Cost-effectiveness of COVID-19 vaccination in South Africa

Clinical outcomes and cost-effectiveness of COVID-19 vaccination in South Africa

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ABSTRACT

Low- and middle-income countries are implementing COVID-19 vaccination strategies in light of varying and uncertain vaccine efficacies and costs, supply shortages, and resource constraints. We used a microsimulation model to evaluate clinical outcomes and cost-effectiveness of a COVID-19 vaccination program in South Africa. We varied vaccination coverage, pace, acceptance, effectiveness, and cost as well as epidemic dynamics. Providing vaccine to at least 40% of the population and prioritizing accelerated vaccine rollout prevented >9 million infections and >73,000 deaths and reduced costs due to fewer hospitalizations. Further, the vaccination program was cost-saving even at the lowest examined levels of acceptance (50%), effectiveness against infection (20%), effectiveness against symptomatic disease (30%), and effectiveness against severe/critical disease requiring hospitalization (40%), and with vaccination costs of up to USD25/person. In summary, a COVID-19 vaccination program would reduce both deaths and health care costs in South Africa across a wide range of assumptions. Vaccination program implementation factors, including prompt procurement, distribution, and rollout, are likely more influential than characteristics of the vaccine itself in maximizing public health benefits and economic efficiency.
INTRODUCTION

The development and licensure of COVID-19 vaccines offers a critically important opportunity to curtail the global COVID-19 pandemic. Even before the efficacy and safety of the leading vaccine candidates were established, many high-income countries (HICs) pre-emptively procured stocks of doses in excess of population need. By contrast, most low- and middle-income countries (LMICs) do not have access to sufficient quantities of vaccine due to cost, limitations in available doses, and logistical challenges of production, distribution, and storage. Meanwhile, the Africa Centres for Disease Control and Prevention have announced a goal of vaccinating 60% of Africans by the end of 2022.

There has been much discussion about reported efficacies and costs of different vaccines. However, factors specific to implementation, including vaccine supply, vaccination pace, and acceptance among communities, are increasingly recognized to be crucial to the effectiveness of a vaccination program in promoting epidemic control in HICs – in some cases, even more so than vaccine efficacy. How these program implementation factors will affect the clinical and health economic consequences of COVID-19 in LMICs has not been well-defined. This is a particularly urgent question given the emergence of SARS-CoV-2 variants, such as B.1.351 in South Africa, that appear to partially reduce efficacy of some vaccines.

We used a microsimulation model to estimate the clinical and economic outcomes of COVID-19 vaccination programs in South Africa, examining different implementation strategies that policymakers could directly influence. Our goal was to inform vaccination program priorities in South Africa and other LMICs.
METHODS

Analytic Overview

We used the Clinical and Economic Analysis of COVID-19 Interventions (CEACOV) dynamic state-transition Monte Carlo microsimulation model to reflect COVID-19 natural history, vaccination, and treatment. We previously used the CEACOV model to project COVID-19 clinical and economic outcomes in a variety of settings, including an analysis of non-pharmaceutical public health interventions in South Africa. In this analysis, we focus on vaccination programs in South Africa and examine different implementation strategies and different vaccine characteristic and epidemic growth scenarios, thereby projecting which have the greatest impact on clinical and economic outcomes and cost-effectiveness.

Starting with SARS-CoV-2 active infection prevalence of 0.1% (or approximately 60,000 active cases, roughly 10 times the number reported in the first 10 days of April 2021), we simulated COVID-19-specific outcomes over 360 days, including daily and cumulative infections (detected and undetected), deaths, resource utilization (hospital and intensive care unit [ICU] bed use), and health care costs from the all-payer (public and private) health sector perspective without discounting. Outside the model, we calculated the mean lifetime years-of-life saved (YLS) from each averted COVID-19 death during the 360-day model horizon, stratified by age (mean 17.77 YLS per averted COVID-19 death across all individuals, Supplement p.8). We did not include costs beyond the 360-day model horizon. We determined the incremental cost-effectiveness ratio (ICER), the difference in health care costs (2020 US dollars) divided by the difference in life-years between different vaccination strategies. Our ICER estimates include health care costs during the 360-day model horizon and YLS over a lifetime from averted COVID-19 deaths during the 360-day model horizon. “Cost-saving” strategies were those resulting in higher clinical benefits (fewer life-years lost) and lower costs than an alternative. Though there is no consensus on an ICER threshold for cost-effectiveness in South Africa, for context, the country’s gross domestic
product per capita in 2019 was approximately $6,000, and a published South Africa cost-effectiveness threshold from an opportunity cost approach was approximately $2,950 (2020 US dollars) per disability-adjusted life-year averted.\textsuperscript{21,22}

Analysis of Vaccination Program Strategies

To understand the trade-offs inherent to policy decisions regarding the total vaccine supply to purchase and the speed with which to administer vaccinations, we compared the clinical and economic outcomes of different strategies of population coverage (vaccine supply) and vaccination pace. We determined the ICER of each strategy compared with other strategies of supply and pace.

Sensitivity Analysis: Vaccine Characteristics and Alternative Scenarios

To understand the influence of extrinsic factors (i.e., those outside the direct control of vaccination program decision makers, such as vaccine effectiveness and costs and epidemic growth), we performed sensitivity analyses in which we varied each of these factors. In each alternative scenario, we projected clinical and economic outcomes and determined the ICER of a reference vaccination program (67% vaccine supply, 150,000 vaccinations/day, similar to stated goals in South Africa) compared with no vaccination program.\textsuperscript{23–25}

Model Structure

Vaccination

In each simulation, we assumed a fixed supply of vaccine that would be administered to eligible and willing individuals, prioritizing older adults, regardless of history of SARS-CoV-2 infection. Available vaccine doses would first be offered to those aged ≥60 years, then to those aged 20-59 years, and finally to those aged <20 years.\textsuperscript{26}
In the base case, we applied characteristics of Ad26.COV2.S (Johnson & Johnson/Janssen), a single-dose vaccine for which administration in South Africa began through a phase 3b study in health care workers in February 2021.\textsuperscript{4,27} To reflect possible implementation of other vaccines, as well as published data and uncertainties around the type of protection provided by each vaccine, we varied vaccine effectiveness against SARS-CoV-2 infection, effectiveness against symptomatic COVID-19 disease, and effectiveness against severe COVID-19 disease requiring hospitalization. We assumed that a single vaccine dose would be given and did not explicitly model a two-dose schedule.

\textit{Natural History and Transmission}

At model initiation, each individual is either susceptible to SARS-CoV-2, infected with SARS-CoV-2, or immune (by way of prior infection). Each susceptible individual faces a daily probability of SARS-CoV-2 infection. Once infected, an individual moves to the pre-infectious latency state and faces age-dependent probabilities of developing asymptomatic, mild/moderate, severe, or critical disease (Supplement p.4, Table S1, Figure S1). Those with critical disease face age-dependent daily probabilities of death. If they survive, they transition to a recuperation state (remaining infectious) before going to the recovery (immune) state. Those in other disease states can transition directly to the recovery state. “Recovered” individuals are assumed immune from repeat infection for the simulation duration and pose no risk of transmission. To capture infection transmission dynamics, all simulated individuals advance through the model simultaneously. Details of COVID-19 transmission and hospital care in the model are described elsewhere and in the Supplement pp.4-7.\textsuperscript{16}
Resource Utilization

Individuals with severe or critical disease are referred to hospitals and ICUs, respectively. If hospital/ICU bed capacity has been reached, the individual receives the next lower available intervention, which is associated with different mortality risk and cost (e.g., if a person needs ICU care when no ICU beds are available, they receive non-ICU hospital care).

Input Parameters

Cohort Characteristics

We defined the age distribution based on 2019 South Africa population estimates, in which 37% were aged <20 years, 54% were 20-59 years, and 9% were ≥60 years (Table 1). We assumed in the base case that, at model initiation, 30% had prior infection and were immune to repeat infection. This assumption was based on an estimate of the proportion of South Africa’s population that had been exposed to the B.1.351 variant by 30 January 2021 (Supplement pp.5-6).

Vaccination Program Strategies

In the reference vaccination program strategy: a) there would be a sufficient supply of vaccine doses to fully vaccinate 67% of South Africa’s population (approximately 40 million vaccinated people); b) pace of vaccination was 150,000 doses/day. Our comparisons of different vaccination program strategies included varying the vaccine supply to that sufficient to cover 0-80% of South Africa’s population and increasing the pace of vaccination up to 300,000 doses/day.

Vaccine Uptake and Effectiveness

In the base case, we assumed that vaccine uptake among those eligible was 67%, accounting for vaccine hesitancy and failure to reach some. Vaccine effectiveness was 40% against infection, 52% against
symptomatic disease, and 86% against severe disease requiring hospitalization. The latter two were based on reported efficacies of the Johnson & Johnson/Janssen vaccine ≥14 days post-vaccination in South Africa.4

Natural History and Transmission

Table S1 indicates daily disease progression probabilities, age-dependent probabilities of developing severe or critical disease, and age-dependent mortality probabilities for those with critical disease. We stratified transmission rates by disease state, adjusting them to reflect an initial effective reproduction number ($R_e$)=1.4 in the base case.34 We also simulated alternative epidemic growth scenarios with lower or higher initial $R_e$ and a scenario in which there were episodic surges above a lower background basic reproduction number ($R_0$), as observed in the South Africa epidemic over the past year (Supplement p.7).

Resource Utilization and Costs

The maximum availability of hospital and ICU beds per day was 119,400 and 3,300 (Table 1).35 We applied costs of vaccination and daily costs of hospitalization and ICU stay based on published estimates and/or cost quotes obtained in South Africa (Table 1). In the base case, we applied a total vaccination cost of $14.81 per person, based on estimated costs in South Africa of $10/dose for the vaccine and $4.81/dose for service and delivery (Supplement pp.10-11).36–38 We varied vaccination costs in sensitivity analysis.

Validation

We previously validated our natural history assumptions by comparing model-projected COVID-19 deaths with those reported in South Africa.16 We updated our validation by comparing the model-
projected number of COVID-19 infections and deaths with the number of cases and deaths reported in South Africa through 10 April 2021, accounting for underreporting (Supplement p.11, Figure S2).^{20,39}

### Sensitivity Analysis

We used sensitivity analysis to examine the relative influence on clinical and cost projections of various parameters around vaccine characteristics and epidemic growth (Table 1). Specifically, we varied:

- vaccine acceptance (50-90% among eligible individuals);
- vaccine effectiveness in preventing infection (20-75%), symptomatic disease (30-79%), and severe/critical disease requiring hospitalization (40-98%);
- cost ($9-75/person); initial \( R_e \) (1.1-1.8); prior immunity (10-50% of population);
- reduction in transmission rate among vaccinated but infected individuals (0-50%); and hospital and ICU daily costs (0.5x-2.0x base case costs). The ranges of vaccine effectiveness against symptomatic disease and severe/critical disease requiring hospitalization were based on efficacies and 95% confidence intervals reported in the Johnson & Johnson/Janssen vaccine trial (Supplement pp.8-10).^{4} We also examined ICERs when the relatively high costs of ICU care were excluded and when all hospital care costs (non-ICU and ICU) were excluded. We performed multi-way sensitivity analysis in which we simultaneously varied parameters influential in one-way sensitivity analysis.
RESULTS

Clinical and Economic Benefits of Vaccination Strategies

The scenario without vaccines resulted in the most infections (21,012,100) and deaths (89,300) and highest costs (~$1.77 billion) (Table 2). Vaccinating 40% of the population decreased deaths to 16,000 and resulted in the lowest total health care costs (~$1.18 billion), representing reductions of 82% (deaths) and 33% (costs) compared with the scenario without vaccines. Increasing the vaccinated population to 67%, the government’s target for 2021, decreased deaths to 14,700 (additional 8% reduction) and raised costs to ~$1.34 billion, resulting in an ICER of $9,960/YLS compared with the 40% supply (Table 2). Increasing the vaccine supply to 80%, while simultaneously increasing vaccine acceptance to 80%, reduced deaths and raised costs further, with an ICER of $4,270 compared with the 40% supply. Due to its higher ICER, the 67% supply strategy was therefore dominated by the 80% supply strategy, meaning that it used resources less efficiently. A vaccine supply of 20%, while less efficient than higher vaccine supply levels, still reduced deaths by 76% and reduced costs by 15% compared with no vaccination. The highest vaccination pace, 300,000 vaccinations daily, resulted in the most favorable clinical outcomes and lowest costs compared with lower paces (Table 2).

Table S2 details the differences between a reference vaccination program (supply 67%, pace 150,000 vaccinations/day) and no vaccination program in age-stratified cumulative infections and deaths, hospital and ICU bed use, and health care costs. The reference vaccination program reduced hospital bed-days by 67% and ICU bed-days by 54% compared with no vaccination program.

When varying both vaccine supply and vaccination pace across different scenarios of epidemic growth ($R_e$), a faster vaccination pace decreased both COVID-19 deaths and total health care costs, while the impact of a higher vaccine supply on deaths and costs varied (Table 3). In all four $R_e$ scenarios, a
vaccination strategy with supply 40% and pace 300,000/day resulted in fewer deaths and lower costs than a strategy with higher supply (67%) and slower pace (150,000/day). At a vaccination pace of 300,000/day, increasing the vaccine supply from 40% to 67% was cost-saving in the two-wave epidemic scenario, while it resulted in ICERs of $520/YLS when $R_e=1.4$, $1,160/YLS$ when $R_e=1.8$, and $85,290/YLS$ when $R_e=1.1$.

Sensitivity Analysis: Vaccine Characteristics and Alternative Scenarios

In one-way sensitivity analysis, the reference vaccination program remained cost-saving compared with a scenario without vaccines across different values of effectiveness against infection, effectiveness against symptomatic disease, effectiveness against severe/critical disease, and vaccine acceptance (Table 4). When increasing the cost per person vaccinated up to $25, the vaccination program remained cost-saving. At cost per person vaccinated between $26 and $75, the vaccination program increased health care costs compared with a scenario without vaccines, but the ICERs increased only to $1,500/YLS (Table 4).

The reference vaccination program had an ICER <$100/YLS or was cost-saving compared with a scenario without vaccines across different values of prior immunity (up to 40%), reduction in transmission rate among vaccinated but infected individuals, and costs of hospital and ICU care (Table 4, Table S3). When there was 50% prior immunity, the vaccination program still reduced deaths but it increased costs, with an ICER of $22,460/YLS compared with a scenario without vaccines. The vaccination program reduced deaths and increased costs compared with no vaccination program in a scenario of $R_e 1.1$ (ICER $3,050/YLS$ or $R_e 1.8$ (ICER $70/YLS$). In a two-wave epidemic scenario, the vaccination program was cost-saving compared with no vaccination (Table 4). Notably, when excluding costs of hospital care and...
ICU care and only considering costs of the vaccination program, the program increased costs, but its ICER compared with no vaccination program was only $450/YLS (Table S3).

The influence of different scenarios into which the vaccination program would be introduced on cumulative infections, deaths, and health care costs is depicted in Figure 1. Varying the prevalence of prior immunity and $R_e$ had the greatest influence on both infections and deaths, while varying the cost per person vaccinated had the greatest influence on health care costs. Vaccine effectiveness against infection and effectiveness against severe disease requiring hospitalization were more influential than effectiveness against symptomatic disease in terms of reductions in deaths and costs.

**Multi-Way Sensitivity Analyses**

In a multi-way sensitivity analysis in which we simultaneously varied vaccine effectiveness against infection and cost per person vaccinated, the reference vaccination program was cost-saving compared with a scenario without vaccines when cost per person vaccinated was $14.81, even when effectiveness against infection was as low as 20% (Figure 2). When cost per person vaccinated was $25, the program was cost-saving when effectiveness against infection was at least 40%. Even at the highest examined cost per person vaccinated ($75) and the lowest examined effectiveness against infection (20%), the vaccination program had an ICER <$2,000/YLS compared with no vaccination program (Figure 2).

We performed several additional multi-way sensitivity analyses in which we simultaneously varied combinations of vaccine supply, vaccination pace, vaccine effectiveness against infection, cost per person vaccinated, $R_e$, and prevalence of prior immunity (Table 1, Figures S3-S7). Of note, to optimize efficiency, increasing vaccination pace was more important than increasing vaccine supply. At a cost of $45 or $75 per person vaccinated, increasing vaccination pace led to similar or lower ICER (greater
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economic efficiency), while increasing vaccine supply led to a similar or higher ICER (less economic
efficiency) (Figure S3). At a cost up to $25 per person vaccinated, the vaccination program was cost-
saving under nearly all strategies and scenarios (Figures S3-S5). Even when the vaccination program
increased costs, the ICERs were <$2,000/YLS compared with a scenario without vaccines (Figures S3-S5).
DISCUSSION

Using a dynamic COVID-19 microsimulation model, we found that vaccinating 67% of South Africa’s population, meeting the government’s goal for 2021, would both decrease COVID-19 deaths and reduce overall health care costs compared with a scenario without vaccines or with a 20% vaccine supply, by reducing the number of infections, hospitalizations, and ICU admissions. Further increasing the vaccine supply to 80%, while simultaneously increasing vaccine acceptance, would save even more lives while modestly increasing costs. Vaccination pace – the number of vaccine doses administered daily, rather than supply itself, may be most influential to maximizing public health benefits and economic efficiency. Increasing the pace would reduce both deaths and overall health care costs. The program remained cost-saving even with conservative estimates of vaccine effectiveness and with higher per-person vaccination costs, highlighting that the characteristics of vaccination program implementation are likely to be more influential than the characteristics of the vaccine itself.

Furthermore, the vaccination program remained economically efficient (either cost-saving or with a relatively low ICER representing good clinical value for additional money spent) across most epidemic scenarios, including various rates of epidemic growth and a broad range of prevalence of prior population immunity.

Much has been made about differences in the leading vaccine candidates and the impact of variants, such as the B.1.351 variant which eventually accounted for over 90% of SARS-CoV-2 infections in South Africa, on vaccine effectiveness. However, we found that even with lower effectiveness than that estimated from studies, a vaccination program would still prevent the majority of COVID-19 deaths that would occur without a vaccination program. For example, decreasing vaccine effectiveness against symptomatic disease and severe/critical disease requiring hospitalization to 40% still reduced COVID-19 deaths by 65,800 (74%) compared with a scenario without vaccines. Although effectiveness against
symptomatic and severe disease have been the focus of vaccine trials, these were even less influential on population-wide health and cost outcomes than effectiveness against infection, which is less commonly reported in trials. Nonetheless, the effectiveness ranges we examined in sensitivity analysis include the point estimates of efficacy against symptomatic and severe disease reported in clinical trials of the AstraZeneca ChAdOx1, Moderna mRNA-1273, and Pfizer-BioNTech mRNA BNT162b2 vaccines. This suggests that all of these vaccines are likely to have both health and economic benefits.

Similarly, we found that vaccination programs remained economically favorable even at relatively high vaccination costs. Though we did not explicitly account for all implementation and scale-up costs of a vaccination program, our estimates of cost per person vaccinated were based on reported costs of both vaccine and delivery in South Africa. We found that the vaccination program would remain cost-saving at a vaccination cost up to $25/person and likely cost-effective even at per-person vaccination cost up to $75/person (ICER $1,500/YLS). This is due to cost offsets in preventing hospitalizations.

A faster pace of vaccination consistently decreased infections, deaths, and costs across a range of epidemic growth scenarios. Yet, this was not always true of a higher vaccine supply. With lower epidemic growth (RE=1.1), which approximates the basic reproduction number in the intra-wave periods in South Africa, a faster pace remained preferable from a clinical and economic standpoint. But with the faster vaccination pace, increasing the proportion of the population vaccinated from 40% to 67% resulted in higher costs while only modestly reducing years-of-life lost, with an ICER of $85,290/YLS, well above commonly reported willingness-to-pay thresholds in South Africa. By contrast, when a higher epidemic growth rate is seen (RE=1.8), as was documented during the first and second waves in South Africa, a faster vaccination pace remained highly preferable, and increasing the proportion of the population vaccinated from 40% to 67% resulted in fewer years-of-life lost and higher costs with a much
lower ICER of $1,160/YLS. Overall, these results demonstrate the importance of rolling out vaccinations quickly, particularly ahead of any future waves of the epidemic – pace of vaccination is at least as important as vaccine supply from both clinical and economic perspectives. Consequently, policymakers should invest both in procuring vaccine doses and establishing a vaccine distribution and administration system to ensure vaccines will be administered as promptly as possible. Because of the importance of speed, all available distribution channels, including those in public and private sectors, should be leveraged.

Our model projections were sensitive to \( R_e \) and to the prevalence of prior immunity to SARS-CoV-2. However, the program was generally economically efficient. The exception was when the prevalence of prior protective immunity was increased to 50%. We assumed that prior infection protects against another SARS-CoV-2 infection for the duration of the simulation period. If this is not the case, either because immunity wanes or viral variants make prior infection poorly protective against re-infection, as appeared to be seen in the second waves in South Africa and Brazil, then the vaccination program could still provide good value even with a high prevalence of prior infection.\(^{43,44}\)

These results should be interpreted within the context of several limitations. We assumed that vaccine effectiveness was constant starting 14 days after administration and continuing throughout the 360-day simulation. Early data suggest that post-vaccination immunity lasts at least for months, with additional data accruing as the studies continue their prolonged observation periods.\(^1,3,45,46\) There may be economies of scale such that the cost per person vaccinated decreases as the vaccine supply or vaccination pace increase and vaccination program resources are used more efficiently. Our modeled vaccination prioritization was based exclusively on age and not on employment type, comorbidity presence, or urban/rural heterogeneity in epidemiology or vaccination delivery. We did not include
lifetime costs of health care beyond COVID-19 nor of sequelae among those who recover. We did not consider the impact of COVID-19 or vaccination on other health care programs (e.g., HIV and tuberculosis care) or on other economic sectors. As with all modeling exercises, our results are contingent on assumptions and input parameters. We selected COVID-19 clinical parameters based on the published literature. Where data were limited, lacking, or uncertain, we conducted sensitivity analyses.

In summary, we found that a COVID-19 vaccination program would reduce infections and deaths and likely reduce overall health care costs in South Africa across a range of possible scenarios, even with conservative assumptions around vaccine effectiveness. Our data underscore that in South Africa and similar settings, acquisition and rapid distribution of vaccines should be prioritized over relatively small differences in vaccine effectiveness and price, as vaccination programs are likely to be cost-saving. The pace of vaccination is as or more important than population coverage, and therefore attention to vaccination program infrastructure is critical. Non-pharmaceutical practices such as mask wearing and physical distancing remain crucial to reduce epidemic growth while vaccination programs are being implemented. Policymakers can use our results to guide decisions about vaccine selection, supply, and distribution to maximally reduce the deleterious impact of the COVID-19 pandemic in South Africa.
DATA AVAILABILITY

This modeling study involved the use of published or publicly available data. The data used and the sources are described in the Manuscript and Supplement. No primary data were collected for this study. Model flowcharts are in the Supplement.

AUTHOR CONTRIBUTIONS

All authors contributed substantively to this manuscript in the following ways: study and model design (all authors), data analysis (KPR, KPF, JAS, FMS, KAF, MJS), interpretation of results (all authors), drafting the manuscript (KPR, MJS), critical revision of the manuscript (all authors) and final approval of the submitted version (all authors).
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### Table 1. Input parameters for a model-based analysis of COVID-19 vaccination in South Africa.

| Parameter                                      | Base case value (Range) | Sources |
|------------------------------------------------|-------------------------|---------|
| **Initial state**                              |                         |         |
| Age distribution, %                           |                         |         |
| <20 years                                      | 37                      |         |
| 20-59 years                                    | 54                      |         |
| ≥60 years                                      | 9                       |         |
| Initial health state distribution, %           |                         |         |
| Susceptible                                    | 69.9 (49.9-89.9)        | Assumption |
| Infected with SARS-CoV-2                       | 0.1                     | Assumption$^a$ |
| Recovered (prior immunity)                    | 30 (10-50)              | $^{15,29-31}$ |
| **Transmission dynamics**                      |                         |         |
| Effective reproduction number, $R_e$           | 1.4 (1.1-1.8)           | $^{34}$ |
| Relative reduction in onward transmission rate among vaccinated individuals, % | 0 (0-50) | Assumption |
| **Hospital and ICU care**                     |                         |         |
| Resource availabilities                        |                         |         |
| Hospital beds, daily, n                       | 119,400                 | $^{35}$ |
| ICU beds, daily, n                            | 3,300                   | $^{35}$ |
| Costs                                          |                         |         |
| Hospitalization, daily, USD                   | 154 (77-309)            | $^{47-49}$ |
| ICU care, daily, USD                           | 1,751 (875-3,502)       | $^{48-50}$ |
| **Vaccination program strategies**             |                         |         |
| Vaccine supply, % of population                | 67 (20-80)              | $^{23}$ |
| Vaccinations per day, n                       | 150,000 (150,000-300,000) | $^{24,25}$ |
| Time to rollout start, days                    | 0 (0-60)                | Assumption |
| **Vaccine characteristics$^b$**                |                         |         |
| Effectiveness in preventing SARS-CoV-2 infection, % | 40 (20-75)           | Assumption |
| Effectiveness in preventing symptomatic COVID-19 disease, % | 52 (30-79)           | $^{4}$ |
| Effectiveness in preventing severe COVID-19 disease requiring hospitalization, % | 86 (40-98)           | $^{4}$ |
| Number of doses required for effectiveness     | 1                       | $^{4}$ |
| Time to efficacy, days post-vaccination        | 14                      | $^{4}$ |
| Vaccine uptake among those eligible, %         | 67 (50-90)              | $^{33}$ |
| Vaccination cost per person, USD               | 14.81 (9-75)            | $^{36-38,48,49}$ |

$R_e$: effective reproduction number. ICU: intensive care unit. USD: United States dollars.

Ranges reflect values examined in analyses of alternative vaccination program strategies and in sensitivity analyses of different vaccine characteristics and epidemic growth scenarios.

$^a$Initial prevalence of each state of infection and disease are in Table S1.

$^b$In the base case, we model a vaccination program based on characteristics of the Johnson & Johnson/Janssen Ad26.COV2.S vaccine. In sensitivity analyses, vaccine effectiveness and cost are varied across a range of possible values to evaluate the influence of these parameters on clinical and economic outcomes and to account for uncertainty around published estimates.
Table 2. Model-projected clinical and economic outcomes and cost-effectiveness of different COVID-19 vaccination program strategies over 360 days in South Africa.

| Parameter / Value | Cumulative SARS-CoV-2 infections | Cumulative COVID-19 deaths | Years-of-life lost | Health care costs, USD | ICER, USD per YLS |
|-------------------|----------------------------------|---------------------------|-------------------|------------------------|------------------|
| Vaccine supply, % of population |                    |                            |                   |                        |                  |
| 40                | 11,784,700                      | 16,000                    | 275,800           | 1,177,742,900          | --               |
| 67                | 10,585,100                      | 14,700                    | 259,600           | 1,338,803,500          | Dominated        |
| 80\(^b\)          | 10,410,000                      | 12,000                    | 217,900           | 1,425,272,800          | 4,270            |
| 20                | 15,489,500                      | 21,800                    | 397,300           | 1,508,890,800          | Dominated        |
| 0                 | 21,012,100                      | 89,300                    | 1,558,700         | 1,766,856,200          | Dominated        |
| Vaccinations per day |                        |                            |                   |                        |                  |
| 300,000           | 5,659,400                       | 7,200                     | 120,300           | 1,016,586,100          | --               |
| 200,000           | 8,191,900                       | 9,600                     | 151,300           | 1,123,694,300          | Dominated        |
| 150,000           | 10,585,100                      | 14,700                    | 259,600           | 1,338,803,500          | Dominated        |
| 0                 | 21,012,100                      | 89,300                    | 1,558,700         | 1,766,856,200          | Dominated        |

USD: United States dollars. ICER: incremental cost-effectiveness ratio. YLS: year-of-life saved.

Dominated: the strategy results in a higher ICER than that of a more clinically effective strategy, or the strategy results in less clinical benefit (more years-of-life lost) and higher health care costs than an alternative strategy.

\(^a\)Strategies are ordered from lowest to highest cost per convention of cost-effectiveness analysis. ICERs are calculated compared to the next least expensive, non-dominated strategy. Displayed life-years and costs are rounded to the nearest hundred, while ICERs are calculated based on non-rounded life-years and costs.

\(^b\)When modeling a vaccination program that seeks to vaccinate 80% of the population, uptake among those eligible was increased to 80% to avoid a scenario in which supply exceeds uptake. If uptake is not increased beyond 67%, then the strategy of vaccinating 67% of the population provides the most clinical benefit and results in an ICER of $9,960/YLS compared with vaccinating 40% of the population.
Table 3. Clinical and economic outcomes of different COVID-19 vaccination program strategies of vaccine supply and vaccination pace under different scenarios of epidemic growth in South Africa.

| Scenario and Vaccination Strategy                                      | Cumulative SARS-CoV-2 infections | Cumulative COVID-19 deaths | Years-of-life lost | Health care costs, USD | ICER, USD per year-of-life saved |
|-----------------------------------------------------------------------|----------------------------------|---------------------------|--------------------|------------------------|----------------------------------|
| **Rₑ = 1.1**                                                          |                                  |                           |                    |                        |                                  |
| No vaccination                                                        | 3,719,500                        | 8,200                     | 123,500            | 382,176,900            | --                               |
| Vaccine supply 40%, pace 300,000 vaccinations per day                 | 860,900                          | 1,300                     | 24,500             | 417,756,900            | 360                              |
| Vaccine supply 40%, pace 150,000 vaccinations per day                 | 1,144,800                        | 1,400                     | 24,300             | 449,386,900            | Dominated                        |
| Vaccine supply 67%, pace 300,000 vaccinations per day                 | 718,900                          | 1,300                     | 21,700             | 652,819,400            | 85,290                           |
| Vaccine supply 67%, pace 150,000 vaccinations per day                 | 1,079,100                        | 1,500                     | 25,400             | 681,669,900            | Dominated                        |
| **Rₑ = 1.4 (base case)**                                              |                                  |                           |                    |                        |                                  |
| Vaccine supply 40%, pace 300,000 vaccinations per day                 | 9,866,800                        | 13,000                    | 211,300            | 969,576,100            | --                               |
| Vaccine supply 67%, pace 300,000 vaccinations per day                 | 5,659,400                        | 7,200                     | 120,300            | 1,016,586,100          | 520                              |
| Vaccine supply 40%, pace 150,000 vaccinations per day                 | 11,784,700                       | 16,000                    | 275,800            | 1,177,742,900          | Dominated                        |
| Vaccine supply 67%, pace 150,000 vaccinations per day                 | 10,585,100                       | 14,700                    | 259,600            | 1,338,803,500          | Dominated                        |
| No vaccination                                                        | 21,012,100                       | 89,300                    | 1,558,700          | 1,766,856,200          | Dominated                        |
| **Rₑ = 1.8**                                                          |                                  |                           |                    |                        |                                  |
| Vaccine supply 40%, pace 300,000 vaccinations per day                 | 21,260,400                       | 38,800                    | 695,700            | 1,541,112,600          | --                               |
| Vaccine supply 40%, pace 150,000 vaccinations per day                 | 24,268,200                       | 69,500                    | 1,410,500          | 1,596,237,800          | Dominated                        |
| Vaccine supply 67%, pace 300,000 vaccinations per day                 | 18,511,000                       | 33,800                    | 593,600            | 1,659,492,700          | 1,160                            |
| No vaccination                                                        | 30,173,000                       | 179,300                   | 3,360,700          | 1,673,830,400          | Dominated                        |
| Vaccine supply 67%, pace 150,000 vaccinations per day                 | 24,217,300                       | 68,900                    | 1,403,000          | 1,803,189,900          | Dominated                        |
| **Two-wave epidemic**                                                 |                                  |                           |                    |                        |                                  |
| Vaccine supply 67%, pace 300,000 vaccinations per day                 | 2,697,100                        | 3,200                     | 49,300             | 780,133,600            | --                               |
| Vaccine supply 40%, pace 300,000 vaccinations per day                 | 6,223,600                        | 7,200                     | 126,900            | 780,274,900            | Dominated                        |
| Vaccine supply 40%, pace 150,000 vaccinations per day                 | 7,758,800                        | 10,600                    | 175,100            | 927,247,000            | Dominated                        |
| Vaccine supply 67%, pace 150,000 vaccinations per day                 | 5,594,000                        | 7,800                     | 133,700            | 1,009,741,300          | Dominated                        |
| No vaccination                                                        | 19,290,400                       | 70,400                    | 1,206,200          | 1,691,805,000          | Dominated                        |
USD: United States dollars. ICER: incremental cost-effectiveness ratio. \( R_e \): effective reproduction number. Dominated: the strategy results in a higher ICER than that of a more clinically effective strategy, or the strategy results in less clinical benefit (more years-of-life lost) and higher health care costs than an alternative strategy.

Within each \( R_e \) scenario, vaccination strategies are ordered from lowest to highest cost per convention of cost-effectiveness analysis. ICERs are calculated compared to the next least expensive, non-dominated strategy. Displayed life-years and costs are rounded to the nearest hundred, while ICERs are calculated based on non-rounded life-years and costs and then rounded to the nearest ten.

Because there are relatively few deaths in the \( R_e=1.1 \) scenario, the impact of changing vaccination program strategies is attenuated. Due to stochastic variation in simulation model results, and extrapolation from a simulated population of 1 million to South Africa’s population of approximately 59 million, results indicate a slight increase in deaths when increasing vaccine supply while pace is maintained at 150,000 vaccinations per day. Also, due to differences in the ages of those who die, there can be discordance between number of deaths and number of years-of-life lost.

In the analysis of an epidemic with periodic surges, the basic reproduction number \( (R_0) \) alternates between low and high values over time, and the \( R_e \) changes day-to-day as the epidemic and vaccination program progress and there are fewer susceptible individuals. For most of the simulation horizon, \( R_0 \) is 1.6 (equivalent to an initial \( R_e \) of 1.1). However, during days 90-150 and 240-300 of the simulation, \( R_0 \) is increased to 2.6. This results in two epidemic waves with peak \( R_e \) of approximately 1.4-1.5.
Table 4. One-way sensitivity analyses of different COVID-19 vaccine characteristic and epidemic growth scenarios in South Africa.

| Parameter / Value | SARS-CoV-2 infections averted, compared with no vaccination | COVID-19 deaths averted, compared with no vaccination | Years-of-life saved, compared with no vaccination | Change in health care costs, compared with no vaccination, USD | ICER, compared with no vaccination, USD per YLSa |
|-------------------|----------------------------------------------------------|--------------------------------------------------|--------------------------------------------------|-------------------------------------------------------------|-------------------------------------------------------------|
| Vaccine effectiveness in preventing SARS-CoV-2 infection, % | | | | | |
| 20                | 5,466,500                                                | 71,600                                          | 1,254,900                                        | -166,032,500                                                | Cost-saving                                                  |
| 40 (base case)    | 10,427,000                                               | 74,600                                          | 1,299,100                                        | -428,052,700                                                | Cost-saving                                                  |
| 50                | 12,758,000                                               | 77,500                                          | 1,349,700                                        | -554,501,500                                                | Cost-saving                                                  |
| 75b               | 16,067,300                                               | 82,000                                          | 1,429,400                                        | -750,946,700                                                | Cost-saving                                                  |
| Vaccine effectiveness in preventing symptomatic COVID-19, %c | | | | | |
| 30                | 8,310,500                                                | 74,000                                          | 1,298,900                                        | -377,101,700                                                | Cost-saving                                                  |
| 52 (base case)    | 10,427,000                                               | 74,600                                          | 1,299,100                                        | -428,052,700                                                | Cost-saving                                                  |
| 67                | 10,625,200                                               | 76,200                                          | 1,332,200                                        | -410,883,200                                                | Cost-saving                                                  |
| 79                | 10,722,500                                               | 75,300                                          | 1,316,800                                        | -399,131,600                                                | Cost-saving                                                  |
| Vaccine effectiveness in preventing severe/critical COVID-19 requiring hospitalization, %d | | | | | |
| 40                | 10,659,300                                               | 65,800                                          | 1,180,100                                        | -80,901,300                                                 | Cost-saving                                                  |
| 86 (base case)    | 10,427,000                                               | 74,600                                          | 1,299,100                                        | -428,052,700                                                | Cost-saving                                                  |
| 98                | 10,690,200                                               | 77,500                                          | 1,341,700                                        | -545,358,200                                                | Cost-saving                                                  |
| Vaccine acceptance among those eligible, % | | | | | |
| 50                | 10,026,700                                               | 71,100                                          | 1,251,600                                        | -272,592,000                                                | Cost-saving                                                  |
| 67 (base case)    | 10,427,000                                               | 74,600                                          | 1,299,100                                        | -428,052,700                                                | Cost-saving                                                  |
| 90                | 10,562,000                                               | 79,200                                          | 1,360,000                                        | -526,334,700                                                | Cost-saving                                                  |
## Table 4, continued.

| Parameter / Value | SARS-CoV-2 infections averted, compared with no vaccination | COVID-19 deaths averted, compared with no vaccination | Years-of-life saved, compared with no vaccination | Change in health care costs, compared with no vaccination, USD | ICER, compared with no vaccination, USD per YLS\(^a\) |
|------------------|----------------------------------------------------------|--------------------------------------------------|-----------------------------------------------|----------------------------------------------------------|--------------------------------------------------|
| Vaccination cost per person, USD | 9 | 10,427,000 | 74,600 | 1,299,100 | -656,846,300 | Cost-saving |
| | 14.81 (base case) | 10,427,000 | 74,600 | 1,299,100 | -428,052,700 | Cost-saving |
| | 25 | 10,427,000 | 74,600 | 1,299,100 | -26,778,000 | Cost-saving |
| | 26 | 10,427,000 | 74,600 | 1,299,100 | 12,601,200 | 10 |
| | 35 | 10,427,000 | 74,600 | 1,299,100 | 367,014,600 | 280 |
| | 45 | 10,427,000 | 74,600 | 1,299,100 | 760,807,300 | 590 |
| | 75 | 10,427,000 | 74,600 | 1,299,100 | 1,942,185,200 | 1,500 |
| \(R_e\) | 1.1 | 2,640,400 | 6,600 | 98,000 | 299,493,000 | 3,050 |
| | 1.4 (base case) | 10,427,000 | 74,600 | 1,299,100 | -428,052,700 | Cost-saving |
| | 1.8 | 5,955,700 | 110,500 | 1,957,700 | 129,359,700 | 70 |
| Two-wave epidemic\(^c\) | 13,696,300 | 62,700 | 1,072,500 | -682,063,700 | Cost-saving |
| Prior immunity to SARS-CoV-2, % of population | 10 | 8,025,900 | 147,200 | 2,581,000 | 85,889,700 | 30 |
| | 20 | 9,087,700 | 119,000 | 2,168,000 | 55,790,700 | 30 |
| | 30 (base case) | 10,427,000 | 74,600 | 1,299,100 | -428,052,700 | Cost-saving |
| | 40 | 7,127,300 | 18,000 | 279,500 | -252,757,900 | Cost-saving |
| | 50 | 608,300 | 1,500 | 24,300 | 545,399,700 | 22,460 |

USD: United States dollars. ICER: incremental cost-effectiveness ratio. YLS: year-of-life saved. \(R_e\): effective reproduction number.

\(^a\)In these scenario analyses, the reference vaccination program (67% supply, 150,000 vaccinations per day) is compared with no vaccination program under different scenarios. Displayed life-years and costs are rounded to the nearest hundred, while ICERs are calculated based on non-rounded life-years and costs and then rounded to the nearest ten. Cost-saving reflects more years-of-life (greater clinical benefit) and lower costs, and therefore ICERs are not displayed.

\(^b\)In the scenario analysis of a vaccine with 75% effectiveness in preventing SARS-CoV-2 infection, the effectiveness in preventing symptomatic COVID-19 disease was increased to 75% to avoid a scenario in which a vaccine has higher effectiveness in preventing infection than it does in preventing symptomatic disease.
Vaccine effectiveness in preventing symptomatic COVID-19 (apart from severe/critical disease) has minimal impact on the number of deaths. Therefore, seemingly counterintuitive results are due to stochastic variability in the microsimulation. In the analysis of a vaccine that is 30% effective in preventing symptomatic COVID-19, the vaccine effectiveness in preventing SARS-CoV-2 infection was decreased to 30% to avoid a scenario in which a vaccine is more effective in preventing infection than in preventing symptomatic disease.

Vaccine effectiveness in preventing severe/critical COVID-19 itself has minimal impact on transmission and the number of infections. Therefore, seemingly counterintuitive results are due to stochastic variability in the microsimulation. In the analysis of a vaccine that is 40% effective in preventing severe COVID-19 requiring hospitalization, the vaccine effectiveness in preventing symptomatic COVID-19 was decreased to 40% to avoid a scenario in which a vaccine is more effective in preventing symptomatic disease than in preventing severe disease requiring hospitalization.

In the analysis of an epidemic with periodic surges, the basic reproduction number ($R_0$) alternates between low and high values over time, and the $R_e$ changes day-to-day as the epidemic and vaccination program progress and there are fewer susceptible individuals. For most of the simulation horizon, $R_0$ is 1.6 (equivalent to an initial $R_e$ of 1.1). However, during days 90-150 and 240-300 of the simulation, $R_0$ is increased to 2.6. This results in two epidemic waves with peak $R_e$ of approximately 1.4-1.5.
FIGURE LEGENDS

Figure 1. One-way sensitivity analysis, influence of each parameter on cumulative SARS-CoV-2 infections, COVID-19 deaths, and health care costs.

This tornado diagram demonstrates the relative influence of varying each key model parameter on clinical and economic outcomes over 360 days. This is intended to reflect the different scenarios in which a reference vaccination program (vaccine supply sufficient for 67% of South Africa’s population, pace 150,000 vaccinations per day) might be implemented. The dashed line represents the base case scenario for each parameter. Each parameter is listed on the vertical axis, and in parentheses are the base case value and, after a colon, the range examined. The number on the left of the range represents the left-most part of the corresponding bar, and the number on the right of the range represents the right-most part of the corresponding bar. The horizontal axis shows the following outcomes of a reference vaccination program: (A) cumulative SARS-CoV-2 infections; (B) cumulative COVID-19 deaths; (C) cumulative health care costs. In some analyses, the lowest or highest value of an examined parameter produced a result that fell in the middle of the displayed range of results, due to stochastic variability when the range of results was narrow.

Figure 2. Multi-way sensitivity analysis of vaccine effectiveness against infection and vaccination cost: incremental cost-effectiveness ratio of vaccination program compared with no vaccination.

Each box in the 4x4 plot is colored according to the incremental cost-effectiveness ratio (ICER). The lightest color represents scenarios in which a reference vaccination program (vaccine supply sufficient for 67% of South Africa’s population, pace 150,000 vaccinations per day) is cost-saving compared with
no vaccination program, meaning that it results in clinical benefit and reduces overall health care costs.

The darker colors reflect increasing ICERs, whereby a reference vaccination program, compared with no vaccination program, results in both clinical benefit and higher overall health care costs. The ICER is the model-generated difference in costs divided by the difference in years-of-life between a reference vaccination program and no vaccination program. In none of these scenarios is the ICER above $2,000/year-of-life saved (YLS).
Cost-effectiveness of COVID-19 vaccination in South Africa

Figure 1.

A

Prior immunity (30%; 50%-10%)
Effectiveness in preventing SARS-CoV-2 infection (40%; 75%-20%)
Reduction in transmission rate among those vaccinated (0%; 50%-0%)
Delay to start of rollout (0 days: 0-60 days)
Effectiveness in preventing symptomatic COVID-19 (52%; 79%-30%)
Vaccine uptake among those eligible (67%; 90%-50%)
Effectiveness in preventing COVID-19 requiring hospitalization (86%; 98%-86%)

B

Prior immunity (30%; 50%-10%)
Effectiveness in preventing SARS-CoV-2 infection (40%; 75%-20%)
Delay to start of rollout (0 days: 0-60 days)
Vaccine uptake among those eligible (67%; 90%-50%)
Reduction in transmission rate among those vaccinated (0%; 50%-0%)
Effectiveness in preventing symptomatic COVID-19 (52%; 79%-30%)

C

Cost per person vaccinated (14.81 USD: 9 USD-75 USD)
Hospital and ICU cost (base case: 0.5x-2.0x base case)
Effectiveness in preventing SARS-CoV-2 infection (40%; 75%-20%)
Effectiveness in preventing COVID-19 requiring hospitalization (86%; 98%-40%)
Delay to start of rollout (0 days: 0-60 days)
Reduction in transmission rate among those vaccinated (0%; 50%-0%)
Vaccine uptake among those eligible (67%; 90%-50%)
Effectiveness in preventing symptomatic COVID-19 (52%; 52%-30%)

Healthcare costs under vaccination strategy, USD (millions)
Figure 2.

Incremental cost-effectiveness ratio vs no vaccination

Vaccine effectiveness in preventing SARS-CoV-2 infection, %

Cost per person vaccinated, USD

- Cost-saving
- 0–500 USD per year-of-life saved
- 500–1,000 USD per year-of-life saved
- 1,000–1,500 USD per year-of-life saved
- 1,500–2,000 USD per year-of-life saved

Cost-effectiveness of COVID-19 vaccination in South Africa