# MODELLING THE COST-EFFECTIVENESS OF TREATMENT OPTIONS FOR THE SOUTH AFRICAN COVID-19 RESPONSE

TECHNICAL APPENDIX

VERSION 1

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MOSAIC
MOdelling COVID-19 Strategies in South AfrICa
Collective

## About

MOSAIC is a health economic modelling collective established to provide rapid policy guidance and public engagement for the South African Covid-19 response. Members are drawn from the Health Economics Unit, School of Public Health and Family Medicine and Alan J Flisher Centre for Public Mental Health at the University of Cape Town, with the Health Systems Research Unit at the Medical Research Council. In alphabetical order, MOSAIC includes Donela Besada MPH; Susan Cleary PhD; Emmanuelle Daviaud MSc; Sumaiyah Docrat MPH; Geetesh Solanki DrPH; Cynthia Tamandjou PhD; and Tommy Wilkinson MSc.

## Overview

This technical appendix has been prepared to clarify the framework, assumptions and input parameters of the MOSAIC models of the cost-effectiveness of treatment strategies for the South African COVID-19 response. The open-access models and their updates can be readily accessed at:

https://zivahub.uct.ac.za/projects/MOdelling_COVID-19_Strategies_In_South_AfriCa_MOSAIC_Collective/80900

To date, models have been created to assess the cost-effectiveness of ICU care as well as the cost-effectiveness of dexamethasone for hospitalized patients. This brief appendix is intended for users who want to learn more about the decision analytic modelling framework and sources of data. Further, we include brief guidance for users to familiarize themselves about the structure and organization of the Excel spreadsheets.

## Introduction

As the COVID-19 pandemic progresses, the demands on the health care system will intensify and will result in critical shortages of resources (hospital beds, intensive care unit (ICU) beds, ventilators, medical workforce), particularly in the public sector. Given the expected downturn in an already weak economy coupled with the increased demand for government resources for economic relief and other measures, the ability of government to commit additional funding to an already under-funded public health sector is limited. In such a context, it becomes imperative that resources are used in the best ways possible; and that decisions about resource allocation are made through careful consideration of the impact of alternatives.

It is also important to highlight that there are high levels of uncertainty about the course and severity of the Covid-19 pandemic in South Africa. While running decision analytic models using international data provides an initial sense of potential costs and outcomes, ideally these models should be updated with local data. To this end MOSAIC has prioritized the provision of open access models which can easily be adapted by policymakers and hospital managers to local settings.

## Decision analytic modelling approach

Our analyses make use of a simple state transition modelling framework with a focus on all patients hospitalized for Covid-19. The analysis takes a provider (health system) perspective and the models allow analyses to be run for public, private or a mixture of both public and private sectors. Costs are expressed in 2020 prices, and no discounting is undertaken given that all costs within the analyses are incurred within a short period of time. Outcomes are expressed as disability adjusted life years (DALYs) and deaths; the models also produce counts of inpatient and ICU days within different strategies.

The models run using a single Markov cycle. A single cycle (as opposed to daily or weekly cycles) is required because available data are expressed as rates and are not suitable for estimating time dependent probabilities. In addition, the major elements of an episode of COVID-19 infection and treatment unfold over a relatively short time-horizon (less than three months), compared to more chronic diseases that may involve multiple disease states of extended periods of time. Lastly, available data indicate large uncertainty in key estimates (such as mortality rates) suggesting that it is preferable to model in as simple a manner as possible as this assists to reveal the uncertainty in results.

The models assess costs and outcomes across a number of health (Markov) states, as shown in Table 1. At entry to the model, patients are classified as severe or critical. Depending on the strategies under investigation, patients are further split by type of management (general ward versus ICU) and use of medication (e.g. dexamethasone). As mentioned, the models can be set to run for the public sector, private sector or for a mixture of public and private. The models include two absorbing states: recovered and dead. The former is assumed to have no morbidity loss (i.e. that the patient returns to their pre-Covid-19 health state) while the latter captures the years of life lost (YLL) for a person dying of Covid-19. The YLL associated with death is taken from secondary data, and is based on expected remaining life expectancy for the average COVID-19 infected patient adjusted for age, sex and serious comorbidities in the South African context (Panda, 2020). This basic modelling structure and these Markov states are used within all MOSAIC's inpatient models, with key changes made to variables (see below) to simulate the impact of the specific treatment strategy that is being investigated. Each of the open access Excel based models provides a detailed diagram that further clarifies the use of each of these Markov states within each specific model.

TABLE 1: COSTS AND OUTCOMES IN EACH MARKOV STATE

| **Markov state name (patient type)** | **Costs per Markov state** | **Outcomes per Markov state** |
|---|---|---|
| General ward public (severe patients) | Public sector cost per hospitalisation in general ward for severe patients | Disability weight for severe patients applied over duration of 1.5 months |
| General ward private (severe patients) | Private sector cost per hospitalisation in general ward for severe patients | Disability weight for severe patients applied over duration of 1.5 months |
| ICU public (critical patients) | Public sector cost per hospitalisation in general ward and ICU for critical patients | Disability weight for critical patients applied over duration of 2 months |
| ICU private (critical patients) | Private sector cost per hospitalisation in general ward and ICU for critical patients | Disability weight for critical patients applied over duration of 2 months |
| Recovered | N/A | No disability weight |
| Dead | N/A | Disability weight for critical patients applied over duration of 0.5 months; Years of Life Lost; count of deaths |

## Variables

The models rest on 5 different types of variables: *mortality rates* based on severity of illness (i.e. severe versus critical) and approach towards disease management (i.e. ICU versus no-ICU; or dexamethasone versus no dexamethasone); *utilisation* data including proportions of hospitalized individuals that are critical versus severe and length of stay data for each patient type and management approach; *unit costs* per inpatient day in general wards and intensive care units specific to public and private sector; and *disability weights* applied to durations of illness for different patient types. A brief overview of each type of data is provided below.

## Mortality rates and utilization

### Search strategy

A search for articles published in English between 01/01/2019 and 31/12/2020 was conducted in Medline/PubMed using the terms: "COVID-19" OR “novel coronavirus” OR "SARS-COV-2" OR COVID-19 OR 2019-nCOV OR “2019 novel coronavirus” AND "clinical characteristics" OR "clinical features" OR "clinical outcomes" AND "death" OR "mortality". Additional manual searching through bibliographies of included articles was also conducted.

### Study selection

As outlined in Figure 1 below, the results of the initial search were screened by title and abstract. The full texts of potentially relevant articles were retrieved and assessed for inclusion. When articles reported information from the same study sites/hospitals but of two different time periods, only the articles with the updated statistics were included in this analysis. Observational studies (cross-sectional or cohort) and case series that reported the outcomes of hospitalized COVID-19 patients were included for quantitative synthesis.

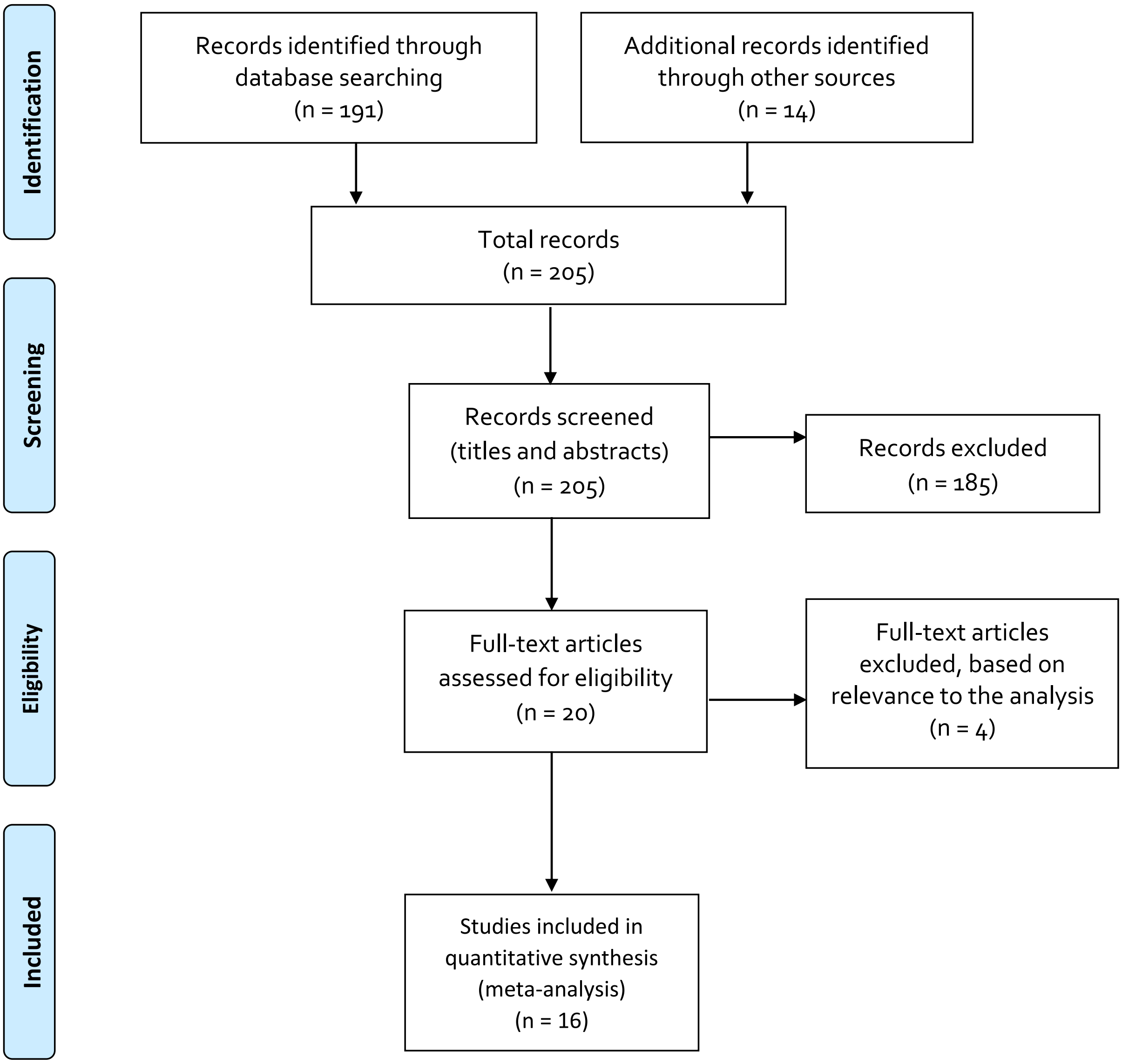


FIGURE 1: FLOW DIAGRAM OF SEARCH STRATEGY AND STUDY SELECTION.

## Mortality rates

**Data extraction:** Extracted information included country, city, study sample size, number of ICU patients, number of non-ICU patients, ICU deaths, non-ICU deaths, ICU survivors, number of patients still in ICU and number of patients discharged from hospital. Note that the number of patients discharged from hospitals was not stratified between ICU and non-ICU patients in the articles included in the quantitative synthesis.

**Quantitative synthesis:** Sixteen studies (1-5; 7-17) were included in this analysis. The outcomes extracted were the case fatality rate (CFR) among ICU patients, and the CFR among non-ICU patients/patients dying in general ward; these were calculated using the formula: Deaths/(Deaths + recovered). To summarize the weighted effect size for each study, weighted pooled estimates were calculated using Microsoft Excel 2013 (Microsoft, Redmond, Washington, USA).

### Utilisation

Seven articles (3-5,7,11,13,15,16) obtained from the systematic search described above were used to estimate (1) utilisation of ICU days, (2) utilisation of general ward days, and (3) utilisation of general ward days for those needing ICU. From these articles, extracted information included: median length of stay in ICU, median length of stay in hospital/general ward of patients remaining in general ward, median length of stay in hospital/general ward of patients prior transfer to ICU, and the ranges of each variable. Weighted pooled estimates for each outcome were calculated using Microsoft Excel 2013 (Microsoft, Redmond, Washington, USA). Please note that interquartile ranges (IQRs) instead of normal ranges were provided in the articles reviewed; these IQRs were used in the sensitivity analysis.

## Unit costs

### Private sector unit costs

Unit costs for the private sector are based on the tariff rates in the "Guidelines on Public Private Collaboration in Response to COVID-19" published by the Department of Health (June 2020). The rates inclusive of VAT as published (and used in the model) are summarised in Table 2 below; the model uses the ICU cost only. For general hospital beds, the published Guideline rate of R5,252 per patient day was used.

TABLE 2: PRIVATE SECTOR UNIT COSTS

| Per Day Tariff | High Care | ICU | Critical Care Rate |
|---|---|---|---|
| Private Hospital | 7 910 | 16 440 | 11 749 |
| Specialist Physician Team | 2 016 | 6 788 | 2 493 |
| Pathology | 588 | 588 | 588 |
| Radiology | 632 | 632 | 632 |
| Allied care (Physiotherapy, Dietetics, Clinical Technology) | 694 | 694 | 694 |
| Global Fee | 11 840 | 25 143 | 16 156 |

### Public sector unit costs

Unit costs for the public sector are based on the Health Systems Trust District Health Barometer (HST-DHB) (12th Edition – 2016/17) datafile (17) which provides hospital-level indicators of public expenditure per patient day equivalent (PDE) for all categories of public sector hospitals (Table 3). All costs from the 2015/16 FY were inflated to real 2020 prices.

Provincial estimates for expenditure per PDE were weighted based on useable beds available for each level of care. The Weighted average expenditure per patient day equivalent (based on usable beds at level of care) across all levels of the health system was R3 727.35. Expenditure per public sector ICU day (ZAR 17 844.88) was then determined based on the differential between the ICU cost and general ward cost in the private sector.

| Hospital Level | EC | FS | GT | KZ | LP | MP | NC | NW | WC | Usable beds | National |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Central Hospitals | 5873.61 | 7464.94 | 4782.01 | 9335.92 | | | | | 6057.77 | 8222.00 | 6702.85 |
| Regional Hospitals | 2367.30 | 3298.58 | 3339.68 | 3808.98 | 3501.12 | 3448.28 | | 3203.42 | 3548.10 | 19936.00 | 3314.43 |
| Tertiary Hospitals | 3524.12 | 3841.35 | 3798.84 | 5162.20 | 4065.75 | 3771.89 | 5389.65 | 3337.35 | 6859.35 | 10393.00 | 4416.72 |
| District Hospitals | 2747.71 | 2914.03 | 3371.14 | 3048.43 | 3497.67 | 2718.37 | 2971.82 | 2801.46 | 2537.56 | 30351.00 | 2956.47 |
| Weighted average (based on usable beds at level of care) | | | | | | | | | | | 3727.35 |
| Cost per ICU day (based on differential between ICU cost and global cost in private sector) | | | | | | | | | | | 17844.88 |

TABLE 3: PUBLIC SECTOR UNIT COSTS

## Disability weights, duration of disability, years of life lost

An important aspect of any cost effectiveness analysis is the way that the effect of the intervention is measured. Simple measures such as "lives saved" or "life-years saved" are useful and relatively easy to calculate and interpret but can miss important treatment effects, such as any improvements in morbidity. The Disability Adjusted Life Year (DALY) is a way to measures health loss due to both fatal and non-fatal disease burden; one DALY can be thought of as one lost year of healthy life (19). The capacity for an intervention to "avert" DALYs is a comprehensive way to measure the impact of an intervention on both mortality and morbidity.

Years of life are lost (YLL) in the population due to premature mortality take into account the age at which deaths occur by giving greater weight to deaths at younger age and lower weight to deaths at older age (20).

Morbidity is accounted for in a DALY by a disability weight that reflects the severity of the disease on a scale from 0 (perfect health) to 1 (equivalent to death). Years Lost due to Disability (YLD) are calculated by multiplying the incident cases by duration and disability weight for the condition.

The disability weight associated with experiencing COVID-19 infection was obtained from the Global Burden of Disease study (6), which is a global initiative to provide quantitative parameters to estimate the morbidity (burden) associated with different disease states and is widely used in cost effectiveness analysis for health interventions. As COVID-19 is a novel disease, there is no unique estimate for the burden associated with infection. The analysis utilised the burden of "severe lower respiratory tract infection" (0.19) as an estimate for patients with severe COVID-19 disease, and "acute respiratory distress syndrome" (0.56) as an estimate for patients with critical COVID-19 disease.

# User guide

## Overview of Excel Workbook

The model workbook consists of a number of worksheets (Table 4). The contents of key worksheets that are common across models is outlined in the table below.

TABLE 4 EXCEL WORKBOOK TABLE OF CONTENTS

| Worksheet name | Contents/Function |
|---|---|
| MOSAIC | About the MOSAIC health economic modelling collective; citation information |
| Overview | Table of contents of the cost-effectiveness model |
| Inputs & Results | Provides model results and an interface for user driven sensitivity analysis |
| Strategy Calcs | Separate sheets summarize the formulae used in each modelled strategy |
| State Trans Diag | Diagrams of model structure |
| Private Hospital Costs | Summarizes private hospital unit costs |
| Public Hospital Costs | Summarizes public hospital unit cots |
| Inpatient Deaths & Utilisation | Summarizes meta-analysis of inpatient inputs |

## How to edit variables

All editable variables are outlined in green within the Worksheet: "Inputs and Results" (Figure 2).

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FIGURE 2: INPUTS AND RESULTS

| | A | B | C | D | E | F | G | H | I |
|---|---|---|---|---|---|---|---|---|---|
| 1 | | **INSTRUCTIONS** | | | | | | | |
| 2 | | 1. Cost-effectiveness results are summarized in 'MODEL RESULTS' | | | | | | | |
| 3 | | 2. Using the 'INPUTS' table, conduct sensitivity analysis and generate new cost-effectiveness results by changing the green highlighted "Editable Value(s)" in column C | | | | | | | |
| 4 | | 3. As you change inputs, see whether and how these changes impact on 'MODEL RESULTS' | | | | | | | |
| 5 | | 4. Potential ranges for sensitivity are provided in columns F and G | | | | | | | |
| 6 | | 5. Methods and data sources for 'INPUTS' are summarized in columns H and I | | | | | | | |
| 7 | | | | | | | | | |
| 8 | | **STRATEGIES** | | | | | | | |
| 9 | | This model assesses costs and outcomes for admitted severe and critical Covid-19 patients | | | | | | | |
| 10 | | A strategy whereby a percentage of admitted patients is managed in the ICU is compared against a modelled no-ICU alternative for the same patient population | | | | | | | |
| 11 | | In addition to provider costs, DALYs and deaths in each strategy, the model calculates number of general ward inpatient days and ICU days needed per admitted patient | | | | | | | |
| 12 | | | | | | | | | |
| 13 | | **MODEL RESULTS** | | | | | | | |
| 14 | | **Strategy** | **Cost** | **DALYs Averted** | **Deaths** | **ICU Days** | **Inpatient Days** | **Incr. Cost per DALY Averted** | **Incr. Cost per Death Averted** |
| 15 | | no ICU - critical patients managed in the general ward | 77 308.75 | 4.04 | 0.27 | - | 18.85 | | |
| 16 | | ICU - critical patients managed in ICU | 103 309.51 | 4.43 | 0.20 | 1.85 | 17.00 | 67 436.36 | 364 156.33 |
| 17 | | | | | | | | | |
| 18 | | **INPUTS** | Edit green cells | | | | | | |
| 19 | | **Description** | **Editable Value** | **Reference in TreeAge** | **Original Value** | **Low Value** | **High Value** | **Method or assumption** | **Reference or source** |
| 20 | | **Unit costs** | | | | | | | |
| 21 | | Cost per inpatient day public | 3 727.35 | cIPDpub | 3 727.35 | | | Average weighted expenditure per patient day equivalent | See 'Public Hospital Costs' worksheet |
| 22 | | Cost per ICU day public | 16 511.25 | cICUpub | 16 511.25 | 8 255.63 | 24 766.88 | Average weighted expenditure per patient day equivalent inflated using cICUpvt/cIPDpvt | See 'Public Hospital Costs' worksheet |
| 23 | | Tariff per inpatient day private | 5 932.58 | cIPDpvt | 5 932.58 | | | Primary data | See 'Private Hospital Costs' worksheet |
| 24 | | Tariff per ICU day private | 26 279.87 | cICUpvt | 26 279.87 | 13 139.93 | 39 419.80 | Primary data | See 'Private Hospital Costs' worksheet |
| 25 | | **Utilisation** | | | | | | | |
| 26 | | Utilisation of inpatient days | 21.25 | uIPD | 21.25 | 7.25 | 43.00 | Literature review | See 'Inpatient deaths & utilisation' worksheet |
| 27 | | Utilisation of ICU days | 8.80 | uICU | 8.80 | 4.30 | 13.30 | Literature review | See 'Inpatient deaths & utilisation' worksheet |
| 28 | | Utilisation of inpatient days in critical patients in absence of ICU | 8.80 | uIPDcritical | 8.80 | 4.30 | 13.30 | *Assumed to be the same as critical patients treated in ICU* | |
| 29 | | Utilisation of general ward days for those using ICU | 1.00 | uIPDICU | 1.00 | - | 3.00 | Literature review | See 'Inpatient deaths & utilisation' worksheet |
| 30 | | Proportion needing ICU | 0.21 | pICU | 0.21 | 0.05 | 0.50 | Literature review | See 'Inpatient deaths & utilisation' worksheet |
| 31 | | Proportion reliant on public health system | 0.83 | ppm | 0.83 | | | Percentage of population without Medical Scheme coverage | Ataguba et al, 2015 |
| 32 | | **Mortality rates** | | | | | | | |
| 33 | | Proportion dying from general ward | 0.11 | pdead | 0.11 | - | 0.13 | Literature review | See 'Inpatient deaths & utilisation' worksheet |
| 34 | | Proportion dying from ICU | 0.54 | pdeadICU | 0.54 | 0.24 | 0.88 | Literature review | See 'Inpatient deaths & utilisation' worksheet |
| 35 | | Proportion of critical patients dying without access to ICU | 0.88 | exmortality | 0.88 | 0.70 | 1.00 | *Base case of 0.88 assumed based on high value on pdeadICU* | |
| 36 | | **Disability weights, duration of disability and years of life lost** | | | | | | | |
| 37 | | Disability weight for severe patients | 0.13 | DWsevere | 0.13 | 0.09 | 0.19 | Disability weight for severe lower respiratory tract infeciton | Saloman et al 2017 |
| 38 | | Disability weight for critical patients | 0.41 | DWcritical | 0.41 | 0.27 | 0.56 | Disability weight for ARDS | Saloman et al 2017 |
| 39 | | Duration of illness in severe patients | 0.13 | dursevere | 0.13 | 0.06 | 0.19 | 1.5 months (range 0.75-2.25); used in DALY calculation | Assumption |
| 40 | | Duration of illness in critical patients | 0.17 | durcritical | 0.17 | 0.08 | 0.25 | 2 months (range 1-3); only used in DALY calculation | Assumption |
| 41 | | Duration of illness prior to death | 0.04 | durdeath | 0.04 | 0.02 | 0.06 | 0.5 months (range 0.25-0.75); used in DALY calculation | Assumption |
| 42 | | Years of life lost if dying from Covid | 5.40 | YLL | 5.40 | | | | PANDA, 2020 |
| 43 | | **Other** | | | | | | | |
| 44 | | Cost-effectiveness threshold per DALY averted | | | 38 465.46 | | | Used to assess value for money; if ICER<CET intervention potentially cost-effective | Edoka et al, 2020 |

Contents | MOSAIC | Overview | Inputs & Results | Sensitivity Analysis | 1. Strategy Calcs | 2. Strategy Calcs | St

## How to interpret cost-effectiveness tables

The results of the model are presented in the Worksheet "Inputs and Results". The cost-effectiveness analysis compares the additional cost of the ICU intervention as compared to management in the general ward (no ICU) and their associated benefits, known as the incremental cost-effectiveness ratio. Benefits are measured as both DALYs and deaths averted. To calculate the ICER, one subtracts the cost of providing general ward (no ICU) care from the cost of providing ICU; this is divided by value resulting from subtracting the DALYS from no-ICU from the DALYs associated by ICU to estimate the DALYs averted.

## Limitations

The objective of any decision analytical modelling exercise is to aid in decision making by providing estimations of costs and impacts. The analysis therefore aims to reflect available evidence and what is currently known about COVID-19 disease rather than creating a perfect representation of all aspects of the pathway of care. This analysis was also completed in a rapid format to enable timely provision of critical information in an urgent decision-making context which limits the opportunity for any primary evidence generation. This creates some reliance on secondary sources for some parameters including expected epidemiology of disease, year of life lost for mortality and effectiveness parameters.

The model is also developed in a single "point in time" (the weeks of late May-early June 2020). Much of the evidence related to the prevention, impact and management of COVID-19 disease is changing rapidly from week to week both in South Arica and internationally and results should be seen in this context. However, by making the model publicly available and all parameters fully modifiable, users can incorporate any significant changes in practice directly.

It is expected that the management of COVID-19 will be highly variable across South Africa and within provinces, and particularly within different private sector hospital groups. This means that cost structures and effect sizes are likely to vary. However, the provision of open access models that can be readily updated by the user as well as a comprehensive sensitivity analysis does largely address the extent of this uncertainty.

## Future research directions

This analysis highlights the potential for rapid, high-quality, policy-relevant and transparent analysis to support policy making in the South African context. There is considerable scope for further analysis both within the COVID-19 environment and broader decision making about the use of health technologies. Particular analysis related to this evaluation includes more specific consideration of aspects of the inpatient pathway of care including any therapeutics, provision of breathing support and oxygen therapies, and large-scale facilities such as field hospitals.

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