as per (16));
- The stage of the outbreak, with higher rates during the early stages of the outbreak as case detection is initially biased towards the more severe cases; and
- Country, location, population density, standard of care, testing and intensity of transmission.

The Imperial College team estimated age specific mortality rates for confirmed cases as outlined in the table above, and these represent a starting point. Other research indicates very variable rates depending on the denominator i.e. all cases or reported cases, and the testing process to produce those reported cases. The research shows that (a case fatality rate is measured relative to reported infections and an infection fatality rate relative to total infections):

- In (14) the researchers estimate a case fatality rate (CFR) for China of 1.38% (95 CI 1.23%-1.53%) and an infection fatality rate (IFR) of 0.66% (95% CI 0.39%-1.33%);
- The WHO/China joint mission (16) estimated an overall CFR of 3.8%, but noted that the CFR began at a very high level (17.3%) and declined as transmission patterns and patterns of care changed and ended the study period at 0.7%;
- In earlier research (17) Imperial College estimated an aggregated IFR of 0.8% (95% CI 0.4%-3.0%) based on very limited early data from China;
- In (27), at the March 3 2020 media briefing, WHO Director-General stated that 3.4% of reported COVID-19 cases have died, compared to the initial WHO reported CFR of 2%;
- In (28), at a press conference, the China National Health Commission reported that the CFR as of February 4 2020 was 2.1%, down slightly from 2.3% at the beginning of the epidemic;
- In (29) a preliminary study published on The Lancet provided an early estimation of CFR of 2.9%, based on limited number of cases in China as at December 2019;
- In (30) and (31), a study on hospitalized COVID-19 patients found that 32% (first study) and 26% (later study) of patients required admission to the intensive care unit (ICU) and 15% (first study) and 4.3% (later study) died, but a number of patients were still hospitalized at the time;
- In (32) the CFR was initially reported by the WHO to be 3-5% during the early stages of the outbreak, but (in 33) this had risen to around 10% by the end , which demonstrates the importance of not misinterpreting and under-estimating a rising CFR in earlier stages of outbreaks;
- The May 2020 CDC Planning Scenarios (39) used age-related mortality rates, which using the United States population distribution assume an average CFR (using symptomatic cases) of between 0.2% and 1.0%, with a most likely estimate of 0.4% - the latest July 2020 figures now show an IFR of between 0.5% and 0.8% (with a best estimate of 0.65%);
- The researcher in the study in (44) projected final CFRs using current data from the United States and a series of progression assumptions, of 1.3% (95% CI 0.6% - 2.1%), using symptomatic cases only;
- In (45) a meta-study of the published research on COVID-19 infection fatality rates estimated the final IFR to be around 0.64%, but noted a large amount of heterogeneity across territories and stated that many countries are likely to experience IFRs quite different from the central estimate;
- The study in (43), using data from France and the Diamond Princess, estimated IFRs and death rates for hospitalised patients by age and sex as per the table below.

Age group	Percent death among those hospitalized			Infection fatality ratio (%)		
	Male	Female	Mean	Male	Female	Mean
<20	0.7 (0.3-1.5)	0.5 (0.2-1.1)	0.6 (0.3-1.3)	0.001 (<0.001-0.003)	0.001 (<0.001-0.002)	0.001 (<0.001-0.002)
20-29	1.3 (0.8-1.9)	0.9 (0.5-1.3)	1.1 (0.7-1.6)	0.008 (0.004-0.02)	0.005 (0.002-0.009)	0.007 (0.003-0.01)
30-39	2.2 (1.7-2.7)	1.5 (1.2-1.9)	1.9 (1.5-2.3)	0.03 (0.02-0.05)	0.02 (0.01-0.03)	0.02 (0.01-0.04)
40-49	3.8 (3.4-4.4)	2.6 (2.3-3.0)	3.3 (2.9-3.7)	0.07 (0.04-0.1)	0.04 (0.02-0.07)	0.06 (0.03-0.09)
50-59	7.6 (7.0-8.2)	5.2 (4.8-5.6)	6.5 (6.0-7.0)	0.3 (0.2-0.5)	0.2 (0.1-0.3)	0.2 (0.1-0.36)
60-69	14.8 (14.1-15.6)	10.1 (9.5-10.6)	12.6 (12.0-13.2)	1.2 (0.7-1.9)	0.6 (0.4-1.0)	0.9 (0.5-1.4)
70-79	24.6 (23.7-25.6)	16.7 (16.0-17.4)	21.0 (20.3-21.8)	3.3 (2.0-5.1)	1.6 (1.0-2.5)	2.4 (1.4-3.7)
80+	37.1 (36.1-38.2)	25.2 (24.4-26.0)	31.6 (30.9-32.4)	17.1 (10.1-26.3)	5.9 (3.5-9.2)	10.1 (6.0-15.6)
Mean	21.22 (20.8-21.7)	14.4 (14.0-14.9)	18..1 (17.8-18.4)	0.8 (0.5-1.3)	0.5 (0.3-0.7)	0.7 (0.4-1.0)

Duration of Illness

Given the short time period of the outbreak so far, there has been very little detailed study of the duration of infection or treatment within each of the sub-populations of infection. The key modelling outputs are the non-infectious incubation period for infected lives, the duration of infection for the unreported asymptomatic or mild cases remain infectious, the duration to isolation for the reported mild cases, the length of stay in hospital and/or critical care for the severe and critical cases and the time to death for the fatalities. The research suggests that:

- In (12) the researchers used the China data to estimate an average latency period of 3.68 days for all cases and an average infectious period of 3.48 days;
- Using a similar model, the research in (35) assumes an average latency period of 4.6 days and an average infectious period of 5 days based on other similar coronaviruses;
- In (18) German epidemiological researchers estimate that peak infectiousness happens within 5 days of infection;
- In (17) the Imperial College researchers assume based on conversation with experts and analysis of previous data that mild cases who are diagnosed will isolate and no longer transmit the virus within one day, severe cases (not requiring critical care) will spend 8 days in hospital and critical care cases 16 days in hospital including 10 days in ICU;
- In their symptoms report (19), Imperial College also demonstrated a very varied time to hospitalisation, but also reported an average time to presenting with pneumonia (the usual reason for hospitalisation of COVID-19 cases) of 5.88 days;

- The China/WHO Joint Mission report (16) outlines a time to clinical recovery of 2 weeks for mild cases and 3-6 weeks for severe cases, and gives time to death from symptom onset as a range between 2 and 8 weeks; and
- The Imperial College paper (19) also gives the mean time to each of the types of treatment sought as well as to death, as shown in the table below.

Outcome	Mean (days)	S.D. (days)	Number of reports
First consultation	2.10	2.65	172
Hospitalised	5.76	4.22	267
Recovered/Discharged	20.51	6.69	65
Death	16.00	8.21	8
Hospitalised duration	14.51	7.36	57

Impact of Interventions

A key component of the modelling process is going to be using models to test the impact of certain interventions, including travel restrictions, social distancing, mandatory isolation and full lockdowns. Again, the research in this area is limited given the time which has elapsed, but some studies have been performed to test the key interventions. These include:

- The Wuhan study (12) observed a 69% reduction in the transmission rate once travel restrictions and isolation were imposed in China on the 23rd of January (the study used a daily transmission parameter which reduced from 1.12 pre-restrictions to 0.35 post-restrictions);
- In (20), a study of cases from Wuhan estimated a reproduction number of 2.35 (95% CI 1.15-4.77) before the restrictions were imposed and 1.05 (95% CI 0.43-2.39 after restrictions were imposed – a reduction in transmission of 55.4%;
- In (21) a study of Italian data calculated that the restrictions imposed on the northern parts of Italy on 8 March 2020 reduced the transmission rate of the virus by approximately 30%;
- The study in (35) outlined that to achieve the results China had done, it would have to have created a 50-60% reduction in R0 through social distancing and an 85% reduction through the lockdown measures, but raised some concerns about generalising these results, citing a reduction of only 35-40% in data on social distancing from Seattle in the US; and
- The Imperial College team (15) also devoted a whole paper to assessing the potential impact of various interventions on the UK. The focus was on utilisation of critical care beds and staff as well as deaths, but some modelling of cases was also undertaken. The graph and tables overleaf show the potential impact of some of the interventions – the most effective interventions by the Imperial College model (measured on bed usage and deaths) were the isolation of diagnosed cases, household quarantine in cases where one family member was diagnosed and mass social distancing.

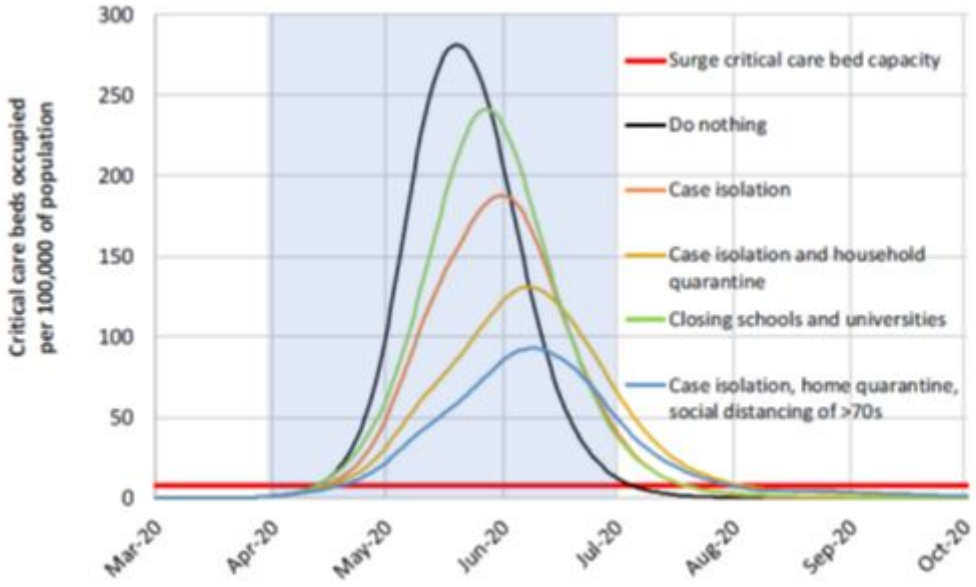


Table 3. Mitigation options for GB. Relative impact of NPI combinations applied nationally for 3 months in GB on total deaths and peak hospital ICU bed demand for different choices of cumulative ICU case count triggers. The cells show the percentage reduction in peak ICU bed demand for a variety of NPI combinations and for triggers based on the absolute number of ICU cases diagnosed in a county per week. PC=school and university closure, CI=home isolation of cases, HQ=household quarantine, SD=social distancing of the entire population, SDOL70=social distancing of those over 70 years for 4 months (a month more than other interventions). Tables are colour-coded (green=higher effectiveness, red=lower). Absolute numbers are shown in Table A1.

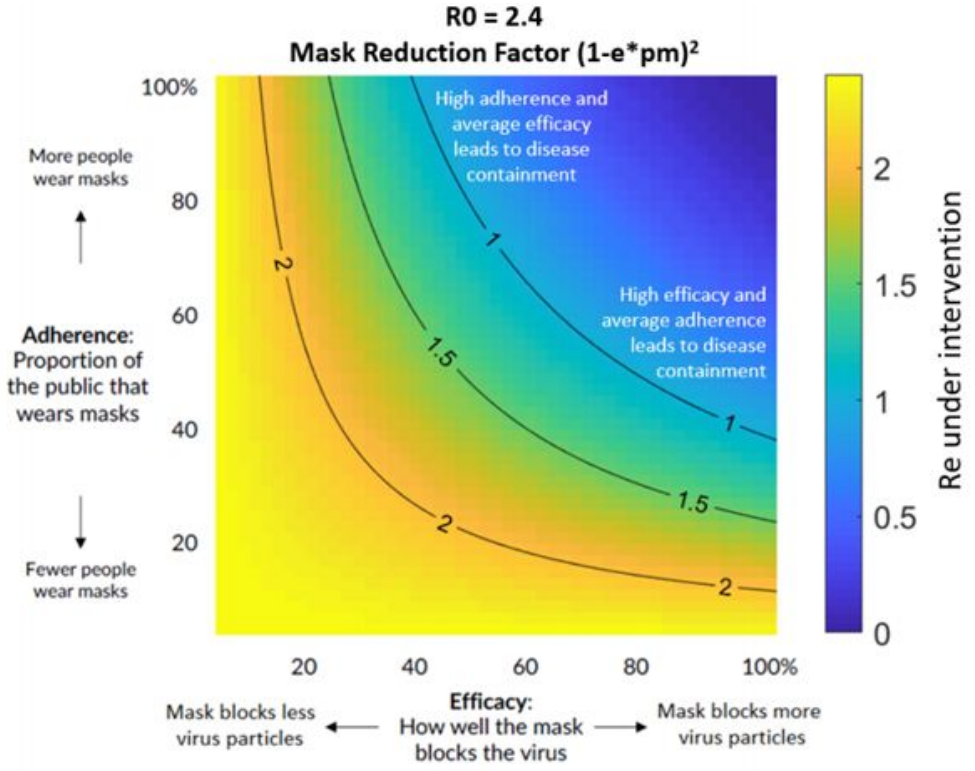
	Trigger (cumulative ICU cases)	PC	CI	CI_HQ	CI_HQ_SD	CI_SD	CI_HQ_SDOL70	PC_CI_HQ_SDOL70
R_0=2.4 Peak beds	100	14%	33%	53%	33%	53%	67%	69%
	300	14%	33%	53%	34%	57%	67%	71%
	1000	14%	33%	53%	39%	64%	67%	77%
	3000	12%	33%	53%	51%	75%	67%	81%
R_0=2.2 Peak beds	100	23%	35%	57%	25%	39%	69%	48%
	300	22%	35%	57%	28%	43%	69%	54%
	1000	21%	35%	57%	34%	53%	69%	63%
	3000	18%	35%	57%	47%	68%	69%	75%
R_0=2.4 Total deaths	100	2%	17%	31%	13%	20%	49%	29%
	300	2%	17%	31%	14%	23%	49%	29%
	1000	2%	17%	31%	15%	26%	50%	30%
	3000	2%	17%	31%	19%	30%	49%	32%
R_0=2.2 Total deaths	100	3%	21%	34%	9%	15%	49%	19%
	300	3%	21%	34%	9%	17%	49%	20%
	1000	4%	21%	34%	11%	21%	49%	22%
	3000	4%	21%	34%	15%	27%	49%	24%

Beyond the Imperial College work, other researchers have attempted to analyse the potential impact of so called non-pharmaceutical interventions (NPIs), including:

- The research in (66) focusing on the impact of mask wearing and physical distancing, which showed that absolute transmission rates can be reduced from between 12% and 18% to between 2.6% and 5.5% through mask-wearing, eye protection and appropriate physical distancing (as shown in the table below);

	Studies and participants	Relative effect (95% CI)	Anticipated absolute effect (95% CI), eg, chance of viral infection or transmission		Difference (95% CI)	Certainty*	What happens (standardised GRADE terminology)*
			Comparison group	Intervention group			
Physical distance ≥1 m vs <1 m	Nine adjusted studies (n=7782); 29 unadjusted studies (n=10 736)	aOR 0·18 (0·09 to 0·38); unadjusted RR 0·30 (95% CI 0·20 to 0·44)	Shorter distance, 12·8%	Further distance, 2·6% (1·3 to 5·3)	−10·2% (−11·5 to −7·5)	Moderate†	A physical distance of more than 1 m probably results in a large reduction in virus infection; for every 1 m further away in distancing, the relative effect might increase 2·02 times
Face mask vs no face mask	Ten adjusted studies (n=2647); 29 unadjusted studies (n=10 170)	aOR 0·15 (0·07 to 0·34); unadjusted RR 0·34 (95% CI 0·26 to 0·45)	No face mask, 17·4%	Face mask, 3·1% (1·5 to 6·7)	−14·3% (−15·9 to −10·7)	Low‡	Medical or surgical face masks might result in a large reduction in virus infection; N95 respirators might be associated with a larger reduction in risk compared with surgical or similar masks§
Eye protection (faceshield, goggles) vs no eye protection	13 unadjusted studies (n=3713)	Unadjusted RR 0·34 (0·22 to 0·52)¶	No eye protection, 16·0%	Eye protection, 5·5% (3·6 to 8·5)	−10·6% (−12·5 to −7·7)	Low‖	Eye protection might result in a large reduction in virus infection

- The research in (67) from the United States shows a significant reduction in the transmission rate number (Rt) for states with interventions which limit mobility, particularly 'stay at home' orders – this impact leads to slower outbreaks and less time spent with Rt above 1;
- The cross-country study in (68) shows that the most impactful interventions in terms of preventing new cases were venue closures (reduction of 36%, 95% CI: 20%-48%) and gathering bans (31%, 95% CI: 19%-42%), while other interventions were less impactful, with school closures and lockdowns having the lowest impact;
- The study in (69) using 26 countries estimates that social distancing reduced the transmission rate of COVID-19 by up 66% using linear regression techniques;
- The study in (70) using data from Hong Kong showed the potential impact of mask wearing, based on the adherence (% of the population who wear masks) and efficacy (the proportion of particles blocked by the mask, and showed that even low adherence to relatively ineffective masks can reduce the transmission rate, but that keeping Rt below 1 requires high adherence to mask wearing as well as effective masks being worn (as per the graph below);



Other Research Areas

Given South Africa's very specific burden of disease and the nature of living conditions in the country, it will be important to understand the potential impact of co-morbidities on the severity of COVID-19 infections as well as the potential impact of population density in light of the many high-density urban areas present in South Africa.

Most studies have focused on broader trends in respect of severity, but some limited research into potentially significant co-morbidities is available. Notably:

- The study in (22) analysed death rates across various population characteristics for known COVID-19 cases in Wuhan and other parts of China – the study shows death rates for various co-morbid conditions and shows that the highest CFR (10.5%) was for those with Cardiovascular disease, followed by Diabetes (7.3%), compared to a 'None' figure of 0.9%; and
- A similar study was performed for the New England Journal of Medicine (23) using different factors, and found that 20% of patients recorded with Diabetes and 14.5% of those recorded with hypertension either died, were admitted to an intensive care unit, or required ventilation, compared to around 0.6% of the overall population; and
- The Imperial College work appears to rely only on age, and doesn't mention co-morbid conditions in its assumptions.

Unfortunately none of the studies appear to consider HIV as a potential co-morbidity. This is likely to be a material factor for South Africa, but only very limited data is available for it. The studies so far are limited to:

- An Italian study (54) which found no evidence of increased risk of COVID-19 hospitalisation or disease severity for patients living with HIV (but based its findings on a sample of 47 patients, mostly with well controlled HIV); and
- An American study (55) using New York City patients found similar outcomes in HIV and non-HIV populations, but using only 31 patients, all of whom had virally suppressed HIV at the time.

It is also important to understand the potential impact of population density on the transmission of COVID-19. Limited evidence is currently available on this, but:

- The Africa Centre for Strategic Studies (24) lists population density as a key COVID-19 risk factor for all African countries, and states that influenza transmission rates have been found to increase where population density exceeds 282 people per square kilometre, and the same is likely true of COVID-19;
- The study in (25) states that the R0 for the Diamond Princess was four times that of Wuhan, and attributes this to density effects; and
- The study in (26), although written before COVID-19, shows some potential methods of modelling transmission rates dependent on population density. It shows that in most epidemics (including animal epidemics) transmission rates increase with population density before flattening out at higher densities.

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Appendix 3: Model structure

Introduction

We outline below the key features of the model version 2, released on 31/07/2020.

Nomenclature

We make use of the mathematical nomenclature below when representing symbols:

Quantity	Symbol	Description
Vector	$\vec{a}$, $\vec{A}$	A vector is represented by an italicised lowercase or uppercase letter with an arrow above the letter.
Matrix	A	A matrix is represented by an italicised uppercase bold letter.
Scalar	a, A	A scalar is represented by either an italicised lowercase or uppercase letter with no additional formatting.
Element-wise multiplication	$\vec{a} \odot \vec{b}$	The operation between two vectors that multiplies each element of the vector together to create a new element.
Dot product	$\vec{a} \cdot \vec{b}$	The dot product of two vectors. Performs element-wise multiplication on the two vectors and sums the result.

Model

A typical SEIR model describes a set of coupled ordinary differential equations between **S**usceptible, **E**xposed, **I**nfectious, and **R**emoved populations. For our purposes, we generalise the infectious and removed states to vector representations to reflect nine age bands (in ten-year bands, from 0-9 to 80+), and split the Removed population into **R**ecovered and **D**eceased vector states. These lead to the following set of differential equations for the homogeneous model:

$$\frac{dS}{dt} = -\alpha S$$
$$\frac{dE}{dt} = \alpha S - \frac{E}{T_{inc}}$$
$$\frac{dI_a}{dt} = \rho_a \frac{E}{T_{inc}} - \frac{I_a}{T_{inf}}$$
$$\frac{dI_m}{dt} = \rho_m \frac{E}{T_{inc}} - \frac{I_m}{T_{inf}}$$
$$\frac{dI_s}{dt} = (1 - \rho_a - \rho_m) \frac{E}{T_{inc}} - \frac{I_s}{T_{inf}}$$

$$\frac{dR_{s\to h}}{dt} = \rho_{s\to h}\frac{I_s}{T_{inf}} - \frac{R_{s\to h}}{T_{s\to h} - T_{inf}}$$
$$\frac{dR_{s\to c}}{dt} = (1-\rho_{s\to h})\frac{I_s}{T_{inf}} - \frac{R_{s\to c}}{T_{s\to c} - T_{inf}}$$
$$\frac{dH_d}{dt} = \rho_{h\to d}\frac{R_{s\to h}}{T_{s\to h} - T_{inf}} - \frac{H_c}{T_{h\to d}}$$
$$\frac{dH_c}{dt} = \rho_{h\to c}\frac{R_{s\to h}}{T_{s\to h} - T_{inf}} - \frac{H_c}{T_{h\to c}}$$
$$\frac{dH_r}{dt} = (1-\rho_{h\to r}-\rho_{h\to c})\frac{R_{s\to h}}{T_{s\to h} - T_{inf}} - \frac{H_r}{T_{h\to r}}$$

$$\frac{dC_r}{dt} = (1-\rho_{c\to d})\left(\frac{R_{s\to c}}{T_{s\to c} - T_{inf}} + \frac{H_c}{T_{h\to c}}\right) - \frac{C_r}{T_{c\to r}}$$
$$\frac{dR_a}{dt} = \frac{I_a}{T_{inf}}$$
$$\frac{dR_m}{dt} = \frac{I_m}{T_{inf}}$$
$$\frac{dR_s}{dt} = \frac{I_s}{T_{inf}}$$
$$\frac{dR_h}{dt} = \frac{H_r}{T_{h\to r}}$$
$$\frac{dR_c}{dt} = \frac{C_r}{T_{c\to r}}$$
$$\frac{D_h}{dt} = \frac{H_c}{T_{h\to d}}$$
$$\frac{D_c}{dt} = \frac{C_d}{T_{c\to d}}$$
$$\alpha = \begin{cases} k\log\left(1 + \frac{f_\beta(t)\beta I}{kN}\right) & \text{if modelling contact heterogeneity} \\ \frac{f_\beta(t)\beta I}{N} & \text{if modelling contact homogeneity} \end{cases}$$

$$\alpha = \begin{cases} k\log\left(1 + \frac{f_\beta(t)\beta I}{kN}\right) & \text{if modelling contact heterogeneity} \\ \frac{f_\beta(t)\beta I}{N} & \text{if modelling contact homogeneity} \end{cases}$$

$$I = \beta_a I_a + I_m + I_s$$

with $f_\beta(t)$ represents the relative beta value over time due to the lockdown, and $p_{\beta,a}$ is relative strength of infectivity for asymptomatic cases.

For the introduction of heterogeneity, we follow the approach taken by Kong et al. (2016), which allows for variation in contacts between individuals by assuming that the number of effective contacts X_i, that is the number of contacts with infectious individuals that would be required for the i-th person in the population to be infected, follows a Poisson distribution with parameter θ_i, which is accordingly

the mean number of contacts made by individual i. In a homogeneous model, these θ_i would be equal for all members of the population; in reality, we know that this varies. θ_i is assumed to follow a Gamma distribution with shape parameter k and rate parameter m (or, equivalently, scale parameter $\frac{1}{m}$). The desirable properties of the Gamma distribution for this purpose include a zero lower bound, positive skew and a wide variety of possible shapes.

The marginal distribution of X_i, given that its conditional distribution given θ_i is Poisson and that θ_i follows a Gamma distribution, is negative binomial with mean $\frac{k}{m}$ and variance $\frac{k(m+1)}{m^2}$. Kong et al. (2016) show that this implies that the differential equation for the Susceptible population in the standard SEIR model changes to:

$$\frac{dS}{dt} = -k\, ln\,(1 + \frac{\beta I}{kN})\, S.$$

The Exposed differential equation changes in consistent fashion.

The effect of reducing k, and hence allowing for greater heterogeneity, is typically a lowering of ultimate projected attack rates as well as lower peaks in hospitalisations and deaths, coupled with more gradual decline in these quantities.

Appendix 4: Immunology of COVID-19

Knowledge of the human immune response to Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), which causes COVID-19, is emerging quickly, though it is far from complete. Understanding the immune response has significant implications for modeling the pandemic, for clinical and public health action, and for development of medicines and vaccines. This section will attempt to address some aspects of immunity with findings from recently published research.

Outcomes of COVID-19 are highly variable and poorly understood

The SARS-CoV-2virus, like other viruses, changes over time (mutates). These are generally small changes that give the virus different genomic (DNA or RNA) signatures that enable epidemiologic tracing of entry of the virus to a population or geography, and its spread. Different variants (strains) are therefore in circulation but it is not clear whether they differ significantly in their transmission rate or disease severity. The extent of exposure i.e. dose (amount of virus) is also an important factor in the development of disease. But most of the dramatic variation in disease outcome, which ranges from no symptoms through to severe illness and death, appears to be host-related (i.e. person-related).

Host and population level variation in immune response may account for several key findings.

- Because it is a new virus, specific immunity to SARS-CoV-2 is not established in any human population. Despite its novelty, a significant proportion of people who encounter the virus experience no symptoms. Most others have only mild symptoms while a small portion become severely ill.
- Clinical risk factors predictive of severe outcomes are now well known (e.g. diabetes, older age, male gender, obesity, chronic lung, heart and kidney disease) but underlying mechanisms that relate these risk factors to outcome are not well understood.

What is the immune system response to infection?

The immune system is a complex host response that has evolved to deal with multiple potential threats to human health. The first line of defense against pathogens (bacteria, viruses, etc) is the innate, or non-specific, immune response which consists of physical, chemical and cellular defenses which quickly prevent the spread and movement of pathogens around the body. The second line of defense against pathogens is the adaptive immune response, also referred to as acquired immunity or specific immunity. The adaptive immune response is specific to the pathogen presented.

The hallmark of the adaptive immune system is so-called clonal expansion of lymphocytes. Clonal expansion is the rapid increase of T and B lymphocytes, specific kinds of white blood cells, from one or a few cells to millions. Each clone that originates from the original T or B lymphocyte ancestor has the same, or very similar, antigen receptors as the original, targeting the same pathogen. The effect of the adaptive immune response is long-lasting, highly specific, and is sustained by memory T and B cells.

Innate immunity is most active within the first 96 hours of an infection. The cells involved include Natural Killer (NK) cells, macrophages, neutrophils, dendritic cells, mast cells, basophils, and eosinophils. Physical barriers such as skin and mucous membranes, and coughing are important in resisting pathogens too.

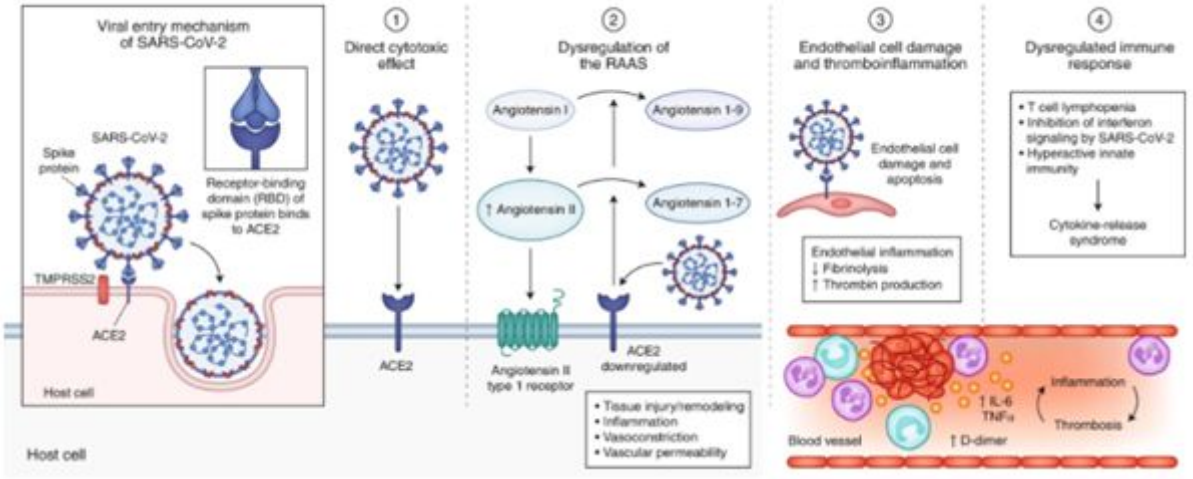
The innate system is responsible for the early response, and it triggers adaptive immunity.
Adaptive immunity occurs later (>96 hours) in the response to infection and involves both T and B lymphocytes. The CD4 cell count that is used to monitor HIV treatment measures a type of T cell/lymphocyte. B lymphocytes make and secrete antibodies which are special protein molecules that bind to antigens (proteins on pathogen surfaces), activating various pathogen killing mechanisms.

Adaptive and maladaptive immune responses

The immune system may respond to eliminate infection but is also involved in maladaptive responses that harm the host (i.e. the patient). Making sense of these complex phenomena requires studies that integrate and correlate immune features with clinical data and disease severity scores that change over time.

How does COVID-19 harm the body?

Proposed mechanisms for COVID-19 disease caused by infection with SARS-CoV-2 include: (1) direct cell damage caused by the virus; (2) impairment of the renin-aldosterone-angiotensin system (RAAS), a hormone system that regulates blood pressure and fluid balance, which leads to tissue injury, inflammation, changes in blood vessel tone and permeability, (3) endothelial (blood vessel lining) damage, causing inflammation and thrombosis (blood clots); and (4) disruption of the immune response including hyperinflammation (excessive inflammation).



Pathophysiology of COVID-19 (Source: Gupta et al. (2020))

Hyperinflammation, immunotype and severe illness

The immune system is always doing a balancing act. An immune response that is too “weak” allows the virus to replicate and overwhelm the host, while an immune response that is too strong can also damage the host.

The hyperinflammation (excessive inflammation) seen in COVID-19 is associated with disruption by the virus of normal immune signaling, depletion of certain kinds of T cells, and T cell dysfunction, proliferation of other (non-lymphocyte) inflammatory cells, and excessive production of certain inflammatory molecules called cytokines (e.g. IL-6 and TNFα), a phenomenon known as the Cytokine Release Syndrome (CRS).

Three patterns or “immunotypes” in COVID-19 patients may reflect different ways patients respond to SARS-CoV-2 infection. Some patients show strong activation and proliferation of CD4 T cells, relative lack of helper T cells (T cells which activate B cells), together with activated or exhausted T cells of another subtype (CD8). This immunotype appears more strongly linked to increased severity of illness. A second subset of patients have a different CD8 T cell response with weaker CD4 T cell and memory B cell responses. A third subgroup of patients (~20%), in which there may be a failure of immune activation, have minimal detectable lymphocyte response. Some autopsies reveal high virus levels in the respiratory tract and other tissues, suggesting this type of ineffective immune responses.

Patients with strong T and B cell activation and proliferation often have low lymphocyte counts in the blood (“lymphopenia”). This pattern, together with increases in other, non-lymphocyte, white blood cells (e.g. monocytes, macrophage) represents a prolonged and potentially harmful period of immune response, with failure to slow the response at the appropriate time. Cytokines activate and recruit these cells, again fitting the concept of an overaggressive immune response and/or storm in a subset of patients.

From a practical standpoint, these patterns may make it possible to infer which therapeutic interventions are useful in specific patients such as in selecting patients for immune modulating treatment (e.g. steroids or other more targeted molecules), while avoiding such treatment in patients with already weak T and B cell responses.

Immune predictors of outcome

As noted, several cytokines and other immunologic parameters have been correlated with COVID-19 severity and therefore could be useful biomarkers to predict disease course. Discovery of predictive biomarkers requires profiling of asymptomatic and mild cases and longitudinal studies that are limited to date. Confounding variables including age, gender, and comorbidities may affect associations observed. Correlation with patient viral load is also important.

During the incubation period and early phase of the disease, the numbers of white blood cell counts including lymphocytes are normal or slightly reduced. After SARS-CoV-2 spreads to other tissues e.g. the gastrointestinal tract and kidneys, increases in non-specific inflammation markers are seen. In more severe cases, a marked release of inflammatory molecules including cytokines occurs, and the lymphocyte count drops (lymphopenia).

Increased IL-6 levels are detected in hospitalized patients, especially critically ill patients, and are associated with ICU admission, respiratory failure, and poor prognosis. Most other cytokines do not seem to have prognostic value because they do not differentiate moderate cases from severe cases or occur early enough in the disease.

Antibodies and the B cell response

Patients who recover from COVID-19 develop virus-specific T cell memory (see below). At the same time their B cells make SARS-CoV-2 specific antibodies, part of the response known as humoral immunity that is critical for clearing viruses. Specific B cell types - Memory B cells – are involved in preventing reinfection and/or reducing illness.

Rapid and near-universal production of three kinds of virus-specific antibodies (IgM, IgG and IgA) occurs in the days following infection. The antibodies of most interest for preventing reinfection and for vaccine response are neutralizing antibodies (NAbs), which can be shown in the laboratory to kill the virus. NAbs include antibodies that bind the viral spike protein, including the receptor binding domain

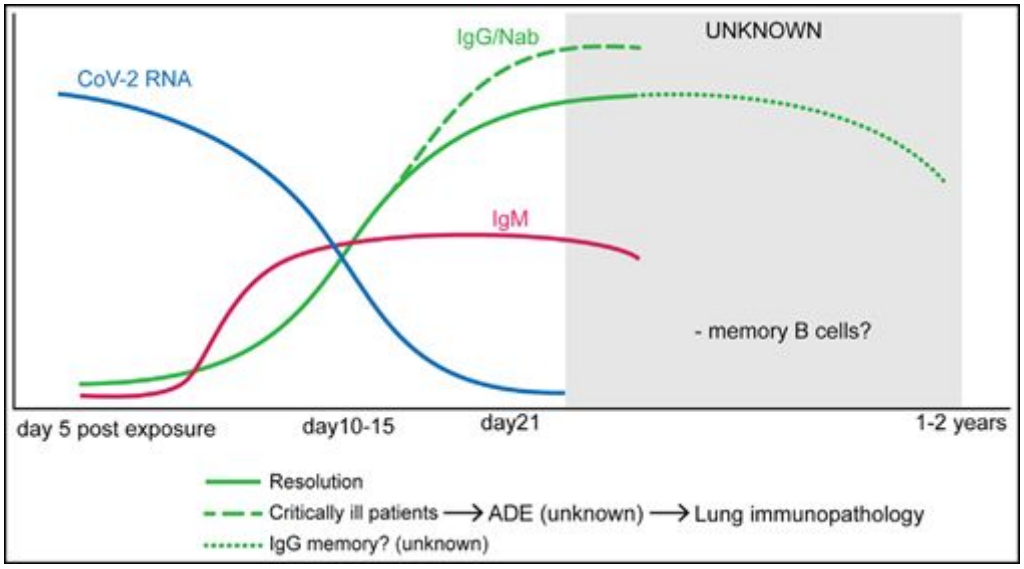
(RBD). This is the part of the spike protein that binds to specific receptors to infect the host (patient), gaining entry to cells lining the respiratory tract.

On average, the antibody response is easily detected between 10-12 days after onset of symptoms. It persists for an unknown time. IgG specific to the spike protein is detectable up to 90 days after symptom onset, but IgG levels appear to decrease about 8 weeks after symptom onset.

In general, the B cell response to a viral infection not only subdues the primary infection, it also usually provides extended immunity against reinfection. It is not yet clear whether detectable antibodies including those identified by current laboratory and point of care tests reliably confer long term immunity to COVID-19.

COVID-19 patients with severe disease have SARS-CoV-2 specific antibodies, raising the question of why these patients are not controlling their disease. Although antibodies are a crucial part of the effective immune response there appears to be a correlation between level of antibody response, disease severity and viral load.

At the other end of the spectrum, low detectable antibody concentrations in recovered patients have been a finding of concern in several studies. Although individuals who recover from COVID-19 may not have measurable high levels of antibody, RBD-specific antibodies with potent antiviral activity may still be present (see Robbiani).



Antibody-Mediated Immunity in SARS-CoV-2 infection (Source: Vabret et al. (2020))

T cell responses are implicated in disease causation but there is no evidence that naturally developed antibodies to SARS-CoV-2 are harmful. Antibody-mediated disease enhancement is a known phenomenon, for example upon re-exposure to Dengue, a virus unrelated to SARS-CoV-2. This has not been seen in COVID-19 but the possibility may need to be considered in vaccine development.

Convalescent plasma (blood donated by Covid survivors) contains neutralizing antibodies and is being used to treat COVID-19 patients in clinical trials. The first published trial showed no benefit for prevention (also no harm) but may have been underpowered (too small) to detect a clinically important difference.

More than 90% of the human population has antibodies to seasonal spreading human coronaviruses. A study by Ng et al identified cross-reactivity between these seasonal human coronaviruses, using specialized (flow cytometry) methods, allowing distinction between pre-existing and new antibody responses, based on the levels of SARS-CoV-2 S-reactive IgG and parallel detection of IgM and IgA. More than 60% of 6-year-olds had cross-reactive antibodies with levels dropping to 5.7% in adults, offering a potential explanation of age-related disease susceptibility differences.

Pre-existing T-cell immunity

T cell studies offer additional evidence of some degree of pre-existing immunity against SARS-CoV-2 in the general population which is of great importance clinically and epidemiologically. Memory T cells that recognize SARS-CoV-2 can mount a faster and stronger immune response upon exposure to SARS-CoV-2 and limit disease severity. Other T cells facilitate the neutralizing antibody response.

Despite SARS-CoV-2 being a new virus, T-cell reactivity to SARS-CoV-2 has been shown in individuals with no history of SARS, COVID-19 or contact with SARS or COVID-19 patients. In a recent study (Sette) T cells in 20-50% of unexposed donors reacted to SARS-CoV-2 antigens. These lymphocytes may originate from memory T cells produced in response to seasonal human coronaviruses that cause the common cold and other illnesses. These exposures, in multiyear cycles and across different locations might correlate with the burden of COVID-19 disease severity or widely differing COVID-19 group susceptibility (e.g. children vs older adults) but this is not yet established. Long-lasting T cell immunity may occur through activity against the SARS-CoV-2 nucleocapsid protein which wraps around the virus genetic material. T cells may also be recognising protein fragments found in animal (beta) coronaviruses.

In the 2009 H1N1 influenza pandemic older people generally fared better than younger adults. This correlated with the circulation of a different H1N1 strain in the human population decades earlier, which presumably generated pre-existing immunity in people old enough to have been exposed to it.

Long term protection

Specialized B cells, called plasma cells, are formed during the acute and recovery phases and they continue to make antibodies. Memory B cells that are also formed during the primary infection can quickly respond to a reinfection by generating new plasma cells. There is great interest in understanding the durability of this B cell memory response to SARS-CoV-2.

Studies of SARS-CoV-1 and MERS-CoV, coronaviruses causing severe diseases that South Africa largely escaped, indicate that antibody responses decrease over time. This is true also of our experience with the seasonal human coronaviruses where reinfection can occur even within the same year. On the other hand, evidence of near-universal antibody production along with the T cell memory response, and the absence of convincing descriptions of reinfection, suggest there will be future protection against reinfection. This is still an uncertain issue with large clinical and social implications. Further studies are required.

Implications for vaccine development

Pre-existing T cell memory could influence vaccination outcomes, leading to a faster or better immune response, including the development of neutralizing antibodies, which generally depend on T cell help. However pre-existing T cell memory could be a confounding factor in vaccine trials if people with pre-existing reactivity are unevenly distributed in different vaccine dose groups. Pre-existing T cell memory against SARS-CoV-2 might be detrimental through eliciting potentially inferior immune

responses owing to pre-existing immune memory to a related pathogen, a problem seen in the past in other vaccine development initiatives.

Conclusion

The immune response to Covid-19 is complex and not fully understood but an enormous global research effort is quickly filling in crucial details such as how the virus evades the immune system, the defining characteristics of individual vulnerability or protection, the role of maladaptive immune responses in COVID-19 disease, and the features of antibody and T-cell responses. This rapidly evolving knowledge is critical for the design and testing of an effective vaccine.

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