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Risk-based cost-benefit analysis of alternative vaccines against COVID-19 in Brazil: Coronavac vs. Astrazeneca vs. Pfizer



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ARTICLE INFO

Article history:

Received 10 January 2022

Received in revised form 12 May 2022

Accepted 13 May 2022

Available online 19 May 2022

Keywords:

Cost-benefit analysis

Risk assessment

Probabilistic epidemiological model

COVID-19

Vaccines

ABSTRACT

We propose a probabilistic model to quantify the cost-benefit of mass Vaccination Scenarios (VSs) against COVID-19. Through this approach, we conduct a six-month simulation, from August 31st, 2021 to March 3rd, 2022, of nine VSs, i.e., the three primary vaccine brands in Brazil (CoronaVac, AstraZeneca and Pfizer), each with three different vaccination rates (2nd doses per week). Since each vaccine has different individual-level effectiveness, we measure the population-level benefit as the probability of reaching herd immunity (HI). We quantify and categorize the cost-benefit of VSs through risk graphs that show: (i) monetary cost vs. probability of reaching HI; and (ii) number of new deaths vs. probability of reaching HI. Results show that AstraZeneca has the best cost-benefit when prioritizing acquisition costs, while Pfizer is the most cost-beneficial when prioritizing the number of deaths. This work provides helpful information that can aid public health authorities in Brazil to better plan VSs. Furthermore, our approach is not restricted to Brazil, the COVID-19 pandemic, or the mentioned vaccine brands. Indeed, the method is flexible so that this study can be a valuable reference for future cost-benefit analyses in other countries and pandemics, especially in the early stages of vaccination, when data is scarce and uncertainty is high.

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1. Introduction

Brazil is the epicenter of coronavirus disease (COVID-19) in Latin America and is the third hardest-hit country globally, with almost 20.78 million confirmed cases and more than 580,000 deaths by the end of August 2021 [46]. During the first year of the pandemic, Brazil suffered from inefficient risk management and public health policies to control the spread of COVID-19, poor risk communication to society, and the delay in mass vaccination programs [9,39,42]. These circumstances, aligned with socio-economic factors (e.g., high population density in urban centers and 'favelas'; economic pressure to come back to business to avoid massive unemployment and starvation), lead to a precarious situation to cope with the pandemic [15]. With the development and approval of vaccines by health authorities [3], this work provides valuable results for developing a Risk-Based Cost-Benefit Analysis (RBCBA) to prioritize mass vaccination programs in Brazil.

Cost-benefit analysis compares the most profitable or least costly measures in scenario-driven applications [8]. We perform

a cost-benefit analysis using a risk-based framework, i.e., RBCBA. Most RBCBA approaches consider risk reduction as the benefit, while the cost refers to financial resources necessary to implement the proposed strategies [7,8,26,27,37]. Regarding COVID-19 vaccines, a recent study addressed the cost-effectiveness of a booster strategy [29].

The main goal of mass immunization is to reach a large proportion of immunized individuals in a short time interval [18]. A typical threshold for this proportion is the herd immunity (HI) that occurs when many resistant individuals control the spread of the infection, protecting the non-immune [45].

We consider risk as a combined measure of the frequency of occurrence and consequence of an undesired event [13]. Then, we here define risk as the probability of not reaching HI within six months, given a hypothetical vaccination scenario (VS). It is urgent to immunize as many people as possible rapidly to avoid the pandemic being again out of control (e.g. due to new variants) and to return to business as usual. In order to assess the best strategies in the short and medium terms, we chose one week as time-step and, then, we obtain results over 26 weeks (six months). Thus, the benefit dimension of our RBCBA approach is the probability of reaching HI within 26 weeks for each VS. We compute the benefit according to Eq. (1):

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$$\begin{aligned} \text{BENEFIT} &= 1 - \text{RISK} = 1 - \Pr(\text{not reaching HI}) \\ &= \Pr(\text{reaching HI}) \end{aligned} \quad (1)$$

Moreover, we assess costs in two separate dimensions: (i) the monetary cost of acquiring the vaccine doses for a VS and (ii) the number of deaths expected to occur during a VS, being the latter fundamental since death reduction is paramount to cope with the COVID-19 pandemic.

Many mathematical models have been proposed to describe the dynamics of the COVID-19 pandemic under mass vaccination programs. We found that both deterministic [1,21,22,24,28,31] and stochastic [23,35] models are addressed. These studies provided significant results and relevant contributions to public health management. However, some lack the inherent uncertainty of the infection dynamics. Thus, by making deterministic evaluations, the results may lead to imprudent decisions and actions by health authorities. Uncertainty should be the main component when evaluating risks of the COVID-19 pandemic [4]. Hence, our model is probabilistic. The great advantage of probabilistic over deterministic approaches is that results entail undesirable consequences and likelihood, so one can measure and communicate uncertainty. Some probabilistic COVID-19 models predict cases in Brazil [5,11,32,40,41]. Still, these models neither considered vaccination plans nor performed a cost-benefit analysis. Thus, this work brings up two main contributions: (i) the first probabilistic epidemiological model that addresses the COVID-19 dynamics in Brazil considering mass vaccination; (ii) it conducts the first cost-benefit analysis of COVID-19 vaccines at the national level (at the best of authors' knowledge, no work has performed a probabilistic cost-benefit analysis of COVID-19 vaccines). We analyzed the three most adopted vaccine brands in Brazil:

- CoronaVac (CV): developed by Sinovac Life Sciences (Beijing, China) that uses the inactivated virus SARS-CoV-2 [14],
- AstraZeneca (AZ): the adenoviral vector vaccine that encodes full-length spike protein, developed by the University of Oxford and AstraZeneca [36],
- Pfizer (PF): a nucleoside modified mRNA encoding full-length spike protein developed by Pfizer and BioNTech [19].

Therefore, we aim to conduct an RBCBA to compare hypothetical mass VSs that assume a single vaccine brand used throughout the simulation, using the model proposed by [40] as our basis and including new features to evaluate the influence of vaccines in the pandemic in Brazil. We can quantify, categorize and compare the cost-benefit of each of these brands when administered at a constant rate for 26 weeks. The motivation was to provide a new approach for cost-benefit analysis of alternative vaccines, test and illustrate its applicability in a real-world problem. Emphasis has been placed on: population modeling to extrapolate individual-level parameters (e.g., infection and death rates, vaccine effectiveness) into population-level effects (i.e., HI); stochastic modeling to account for variability and uncertainty in parameters to provide uncertainty in results; cost-benefit categorization to simplify the communication of results to health managers. Then, more informed decisions can be taken regarding the vaccine brand that should be prioritized.

The paper unfolds as follows. Section 2 describes the general steps for conducting RBCBA for each VS, the proposed model structure, and the cost-benefit categories. Section 3 presents the approach application in Brazil, evaluating the cost-benefit of CV, AZ, and PF for 26 weeks. The results are discussed in Section 4, and Section 5 concludes this paper.

2. RBCBA approach

This section presents the RBCBA approach in a general and flexible way, in the sense that it is not constrained to the simulated scenarios in Brazil and can be applied to other countries, scenarios and time periods. We present: a) the steps for conducting the RBCBA; b) the probabilistic epidemiological model structure to be used as a basis; c) the cost-benefit categorization for the better communication of results; and d) a flowchart for the Monte Carlo simulations. Our RBCBA approach steps are adapted from a Quantitative Microbial Risk Assessment (QMRA) methodology [13] that has already assessed risks to the public health of schistosomiasis disease [12], and COVID-19 pandemic [40].

QMRA is the formal process of estimating the probability of undesired consequences to humans due to exposure to one or more microbial pathogens [13,20]. The main objective of a QMRA is to predict relative risks for future scenarios and evaluate the effectiveness of different containment measures. Conversely, we seek to estimate the desired consequence (benefit) in this work that is to reach HI. The accurate HI threshold proportion (p_{HI}) for COVID-19 is still unknown. We assume 70%, which is also a minimum threshold for HI suggested by [17]. This parameter can be easily updated in the light of new information.

2.1. The steps of the RBCBA

We propose the following steps to conduct RBCBA (adapted from, [12,13,40]) (i) characterization of the problem; (ii) description of VSs; (iii) model structure and parameterization; (iv) frequency assessment; (v) exposure assessment; (vi) cost-benefit quantification and categorization. Each of these steps obtains specific results; Fig. 1 depicts the methodology. We adopted RAMAS[®] Metapop v.6.0 software [2] for running fast Monte Carlo simulations with 10,000 replications (less than one minute in a Intel[®] Core™ i7-8550U and 8 GB RAM) to perform the cost-benefit quantification and categorization, Fig. 2 details one out of these replications.

2.2. The model structure

Our model is stochastic (i.e., the model parameters are random variables), flexible, and provides results for each VS. We structured each subpopulation into four stages: Susceptible (*S*); Infected (*I*); Fully Vaccinated (*V*) and Immunized (*M*) (see Fig. 3 for a schematic representation and Table 1 for the model variables and initial conditions).

Our model is based on the following assumptions:

- When Susceptible individuals become Infected, they may be Immunized or die.
- Fully Vaccinated individuals receive two doses of a given vaccine. Then, they can transit to the Immunized or Infected stage depending on the vaccine effectiveness (η_k), i.e., the relative risk reduction of an individual becoming infected [38]. In summary, if an individual is vaccinated with a vaccine that has $\eta_k = x\%$, then the probability of this individual getting infected is $x\%$ lower when compared to a non-vaccinated one. For more details about the concepts and methods to evaluate vaccines' effectiveness, see [44].
- Individuals that recover from the Infected stage can also transit to the Immunized one. A recent study suggests that after an infection, most individuals have protection against new infections for at least one year, which supports our conservative

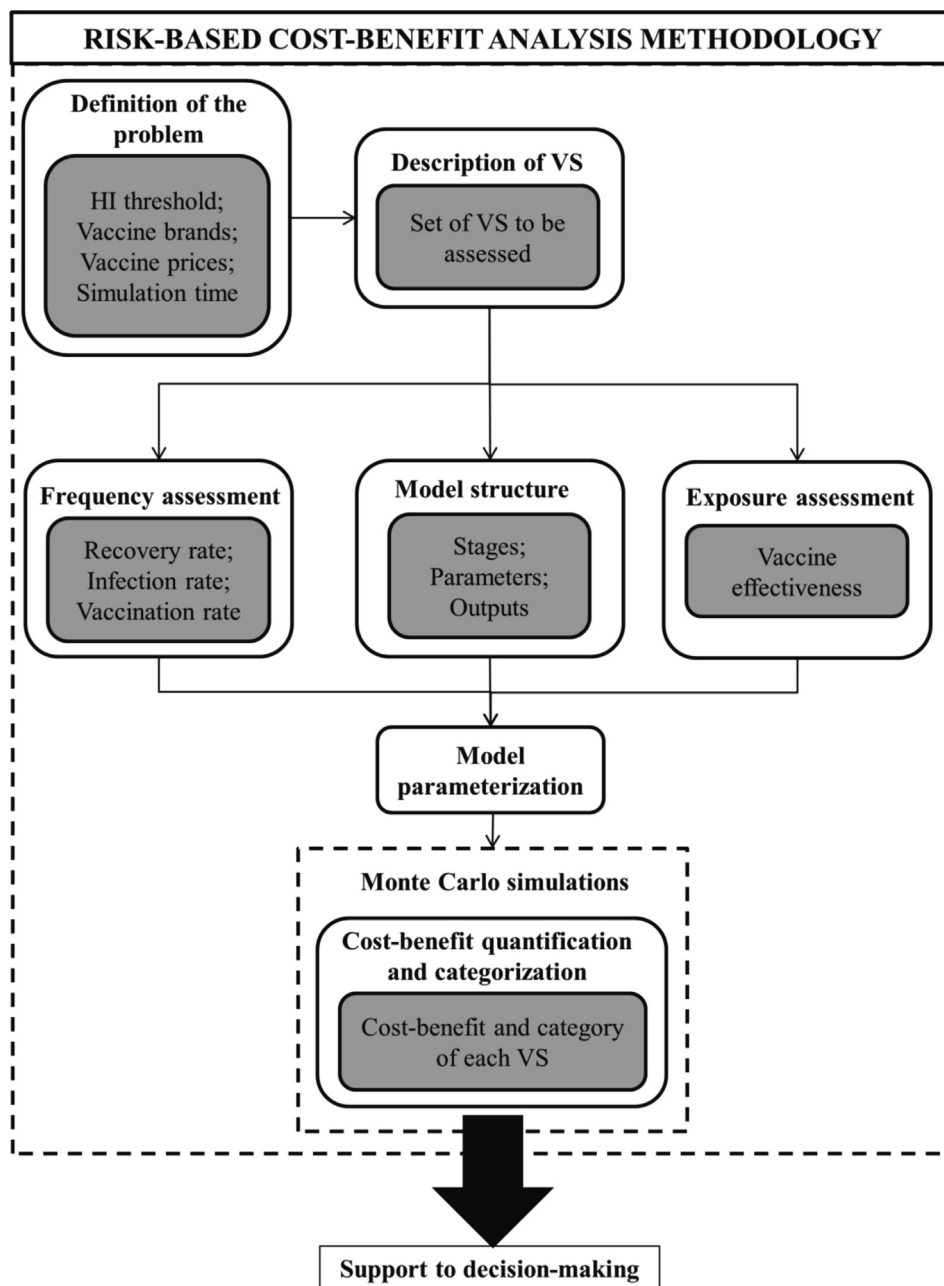


Fig. 1. Illustration of the RBCBA approach. The outputs of each step are in the grey boxes.

hypothesis (i.e., in the sense that they increase the time to HI) that Immunized individuals have 100% immunity against COVID-19 for at least 6 months [16,34].

The following matrix model estimates the population from a time step t to $t + 1$ (the model variables are described in Table 1):

$$\begin{bmatrix} S(t+1) \\ I(t+1) \\ V(t+1) \\ M(t+1) \end{bmatrix} = \begin{bmatrix} a_{11} & 0 & 0 & 0 \\ 0 & a_{22}(t) & 0 & 0 \\ 0 & 0 & a_{33}(t) & 0 \\ 0 & a_{42}(t) & a_{43}(t) & a_{44}(t) \end{bmatrix} \times \begin{bmatrix} S(t) \\ I(t) \\ V(t) \\ M(t) \end{bmatrix} - \begin{bmatrix} 0 \\ \alpha_2 * I(t) \\ 0 \\ 0 \end{bmatrix}$$

where a_{su} is the transition rate from state u to state s , and a_{uu} is the permanence rate in state u ($u, s \in \{1, 2, 3, 4\}$). For instance, a_{43} is the transition rate from Fully Vaccinated to Immunized, while a_{11} is the permanence rate in the Susceptible stage; α_2 is the mortality of infected individuals.

In population dynamics, resources are often limited in the environment. The modification in the influence of any factor that affects the population growth as the population density changes are known as Density-Dependence [2]. Analogously, the SARS-CoV-2 competes for susceptible people to infect. The more infected people, the fewer resources available for SARS-CoV-2 [40]. To model the infection rate as a function of the infected group at time t , we adopted the Contest-type DD that occurs when resources are shared unequally and randomly amongst the individuals, leading to the survival and reproduction of some at the expense of others [2].

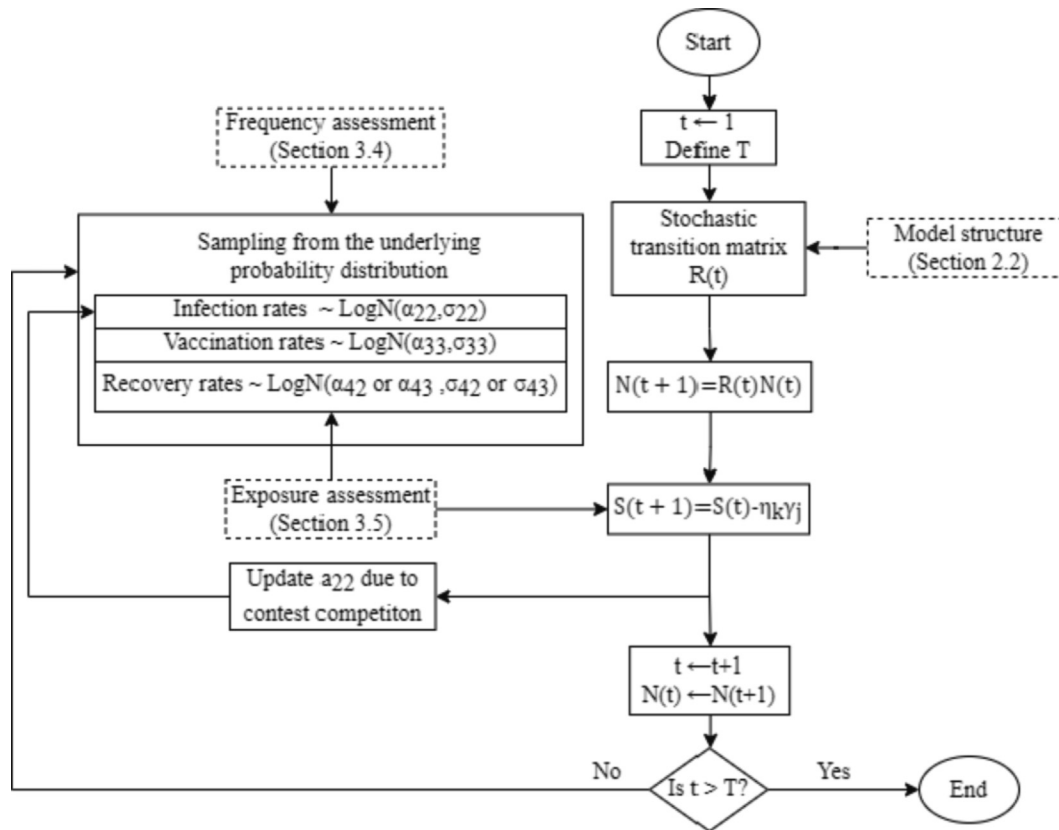


Fig. 2. A flowchart representing one out of 10,000 replications for the stochastic simulation of a given VS.

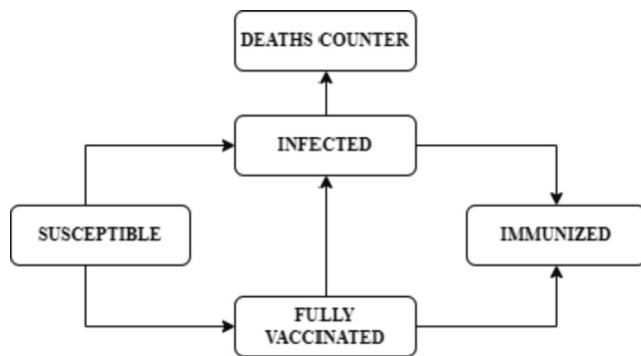


Fig. 3. Simplified schematic of the proposed model to assess the COVID-19 dynamics in Brazil under vaccination scenarios.

Then, the lower the size of the susceptible population exposed to the virus, the lower the infection rates. Hence, fewer resources would allow the virus to spread as it \ competes for susceptible bodies to infect until the host population reaches HI, making the

spread of the disease more unlikely. Such an approach for DD has recently been proposed in an epidemiological model for COVID-19 [40]. We model DD effect on the infection rate (a_{22}) through the Beverton-Holt equation [2]:

$$a_{22}(t) = \frac{\beta_{max,1} \cdot S(t)}{\beta_{max,1} \cdot I(t) - I(t) + S(t)} \tag{2}$$

where β_{max} is the maximum infection rate observed; $S(t)$ is the susceptible population, which is equivalent to a time-dependent Carrying Capacity (CC) for the number of infections, i.e., the maximum number of infections that can occur at time t . For a given VS, the weekly rate of vaccination is denoted by $\lambda_j (j = 1, 2, 3)$, a constant parameter. We can define a general equation (Eq. (3)) for the susceptible population at each time step, which decreases each stime step according to the vaccinated per week and the vaccine effectiveness:

$$S(t) = S(t - 1) - \eta_k * \lambda_j \tag{3}$$

During the pandemic, considering the time range of the data used in this work (from February 26th, 2020 to August 30th, 2021), several variants (e.g., Gamma, Delta) emerged with different

Table 1
Variables and initial conditions of the model.

Variable	Symbol	Description	Initial condition ($t = 0$) (in millions) (From the OWD database)
Number of susceptible individuals at time t	$S(t)$	The number of individuals who are not infected with COVID-19 and may become infected.	106.35
Number of infected individuals at time t	$I(t)$	The number of individuals who are infected with COVID-19.	20.78
Number of vaccinated individuals at time t	$V(t)$	The number of individuals who are fully vaccinated (two doses) against COVID-19.	62.7
Number of immunized individuals at time t	$M(t)$	The number of individuals who have immunity against COVID-19.	19.74

infection rates and vaccine resistance. The impact of these variants is incorporated into the assessment since the data used to estimate the infection rate (a_{22}) already entails the emergence of these variants in the history of cases. As a result of these variants, the variability of a_{22} increases, and so does the uncertainty of outcomes.

The Immunized individuals are originated after the second dose (a_{43}) based on the vaccine effectiveness (η_k), and after recovering from an infection (a_{42}). We acknowledge that our model accounts for uncertainty neither in vaccine effectiveness due to these variants nor in infection rates nor in vaccine effectiveness caused by variants that emerged after development of this model (e.g., Omicron). Other parameters are shown in Table 2, with a mean (μ) and a standard deviation (SD) (σ). The rationale for estimating them is further detailed in Section 3.3 (Model parameterization).

2.3. Cost-benefit categorization

In Quantitative Risk Assessment (QRA), risk categorization has been used to make communication easier (e.g., microbial QRA of human parasites that cause disease and death [12]). It transforms quantitative measures into qualitative risk classes and, then, helps inform the general public.

RBCBA results can be provided as a cost-benefit ratio; then, the higher the metric, the better that scenario [26,27]. However, these results are not given in categories that combine cost with benefit. Thus, in the lack of risk-based cost-benefit categories for vaccination programs, we propose three classes to ease the communication of the probability of achieving HI versus the cost (acquisition cost or deaths) (adapted from [13,40]):

- GOOD: the probability of reaching HI > 50% with half the maximum cost;
- FAIR: the probability of reaching HI > 50% with over half the maximum cost, or the probability of reaching HI < 50% with half the maximum cost;
- POOR: the probability of reaching HI < 50% with over half the maximum cost.

Table 2
Parameters of the model.

Parameter	Symbol	The data source or rationale	μ	σ
Infection rate	a_{22}	This parameter is a function of the susceptible population and the maximum infection rate registered. The SD was obtained from the OWD database.	See Equation (1)	0.010407
Vaccinated per week	λ_j	The number of people that receives the second dose weekly. It is estimated from the OWD database.	$\begin{cases} 2\text{million}, j = 1 \\ 4\text{million}, j = 2 \\ 6\text{million}, j = 3 \end{cases}$	–
Vaccination rate	a_{33}	It transforms the quantity denoted by λ_j into a weekly rate.	$\begin{cases} 1.02453, j = 1 \\ 1.03958, j = 2 \\ 1.05058, j = 3 \end{cases}$	0.02092, $j = 1, 2, 3$
Fatality rate	α_2	Estimated from the OWD database. See Section 4.4.	0.00084	0.00034
The recovery rate from infection	a_{42}	Typically, an infected individual that survives takes two weeks to recover [25]. $a_{42} = \frac{1}{2}(a_{22} - 1)(1 - \alpha_2)$	0.01640	0.00465
Vaccine effectiveness	η_k	The relative risk reduction of a vaccinated individual becoming infected compared to a non-vaccinated one [14,19,36].	$\begin{cases} 0.507, k = 1 \\ 0.790, k = 2 \\ 0.915, k = 3 \end{cases}$	$\begin{cases} 0.090, k = 1 \\ 0.071, k = 2 \\ 0.004, k = 3 \end{cases}$
The immunization rate from the vaccination	$a_{43}(t)$	The proportion of vaccinated individuals that acquires immunity through vaccination [38]. $a_{43} = (a_{33} - 1) * \eta_k$	$\begin{cases} 0.01244, j = 1, k = 1 \\ 0.01938, j = 1, k = 2 \\ 0.02245, j = 1, k = 3 \\ 0.02007, j = 2, k = 1 \\ 0.03127, j = 2, k = 2 \\ 0.03622, j = 2, k = 3 \\ 0.02564, j = 3, k = 1 \\ 0.03995, j = 3, k = 2 \\ 0.04628, j = 3, k = 3 \end{cases}$	$\begin{cases} 0.01155, k = 1 \\ 0.01692, k = 2 \\ 0.01944, k = 3 \end{cases}$
Permanence as Immunized	$a_{44}(t)$	We assume there is no immunity loss (author input).	1.0	–
Herd immunity threshold	p_{HI}	The percentage of the population required to achieve HI [17]. The number in parenthesis indicates the required number of Immunized individuals in Brazil.	70%(147.7million)	–

The main reason to propose those categories is that we can provide a broader outlook for all VSs. We focus not on the absolute cost-benefit of a specific VS, but rather on the relative cost-benefit among VSs. Thus, one can identify the best cost-benefit to prioritize, following the categorization and proper comparison.

3. Results

This section illustrates the application of the proposed RBCBA approach to the specific case of COVID-19 in Brazil and the vaccines CV, AZ, and PF from August 31st 2021 to March 3rd 2022. The input data for the model were collected from February 26th, 2020 to August 30th, 2021, in Brazil from a public database i.e., the Our World in Data (OWD) COVID-19 database [33]. Next, we present the detailed results of each step of the RBCBA.

3.1. Definition of the problem

The main goal of performing RBCBA is to provide helpful information to health managers in Brazil regarding the relative cost-benefit of CV, AZ, and PF in hypothetical VSs, where a single brand would be used in the entire mass vaccination program. We consider the cost of each vaccine in Brazil as deterministic values since no variability among prices was found, as follows [30]:

- CoronaVac: US11.20 per dose;
- AstraZeneca: US3.16 per dose;
- Pfizer: US12.00 per dose.

When a population is near the HI threshold, the infections are kept under control since it is harder for the virus to find susceptible hosts [45]. We addressed this behavior in our model, considering that infections could be modeled as a Contest-type competition (Section 2.2).

3.2. Description of vaccination scenarios

We processed the input data and estimated that 2 million people on average receive the second dose of vaccines per week, and

we denote this parameter as λ_2 [33]. We can also assess different VSs by changing this rate; Table 3 summarizes the VSs. For instance, VS AZ-3 considers only the application of the AZ vaccine at a rate $\lambda_3 (= 3\text{million second doses per week})$.

3.3. Model parameterization

Tables 1 and 2 summarize the model’s variables, parameters, and initial conditions. The stochastic parameters are those with non-zero standard deviation (σ column in Table 2). We can estimate the infection, fatality and vaccination rates from the OWD database [33]. Furthermore, we found the mean time taken to recover from an infection [25] and the vaccine effectiveness [38].

Stochasticity is a vital model feature. Hence, we can treat the model parameters as random variables rather than deterministically, accounting for natural fluctuations and uncertainty. We can use a Lognormal probability distribution, parameterized by mean (μ) and standard deviation (σ) [2]. The rationale for using this distribution is that it does not allow negative values; thus, we have physically coherent values for the parameters.

3.4. Frequency assessment

The infection rates are the frequencies at which new infections occur. Likewise, the vaccination and fatality rates account for vaccinations and deaths at each time step respectively. We can estimate these weekly rates by processing the data [33] through an iterative process to remove outliers, i.e., points that lie beyond a 99.7% confidence interval ($\mu \pm 3\sigma$). The algorithm to perform this process can be found in the supplementary material. Table 1 defines the vaccination rates for each VS, while Table 2 shows the final mean and SD values of these parameters.

The recovery rates (a_{42}, a_{43}, a_{44}) (i.e., the daily transition rate to the Immunized stage) can be estimated based on the infection period of those who develop symptoms and the vaccine’s effectiveness. During the reviewing process of this paper, new light was shed concerning the mean recovery time, i.e., about 5 days of quarantine would be enough to avoid transmitting the disease [10]. Still, we consider a conservative assumption to take the recovery time as 14 days [25]. After two weeks, it is improbable that an infected individual would still be in the transmission period. Thus, we estimated the mean recovery rate $\alpha_{42} = (\frac{1}{2\text{weeks}}) * (1 - \alpha_2)(a_{22} - 1)$.

We estimated the immunization rate due to vaccination as a function of the vaccination rate and the vaccine’s effectiveness, i.e., $a_{43} = (a_{33} - 1) * \eta_k$. Then, we consider that only a portion of the vaccinated will gain immunity based on each vaccine’s effectiveness. As new studies suggest that individuals acquire immunity against new infections for at least one year after infection, we assume there is no waning immunity throughout the simulation (i.e., 26 weeks) [16,34]. Thus, we assume this rate as $a_{44} = 1.0$, Table 2 presents these parameters.

Table 3
Summary of VSs, which combine the vaccine with the second dose application rate.

Vaccine	Weekly second doses application rates		
	$\lambda_1 (= 1\text{million})$	$\lambda_2 (= 2\text{million})$	$\lambda_3 (= 3\text{million})$
CoronaVac	CV-1	CV-2	CV-3
AstraZeneca	AZ-1	AZ-2	AZ-3
Pfizer	PF-1	PF-2	PF-3

3.5. Exposure assessment

The vaccine effectiveness (η_k) is a measure of the proportional reduction (relative risk drop) of the specific outcome of interest (e.g., becoming infected) among vaccinated individuals compared to unvaccinated ones under real-world conditions, such as in phase IV studies [38]. Table 4 summarizes the conservative effectiveness, i.e., the lowest effectiveness found in the literature. Although the effectiveness is given within a confidence interval (CI), we consider this rate deterministically, using the value in the Effectiveness column.

3.6. Cost-benefit quantification and categorization

The main result of our assessment is the cost-benefit graph presented in Fig. 4. The summary of the cost-benefit analysis is also shown in Table 5. We provide the expected values for the benefit, the acquisition cost, and the number of deaths. The supplementary material offers the infections, deaths, and probability of reaching HI during the six-month simulation for all VSs (Figs. A1–A3).

The vaccination strategy AZ-3 is the only labeled as GOOD, providing the best cost-benefit compared to the others. The strategy PF-3 offers the best overall benefit. However, it is expensive, which results in the FAIR category. On the other hand, AZ-1 and AZ-2, both categorized as FAIR, are cheaper, but their probability of reaching HI is low. When considering cost as the expected deaths in the assessment (Fig. 4B and Table 5), it does not vary significantly amongst the VSs. However, there are substantial differences in the probabilities of reaching HI. Note that due to uncertainty bounds, the VS can have two categories. Since the acquisition costs are deterministic values, we do not observe a VS in more than one category. The strategies PF-3 and AZ-3 present the best cost-benefit in this case, with the highest probabilities, and should be prioritized.

As the strategies AZ-3 and PF-3 are the most cost-beneficial in both dimensions, labeled from FAIR to GOOD, we maintained them for one year (6 months longer than the initial simulation) and evaluated the impacts on infections and deaths. We also included a ‘No Vaccines’ scenario to assess the probability of reaching HI without vaccination. Fig. 5 depicts the results, where the lines represent the expected values and the vertical bars correspond to 68.3% CI ($\mu \pm \sigma$). Fig. 5A only shows the probability of achieving HI within one year. Each point in the graph indicates a Y% cumulative probability of achieving HI until time step T.

We can see that achieving HI in a scenario without vaccination is unlikely. Note that the number of Immunized in a ‘No Vaccine’ scenario remains below the HI threshold (Fig. 5B). The recoveries progress faster with vaccination, and HI is reached more quickly. For both VSs, the infections (Fig. 5C) reach a steady level after some time (approximately 39 weeks for AZ-3 and 35 weeks for PF-3). Then, the spread of the disease is expected to be under control from that point.

We can highlight the following outcomes:

- CV: This scenario presents the worst cost-benefit, with categories ranging from POOR to FAIR for all VSs.

Table 4
Effectiveness of the primary vaccines applied in Brazil.

	Effectiveness	95% CI	Source
CoronaVac	50.7%	(33%, 62.5%)	[14]
AstraZeneca	79%	(65%, 88%)	[36]
Pfizer	91.5%	(90.7%, 92.2%)	[19]

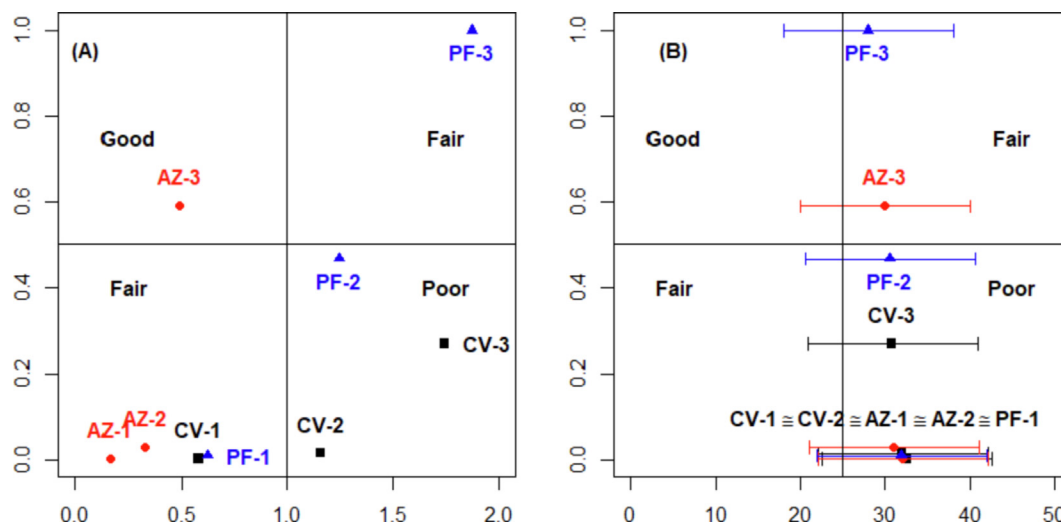


Fig. 4. Cost-benefit charts for each vaccination strategy. (A) Cost as the acquisition cost in billions of US\$. (B) Cost as thousands of new deaths.

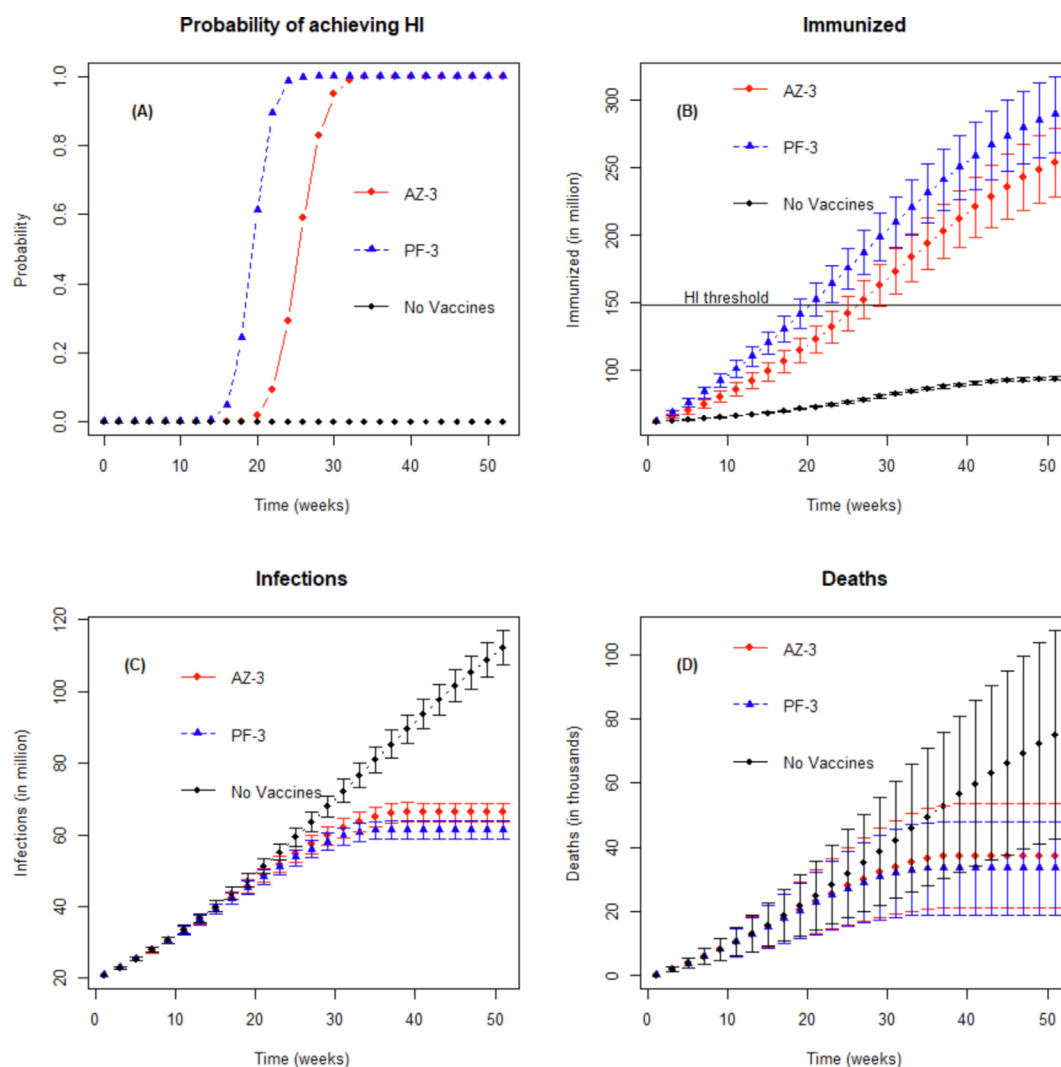


Fig. 5. Main outputs of the model. (A) Probability of achieving HI, (B) Immunized, (C) Infections, and (D) new deaths for AZ-3 and PF-3 applied during one year. We also simulated a No Vaccines scenario, represented by the black lines.

Table 5
Top-to-bottom ranking of the cost-benefit VSs. The VSs within the same category are ranked according to the highest benefit.

VS	Benefit	Cost	Category	VS	Benefit	Cost	Category
		(billion US\$)				(thousands deaths)	
AZ-3	0.589	0.493	GOOD	PF-3	0.999	28.005	FAIR TO GOOD
PF-3	0.999	1.872	FAIR	AZ-3	0.589	29.936	FAIR TO GOOD
AZ-2	0.029	0.329	FAIR	PF-2	0.466	30.606	POOR TO FAIR
PF-1	0.009	0.624	FAIR	CV-3	0.268	30.852	POOR TO FAIR
AZ-1	0.002	0.164	FAIR	AZ-2	0.029	31.030	POOR TO FAIR
CV-1	0.002	0.581	FAIR	CV-2	0.015	32.084	POOR TO FAIR
PF-2	0.466	1.248	POOR	PF-1	0.009	32.015	POOR TO FAIR
CV-3	0.268	1.744	POOR	AZ-1	0.002	32.104	POOR TO FAIR
CV-2	0.015	1.163	POOR	CV-1	0.002	32.630	POOR TO FAIR

- AZ: the best one when the priority is to optimize acquisition costs. AZ-3 was the only GOOD cost-benefit when considering the acquisition costs. Compared to PF-3, the costs are reduced by approximately 73.67% (expected savings of US1.38bi).
- PF: the best one to minimize deaths and, then, quickly reach HI. PF-3 was the only strategy that almost guaranteed (99.9% probability) reaching HI within 26 weeks, against 58.9% for AZ-3. Also, compared to AZ-3, the number of deaths in PF-3 was reduced by 3.3% (i.e., expected 930 fewer deaths).
- Vaccination programs should be carried out to ensure the population will reach HI. The simulations indicate that it is impossible to reach such a level only with the immunized from the infections.

4. Discussion

The main advantage of the cost-benefit analysis we performed is the stage-structured probabilistic epidemiological model that evaluates the infection dynamics under several VSs. Our model parameters are stochastic: they can account for parameter variability and uncertainty, propagate uncertainty in results, and support decision-making under uncertainty. The proposed risk-benefit categories can simplify communicating the results to health authorities and decision-makers. The model is flexible and can be adapted to apply to other pandemics or epidemics or in other countries when vaccines are available to the population. Thus, the application of the method is not limited to the case of Brazil.

However, we acknowledge some limitations of our model. Our assessment is restricted only to vaccines' acquisition cost. It does not consider additional costs to maintain a VS, such as logistics (e.g., transportation, storage) and operational costs (e.g., human resources for vaccine application). We claim that these additional costs would be similar whichever brand of vaccine is evaluated. Despite recent studies suggesting a waning immunity [48], we did not assess this factor on the results and the need for booster

doses. The model's flexibility allows updating this parameter as new information arises though.

New studies provide that recovery time is shorter than our assumption. Considering this new value, we could expect a faster growth of Immunized individuals and higher HI probabilities. The effects of variants that emerged until the time this model was developed are considered in the variability of infection rates and, then, in the uncertainty of results. However, the model does not feature variability in the vaccine effectiveness (η_k). We did not assess and compare the risks of possible common (e.g., injection pain site, fatigue) and rare (e.g., thrombosis) side effects [47] on individuals caused by the vaccines.

We acknowledge that, in practice, different brands of vaccines are used simultaneously in vaccination programs. Still, we aim to assess and track separately the leading brands' cost-benefit. This result does not mean that a country should only administer one brand of the vaccine, but that they will have helpful information to make an informed decision and, then, answer a few questions. For instance, which vaccine to prioritize concerning a specific objective: to minimize cost or time to achieve HI; a basis for negotiating the purchase price of each vaccine with the supplier by furnishing the actual cost-benefit of their vaccine brand for the country, rather than relying on the information provided by producers. Thus, although these scenarios (applying different brands of vaccines simultaneously) are closer to reality, they would not be helpful for the purposes of this work (i.e., comparison between market leaders).

We consider in our assessment the costs concerning the acquisition of the vaccines and the number of fatalities. Although we only provide optimal results considering these two dimensions separately, we acknowledge that the decision-making process under these circumstances is a challenging task. Invariably, ethical conflicts may arise in decision-making contexts involving public funds (i.e., funds that should be allocated equitably among individuals)[6]. Health demands outweigh available resources and, therefore, decisions based on specific ethical values need to be taken.

Hence, it is a choice made by decision-makers to prioritize the purchase of low-cost vaccines, but that reflects in fewer lives saved or those that, despite committing a greater portion of the public budget, would be more beneficial to public health. Such decisions, for example, could be guided by the principles of public utility and equity, so the limit between the cost covered by the state and the benefit is satisfactorily achieved [43].

5. Conclusions

We have performed an RBCBA of mass vaccination to cope with the COVID-19 pandemic in Brazil, considering the main vaccines being administered: CoronaVac, AstraZeneca, and Pfizer. We evaluated the costs as both the acquisition costs and the number of deaths and the benefit as the probability of reaching HI. We quantified and categorized the cost-benefit for each of the three brands, considering three application rates, totaling nine VSs. Therefore, we provide helpful information that can aid decision-makers and public health authorities in prioritizing the acquisition of the best brands and VSs. Also, we acknowledge that decision-making considering these aspects (i.e., acquisition costs and expected deaths for a VS) may face some ethical issues, and decisions must be taken with care.

The results emphasize the need of mass vaccination to cope with the pandemic, which makes the population to reach HI faster. Furthermore, our approach is not restricted to Brazil, nor the COVID-19 pandemic, nor the three mentioned vaccine brands. The method is flexible so that this study can be a valuable reference for future RBCBAs in other countries and pandemics, especially in the early stages of vaccination programs, when data is scarce, and uncertainty is high.

We performed an RBCBA that presents a few shortcomings: (i) the variability and uncertainty in the vaccine effectiveness due to COVID-19 emerging variants is not addressed; (ii) we have not combined different vaccine brands in VSs; and (iii) we assumed a conservative recovery time, which impacts the evolution of Immunized and decreases the benefit (i.e., it rises the time to HI). For future works, we propose: accounting for variability and uncertainty in the vaccine effectiveness parameter due to the emergence of new variants, which can be done by modeling η_k as a random variable; and combining different vaccine brands in integrated VSs, which can be done by averaging the effectiveness weighted according to the portion of each vaccine brand in the VS.

Authors Contribution

PGS and HOD conceptualized and defined the aims of the study. PGS, under the guidance of HOD, collected and processed the data, constructed the probabilistic model, performed all the simulations and drafted the first version of the manuscript. HOD and MCM contributed to the writing and critical revision of the manuscript. All the authors contributed to the interpretation of the results and approved the final version of the manuscript.

Funding

This research was funded by the Humans Resource Program (PRH 38.1) entitled “Risk Analysis and Environmental Modeling in the Exploration, Development, and Production of Oil and Gas”, managed by the Brazilian Agency for Petroleum, Natural Gas and Biofuels (ANP) and the Brazilian Funding Authority for Studies and Projects (FINEP). This study was also financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – Brasil (CAPES), Fincance Code 001.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.vaccine.2022.05.038>.

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