Vaccine 40 (2022) 6616–6624

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Modelling optimal vaccination strategies against COVID-19 in a context of Gamma variant predominance in Brazil

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ARTICLE INFO

Article history:
Received 25 June 2022
Received in revised form 21 September 2022
Accepted 23 September 2022
Available online 3 October 2022

Keywords:
Modelling
COVID-19
Immunization
Vaccines

ABSTRACT

Introduction: Brazil experienced moments of collapse in its health system throughout 2021, driven by the emergence of variants of concern (VOC) combined with an inefficient initial vaccination strategy against Covid-19.
Objectives: To support decision-makers in formulating COVID-19 immunization policy in the context of limited vaccine availability and evolving variants over time, we evaluate optimal strategies for Covid-19 vaccination in Brazil in 2021, when vaccination was rolled out during Gamma variant predominance.
Methods: Using a discrete-time epidemic model we estimate Covid-19 deaths averted, considering the currently Covid-19 vaccine products and doses available in Brazil; vaccine coverage by target population; and vaccine effectiveness estimates. We evaluated a 5-month time horizon, from early August to the end of December 2021. Optimal vaccination strategies compared the outcomes in terms of averted deaths when varying dose intervals from 8 to 12 weeks, and choosing the minimum coverage levels per age group required prior to expanding vaccination to younger target populations. We also estimated dose availability required over time to allow the implementation of optimal strategies.
Results: To maximize the number of averted deaths, vaccine coverage of at least 80 % should be reached in older age groups before starting vaccination into subsequent younger age groups. When evaluating varying dose intervals for AZD1222, reducing the dose interval from 12 to 8 weeks for the primary schedule would result in fewer COVID-19 deaths, but this can only be implemented if accompanied by an increase in vaccine supply of at least 50 % over the coming six-months in Brazil.
Conclusion: Covid-19 immunization strategies should be tailored to local vaccine product availability and supply over time, circulating variants of concern, and vaccine coverage in target population groups. Modelling can provide valuable and timely evidence to support the implementation of vaccination strategies considering the local context, yet following international and regional technical evidence-based guidance.

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https://doi.org/10.1016/j.vaccine.2022.09.082
0264-410X/

1. Introduction

By the end of 2021, Brazil had reached over 600,000 deaths due to Covid-19, ranking second in the world for the absolute number of Covid-19 deaths [1]. Brazil's first Covid-19 case was identified in March 2020, and the first wave of the epidemic on a national level peaked in July and lasted until October 2020, when>5 million confirmed cases and at least 150.000 deaths had been registered [2]. The downward trend that lasted 16 weeks ceased in late November 2020, when a new rise in cases and deaths was observed [3]. This coincides with the detection of new variants of concern (VOC) in the country, challenging Brazil's Universal Health Care System (SUS) and the government's public response. As the fifth-largest world country, Brazil presented multiple and different epidemic curves according to the transmission of SARS-CoV-2 between regions in 2020, progressively reaching countryside smaller cities and developing a national synchronization process between 2020 and 2021 where epidemics caused by VOC including Delta and Gamma were important drivers of sustainable viral transmission in the population [4,5]. The Gamma variant (*P*1 lineage or GR/501Y.V3), first identified in Brazil [3], spread throughout the country before the national vaccination campaign that started in January 2021, resulting in numerous surges throughout the country [5]. In the tenth epidemiological week (EW) of 2021, there was an impressive number of 40,797 hospital admissions at a national level, representing a 2-fold increase when compared to the worst week of the epidemic in 2020 (EW 28) [6].

Brazil's Covid-19 national vaccination rollout started on late January 2021, following the prioritization strategy recommended by the World Health Organization (WHO) [7], initially targeting health care professionals, older adults, and people with comorbidities. The vaccination pace started and progressed slowly from January to March 2021, restricted by limited vaccine availability in the country. The average number of daily doses administered was around 200,000, much smaller than the daily doses of influenza administered during national campaigns in previous years. Only after April did the daily number of vaccines administered reached 700 thousand [8]. Covid-19 vaccines registered and in use in Brazil include AZD1222 (AstraZeneca/Oxford/Fiocruz), a viral vector platform vaccine, in a 2-dose primary schedule initially administered with 8-weeks dose-interval; BNT162b2 (Pfizer/BioNTech), a two-dose mRNA vaccine, also initially administered with 8-weeks dose-interval; CoronaVac (Sinovac/Butantan), a 2-dose inactivated virus vaccine, administered with a 4-weeks dose-interval; and Ad26.COV2.S (Janssen) a single dose viral vector vaccine.

National vaccination rollout and strategy were determined during the context of high first-dose efficacy against the original wild-type virus strain [9–11]. With the emergence of new VOCs and amid an intense second wave of the pandemic, in late August 2021, the Brazilian Ministry of Health (MoH) opted to extend the dose interval of 2 of the available vaccines at the time (AZD1222 and BNT162b2 vaccines) to 12 weeks, following WHO recommendations [12,13]. The objective was to increase the number of vaccinated high-risk individuals with at least one dose, thus increasing the population-level impact in the context of limited global vaccine supply.

Differently from what would be expected in a country with a robust National Immunization Program, Covid-19 vaccination in Brazil has faced several obstacles. These included a lack of national coordination and support for evidence-based decision-making, inconsistent vaccine supply, and availability over time, limited social communication strategies, and widespread misinformation about vaccine safety and efficacy in social networks. In addition, the anti-vax movement in the country has been gaining strength during the pandemic [14]. From the operational point of view, decisions about the Covid-19 vaccination rollout were scattered, with different vaccination strategies being adopted at state and municipal levels due to lack of central coordination. As such, vaccines were progressively made available to adults without increased risk conditions, by age, irrespective of vaccine coverage levels reached in priority risk populations. One critical point is that, in this age-based strategy, a minimum coverage goal set by age group was not established before the vaccine was made available for younger groups. This progression was based on an arbitrary temporal criterion of vaccination campaign (for example, a one-week period designated for each age group), varying by state and municipality.

To support decision-makers in formulating a COVID-19 immunization policy that prioritizes minimizing the number of deaths in the population in the context of limited vaccine availability, and evolving variants over time, we evaluate optimal strategies for Covid-19 vaccination in Brazil in 2021, when vaccination was rolled out during Gamma variant predominance.

We specifically aim to address three programmatic questions: a) what should be the minimum vaccination coverage of an age group before starting vaccination in a subsequent younger group?; b) What should be the ideal interval between doses of AZD1222 vaccine that would result in maximizing the number of averted deaths (considering intervals between 8 and 12 weeks, assuming available vaccine supply over time?; and finally, c) what is the minimum number of AZD vaccine doses to be made available over time that will allow the implementation of the optimal interval between doses?

2. Methods

2.1. Data inputs and sources

The following Covid-19 vaccines registered for use and introduced in Brazil were considered: AZD1222 (AstraZeneca/Oxford/Fiocruz), CoronaVac (Sinovac/Butantan), and BNT162b2 (Pfizer/BioNTech). Since our goal is to estimate optimal strategies considering the interval between vaccine doses, we have not included the Ad26.COV2.S vaccine in the model, as this is a single dose vaccine, and given the very small number of individuals that received or will receive this vaccine (4.5 million people out of 211 million people, representing<2 % of the population).

We obtained the number of vaccinated individuals from Brazil's National Immunization Program Information System (SI-PNI) (up to Sept 8th, 2021) which contains anonymized information of each vaccinated individual in Brazil, including vaccine product, dose, vaccination date, and age of vaccine recipient [8].

We considered the number of vaccine doses procured by the Brazilian MoH and anticipated to be delivered by the end of 2021 [8]. The time-horizon considered was 5 months, from Aug 9th to Dec 31st 2021, as this was the period for which data on vaccine dose availability was available. Since the number of doses is projected by month or quarter, we assume a constant rate of vaccine delivery or production (for locally produced vaccines), distribution, and administration rates in each time interval considered in the model (See Supplementary material, SM). We then estimated the number of individuals who would receive one or two vaccine doses by product, for each age group, during the study time horizon, as well as the time elapsed since receiving the first-dose at each point in time. These data were inputted into the model, further described in the next section.

2.2. Model structure and assumptions

We developed a simplified discrete-time disease transmission model, in which we assumed a constant probability of infection. Infection transmission dynamics are encoded in a transition matrix that provides the proportion of individuals moving through model compartments daily [15]. Model structure is an extended SEIR compartmental model [16], accounting also for asymptomatic, hospitalized, and deceased individuals, thus described as SEAIRHD [17]. The model is structured in 10-year age sub-groups. The structure is replicated for vaccine product (AZD1222, CoronaVac, and BNT162b2), and dose (first and second dose), with vaccines then modelled simultaneously (see Fig. 1).

The vaccination rollout is modeled following an age-based priority rule. Older individuals are the ones initially eligible for vaccination. After achieving the desirable coverage (defined by the scenario studied) in the older age group, the next younger age group (following 10-year bins) is made eligible for vaccination. This procedure follows until depletance of unvaccinated individuals or time. When multiple age groups are eligible for vaccination, the proportion of doses allocated to each age group is defined by the number of unvaccinated individuals in each age group. For more details see the SM.

To estimate the number of vaccine doses that should be allocated for the first or second dose, we use a modified version of the dose optimization model developed previously and described in further detail elsewhere [17], that accounts for varying vaccine production and deployment rates, as well as individuals vaccinated with only one dose (see further details on the SM). This optimization model calculates the number of first or second doses administered by day, given a pre-specified production rate and dose interval, minimizing the number of doses that should be kept in stock while guaranteeing that individuals receive the second dose in a timely manner.

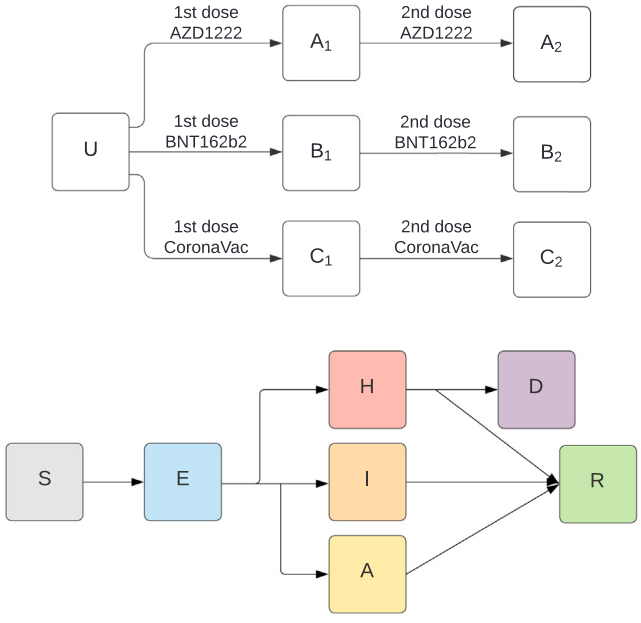

Fig. 1. Model Structure. The first diagram (**Top**) describes vaccination pathways. U accounts for unvaccinated individuals; A, B, and C accounts for individuals vaccinated with AZD1222, BNT162b2, and CoronaVac, respectively. The subscripts account for the first (1) or second (2) dose. The second diagram (**Bottom**) describes the infection pathways. A susceptible (S) individual is transferred to a pre-symptomatic (or exposed, E) compartment after infection. After the incubation period, the individual evolves into an asymptomatic (A), mild (I), or severe (H) infection. The individual eventually recovers (R) or dies (D), if severe. The infection diagram is repeated for every vaccination status.

We assumed a single model for the whole country. We also assume that after initially targeting high-risk populations, vaccination rollout was expanded over time, following a decreasing age-prioritization strategy. We considered the number of administered doses by vaccine over time as being proportional to the total number of doses of each vaccine made available at the time of vaccination. We considered that the vaccination rate in each age group is proportional to the unvaccinated population in this group (more details in the SM).

We limited the analysis of optimal inter-dose time interval (and the required dose supply) to AZD1222 for the following reasons: 1) there is no evidence to support the use of CoronaVac vaccine in a longer interval than the recommended four weeks; 2) BNT162b2 vaccine used in Brazil, differently than AZD1222 and CoronaVac, is imported and not produced locally, and as such, there is no possibility of expanding production and distribution capacity. Further, at the time of our modelling, there was no data on BNT162b2 effectiveness against the Gamma variant. Also, we considered 8–12-week intervals between doses, as recommended in current guidelines (11).

2.3. Model parameters and scenarios considered

We considered four scenarios of infection probability: very low, low, medium, and high (assuming SARS-CoV-2 infection probability, including asymptomatic infection, of 0.0001, 0.0025, 0.005, and 0.01, respectively). These values were chosen by the authors as the probability of infection was unknown in Brazil in the period evaluated. We also considered an additional scenario of age-dependent probability (yet, constant on time) of infection. We used the average number of daily contacts an individual might experience due to their age from the work described in [18] to compute a population-weighted probability of being infected of 0.01 to facilitate comparison with the high transmission scenario. More details in the SM.

Since Brazil does not have systematic serological inquiries, the exact SARS-CoV-2 prevalence in the population at the time of modelling was unknown. We assumed the percentage of recovered individuals at the start of the simulation period drawing from a uniform distribution ranging from 40 % to 60 %, based on existing seroprevalence estimates [19,20].

Vaccine effectiveness estimates were obtained from the literature, according to the best available evidence. The effectiveness estimates for CoronaVac, AZD1222, and BNT162b2 vaccines stratified by age, outcome, and vaccine dose considered in this study are presented in Tables 1, 2, and 3, respectively. We considered estimates reported by Cerqueira-Silva et al. [21], who evaluated AZD1222 and CoronaVac effectiveness in Brazil during Gamma predominance, in a retrospective cohort of>60 million individuals. Considering the available evidence, we assumed CoronaVac effectiveness against SARS-CoV-2 infection to be zero, as it is an inactivated vaccine [22]. We draw the values of the effectiveness of the vaccines from the Beta distributions that obey the confidence interval of each estimate.

Each scenario of the infection probability and vaccination strategy considered are simulated with the same values of seroprevalence and vaccine effectiveness, thus ensuring the comparability of strategies. Each scenario was run using 500 combinations of values for each result shown in the next section.

3. Results

Results are presented below considering three programmatic questions addressed by our modelling.

What should be the vaccination coverage of an age group before starting vaccination in a subsequent younger group?

Table 1
CoronaVac vaccine effectiveness against Gamma Variant of Concern, by outcome, age group, and vaccine dose.

Outcome	Age group	One-dose effectiveness (% and 95 % confidence interval)	Two-doses effectiveness (% and 95 % confidence interval)	Reference
Asymptomatic Infection	All	0*	0*	Assumed
Symptomatic disease	All	16 (14–18)	67 (65–69)	Jara et al. [34]
Hospitalisation	< 60	33.7 (27.1–39.7)	84.2 (81.3–86.7)	Cerqueira-Silva et al. [21]
Hospitalisation	60–69	29.5 (25.8–33.0)	78.2 (76.3–79.8)	Cerqueira-Silva et al. [21]
Hospitalisation	70–79	32.5 (29.9–35.1)	74.0 (72.6–75.4)	Cerqueira-Silva et al. [21]
Hospitalisation	80–89	8.2 (2.1–13.8)	63.0 (59.9–66.0)	Cerqueira-Silva et al. [21]
Hospitalisation	> 90	0*	32.7 (22.8–41.3)	Cerqueira-Silva et al. [21]
Death	< 60	41.7 (26.4–53.9)	70.5 (51.4–82.1)	Cerqueira-Silva et al. [21]
Death	60–69	35.7 (30.3–40.7)	76.5 (66.9–83.3)	Cerqueira-Silva et al. [21]
Death	70–79	38.2 (34.7–41.5)	78.7 (76.6–80.0)	Cerqueira-Silva et al. [21]
Death	80–89	10.1 (2.7–10.7)	67.3 (63.6–70.6)	Cerqueira-Silva et al. [21]
Death	> 90	0*	35.4 (23.8–45.1)	Cerqueira-Silva et al. [21]

*CoronaVac effectiveness against asymptomatic infections is considered zero in this model.
**Confidence intervals including zero or negative results were considered zero (0) in this table.

Table 2
AZD1222 vaccine effectiveness against Gamma Variant of Concern, by outcome, age group, and vaccine dose.

Outcome	Age group	One-dose effectiveness (% and 95 % confidence interval)	Two-doses effectiveness (% and 95 % confidence interval)	Reference
Asymptomatic Infection	All	63.9 (46–75.9)	59.9 (35.8–75.0)	Voysey et al. [35]
Symptomatic disease	< 60	50 (27–66)	100**	Nasreen et al. [36]
Symptomatic disease	> 60	33.4 % (26.4–39.7)	77.9 % (69.2–84.2)	Hitchings et al [37]
Hospitalisation	< 60	64.1 (62.6–65.5)	94.2 (89.8–96.6)	Cerqueira-Silva et al. [21]
Hospitalisation	60–69	44.9 (42.4–47.4)	91.7 (84.3–95.6)	Cerqueira-Silva et al. [21]
Hospitalisation	70–79	32.9 (25.2–39.8)	88.4 (84.6–91.2)	Cerqueira-Silva et al. [21]
Hospitalisation	80–89	32.9 (28.0–37.4)	86.9 (84.9–88.7)	Cerqueira-Silva et al. [21]
Hospitalisation	> 90	0*	54.9 (35.4–68.5)	Cerqueira-Silva et al. [21]
Death	< 60	64.8 (61.8–67.6)	93.3 (72.1–98.4)	Cerqueira-Silva et al. [21]
Death	60–69	45.4 (41.0–49.4)	89.6 (71.8–96.2)	Cerqueira-Silva et al. [21]
Death	70–79	37.1 (26.9–45.8)	92.5 (88.1–95.3)	Cerqueira-Silva et al. [21]
Death	80–89	38.1 (32.2–43.4)	91.2 (89.1–92.9)	Cerqueira-Silva et al. [21]
Death	> 90	0*	70.5 (51.4–82.1)	Cerqueira-Silva et al. [21]

* Negative results were considered zero (0) in this table.
** Considered 99% in this model.

We calculated the excess number of Covid-19 deaths resulting from initiating vaccination in a younger age group given that a specific coverage threshold in the older group was achieved. We compared these values to the number of deaths that to that resulted from the strategy that only initiated vaccination on the younger age group once the older age group was fully vaccinated. As shown in Fig. 2, the lower the vaccination coverage reached in older age groups, the greater the estimated excess of deaths, regardless of the probability of infection. Furthermore, vaccine coverage of at least 90 % is necessary for a minimal excess of deaths to be reached, varying from 11 (95 %CI: 8–13) to 886 (95 %CI: 638–1,095), depending on the probability of infection. Nevertheless, starting vaccination in a younger age group when at least 80 % of vaccination coverage had been reached in older age groups resulted in a third of excess Covid-19 deaths compared to starting vaccination when only 40 % coverage had been reached, as shown in Fig. 2. The magnitude of the impact varies by the probability of infection, being smaller when the probability of infection is lower. The estimates for all values of threshold are presented in the SM.

What should be the ideal interval between doses of AZD1222 vaccine that would result in the greatest impact (considering intervals between 8 and 12 weeks), assuming available vaccine supply over time?

Although the results of our model show that a 90 % vaccine coverage rate is the minimal coverage required in older age groups before expanding vaccination to younger age groups, ~~in order~~ to reduce excess deaths to minimum levels we consider a conservative estimate of 80 % as a feasible target. We then estimated the difference in Covid-19 deaths estimated when considering AZD1222 vaccine schedules with different dose intervals (8, 9, 10, and 11 weeks) compared to the standard initially recommended 12-week interval (Fig. 3). We assumed a scenario without limitation of AZD1222 vaccine supply, i.e., we ran the model assuming a number of doses up to ten times higher than the number of AZD1222 doses currently and projected to be made available during the study time-horizon. We found that the lower dose-interval of 8 weeks leads to a greater reduction in the number of Covid-19 deaths, varying from 100 (95 %CI: 64–134) deaths averted in the lower probability of infection scenario to 10,024 (95 %CI: 6,700–13,404) in a scenario of a high probability of infection. All estimates are presented in the SM.

This result leads to whether the strategy of using a lower dose-interval for AZD1222 would be effective considering the currently projected vaccine supply (until the end of 2021). We observe that vaccine supply over time is a bottleneck to the strategy of dose-interval reduction, as the reduction in deaths is negligible regardless of the probability of infection, in the scenario of the current vaccine supply (Fig. 4).

What is the minimum number of AZD vaccine doses to be made available over time that will allow the implementation of the optimal interval between doses?

Considering the different dose-intervals for the AZD1222 vaccine, we estimate that the number of vaccine doses administered had to be increased by at least 50 % to avoid supply bottlenecks and result in a significative reduction of Covid-19 deaths (Fig. 5). When comparing these estimates to the ones presented in Fig. 3, we can observe the different population impact of the strategy when considering a scenario in which sufficient vaccine doses

Table 3
BNT162b2 vaccine effectiveness against Gamma Variant of Concern, by outcome, age group and vaccine dose.

Outcome	Age group	One-dose effectiveness (% and 95 % confidence interval)	Two-doses effectiveness (% and 95 % confidence interval)	Reference
Asymptomatic Infection	All	60 (53–66)	92 (88–95)	Dagan et al. [38]
Symptomatic disease	All	65 (56–71)	85 (70–93)	Nasreen et al. [36]
Hospitalisation/Deaths	All	83 (75–88)	98 (82–100)	Nasreen et al. [36]

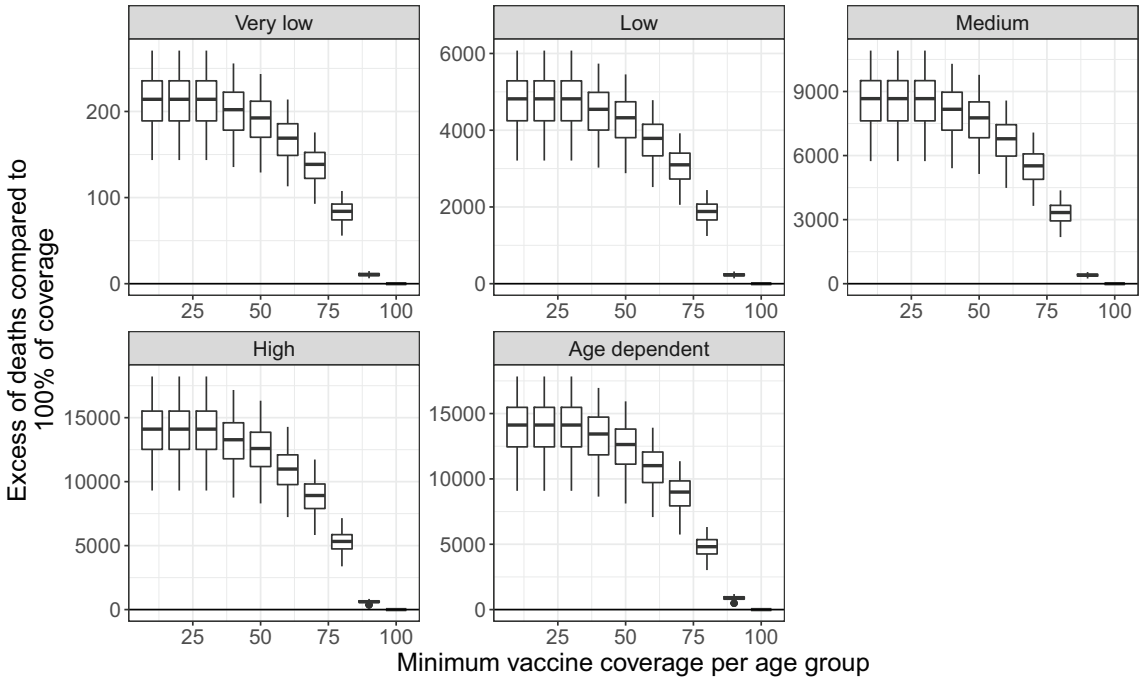

Fig. 2. Covid-19 number of excess deaths (median and interquartile ranges) (y-axis) by minimum 2-dose coverage threshold (x-axis) reached before initiating vaccination of younger age groups, stratified by the probability of infection (panels), given by very low, low, medium, high (with numerical values 0.0001, 0.0025, 0.0050, and 0.0100, respectively), and age dependent (see Methods) values.

are available to meet the entire demand (Fig. 4), and a scenario in which an insufficient number of vaccine doses is available to meet the demand, thus requiring an increase in vaccine supply (Fig. 5). Even with a 100 % increase in vaccine supply, the impact of reducing the time between doses to 8 weeks is reduced to at least about one-fifth of the maximum potential impact (reduction from 10,024 (95 %CI: 6,700–13,404) to 1,710 (95 %CI: 1,130–2,272) deaths averted in the scenario of a high probability of infection). A higher increase in vaccine supply was not considered as we assumed that this scenario was unfeasible.

4. Discussion

Our findings support that, to reach a higher impact in the context of gamma variant predominance in Brazil, resulting in an increase in the number of averted deaths, Covid-19 vaccine coverage rates in high-risk groups should be maximized, reaching a minimum of 80 % 2-dose coverage before expanding vaccination to populations of younger age. We further demonstrate that assuming vaccine effectiveness estimates against the Gamma variant, reducing the inter-dose interval from 12 to 8 weeks for AZD1222 ensures the highest reduction in Covid-19 deaths independently of infection transmission rates, reaching up to 10 thousand deaths in the high transmission scenario.

Routine monitoring & evaluation of disease transmission dynamics and local epidemiology are required, and its use is of utmost importance during a pandemic scenario, and should guide the formulation, implementation, and adjustments of public health policies. The emergence of new variants of concern (VOC), such as the Gamma variant [23] first identified in Brazil in late 2020, can pose additional challenges to public policy making. Being flexible and rethinking strategies has been mandatory in the context of the pandemic, particularly in settings present in Brazil, a large and diverse country, where many were the challenges faced for mitigating Covid-19 and efficiently rolling out its national Covid-19 vaccination strategy [24].

Considering the available evidence at the time of significant protection with one-dose against the original wild virus strain, Brazil and many other countries prioritized the administration of one vaccine dose to the greatest number of people, ensuring some protection, and spacing out the second dose for the maximum period of time stipulated by the manufacturers (i.e., 12 weeks). With the predominance of a new variant, this assumption no longer held true, as the protection conferred by one dose against Gamma variant was not adequate.

In addition, the eagerness to reach a higher number of vaccinated individuals quickly led many states and municipalities to expand vaccination to younger age groups, beyond the priority target population, including early on younger populations. This decision was made without defining *a priori* a minimum coverage to be reached in the priority groups prior to expanding vaccine to other groups, which, as we demonstrate, resulted in reduced population impact of vaccination.

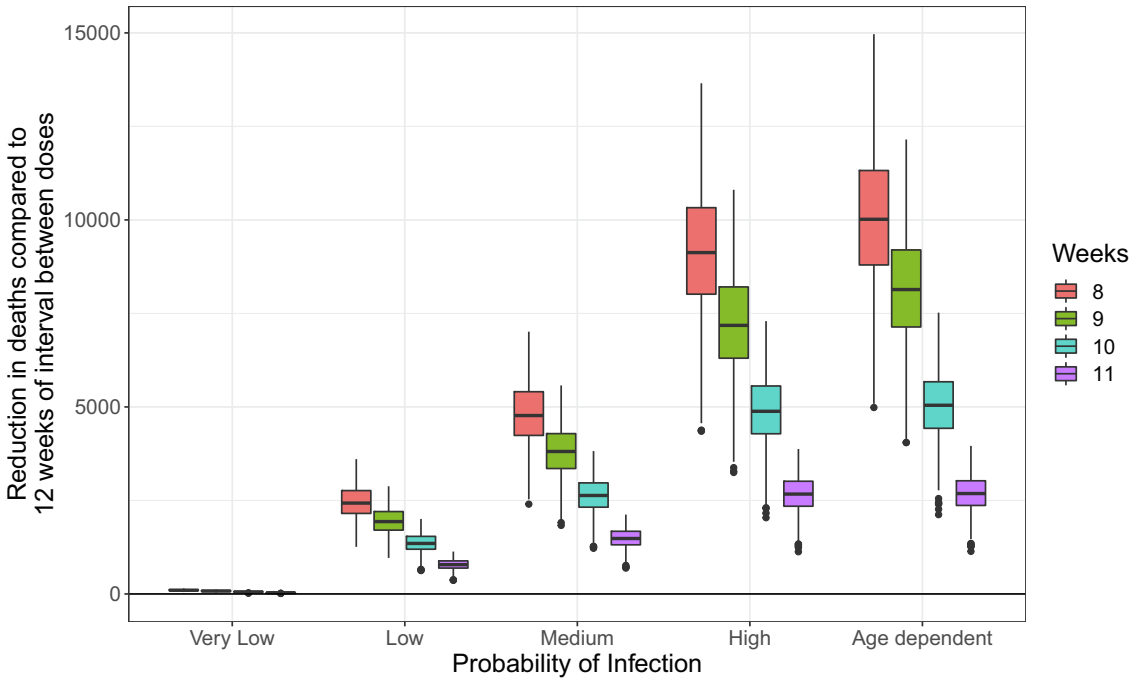

Fig. 3. Covid-19 deaths averted (median and interquartile ranges) (y-axis) by different dose intervals (colour) compared to 12 weeks, stratified by the probability of infection (x-axis), under the scenario of no limitation of AZD1222 vaccine supply. The probabilities of infection are given by very low, low, medium, high (with numerical values 0.0001, 0.0025, 0.0050, and 0.0100, respectively), and age dependent (see Methods) values.

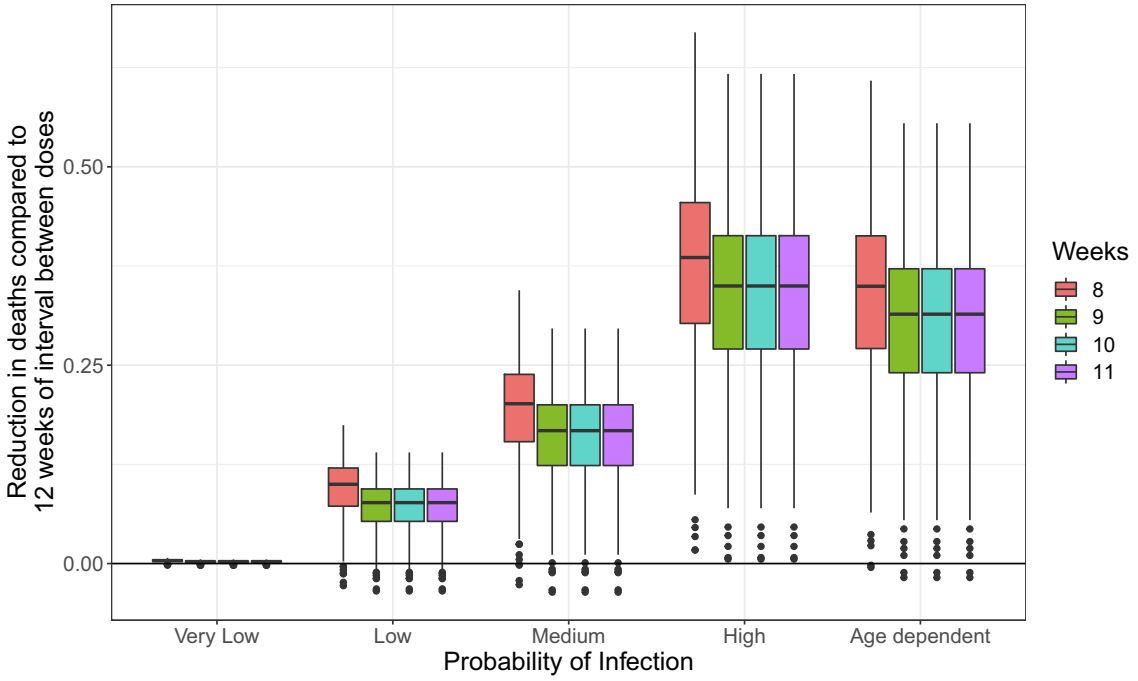

Fig. 4. Reduction in deaths (in median percentage and interquartile ranges) (y-axis) by different dose-intervals (colour) compared to 12 weeks, stratified by the probability of infection (x-axis), under the scenario of the currently projected AZD1222 vaccine supply. The probabilities of infection are given by very low, low, medium, high (with numerical values 0.0001, 0.0025, 0.0050, and 0.0100, respectively), and age dependent (see Methods) values.

In the context of scarce global-level vaccine supply, it is crucial to ensure that at-risk individuals are adequately and timely protected against Covid-19. Since our model is limited to age-stratified populations, ignoring other groups such as pregnant women and immunosuppressed individuals, we can only measure the effect of different thresholds of older individuals' coverage before making vaccine doses available to younger individuals. Ensuring good vaccine coverage for older individuals (at least 90 % of coverage) reduces the number of Covid-19 deaths considerably, as expected. However, and more important than that, even assuming lower coverages (lower than 80 %) as a threshold generates a sharp increase in the number of additional averted deaths compared to vaccinating the whole population of older individuals beforehand. Thus, the first strong recommendation we provided to

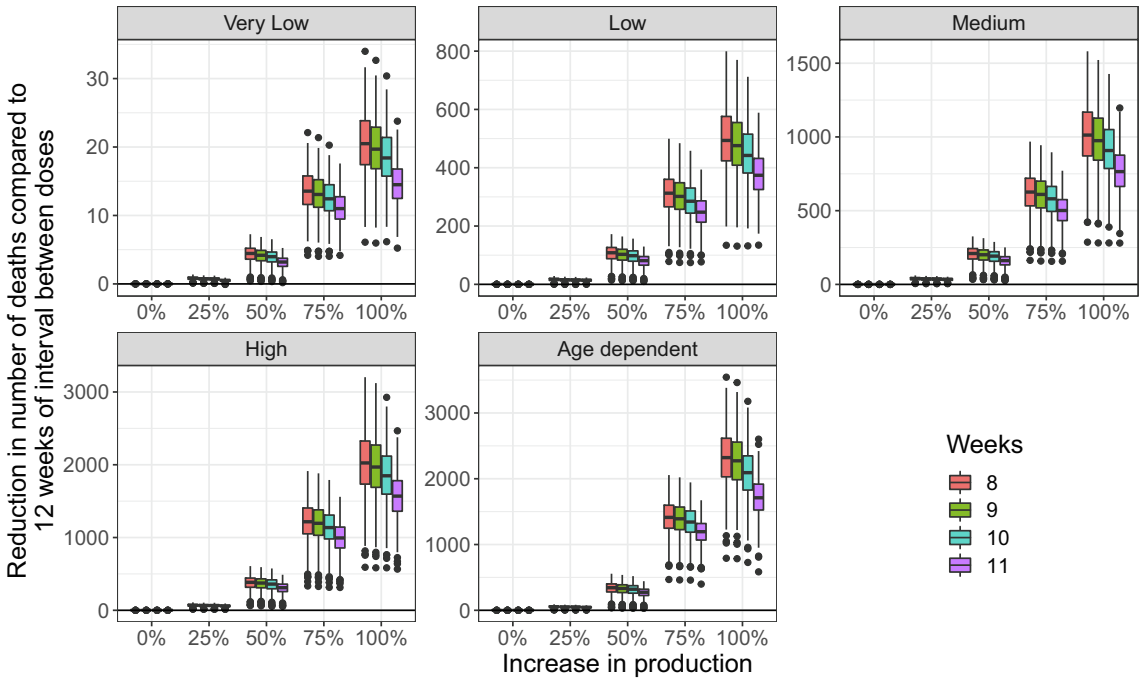

Fig. 5. Covid-19 deaths averted (median and interquartile ranges) (y-axis) when considering lower dose-intervals (colour) compared to 12 weeks, by percent increase in AZD1222 vaccine supply (when compared to current projections) (x-axis), stratified by the probability of infection (panels), given by very low, low, medium, high (with numerical values 0.0001, 0.0025, 0.0050, and 0.0100, respectively), and age dependent (see Methods) values.

policymakers based on our model results is that resuming efforts to achieve minimum coverage of 80 % in older age groups should be prioritized, and only then vaccination should be expanded to younger age groups. This calls for urgent measures from government policymakers, including social mobilization and communication campaigns, in addition to an active search for unvaccinated individuals.

Structured in 1973 at the end of the smallpox eradication initiative, The Brazilian National Immunization Programme (PNI) represents a robust public health intervention, providing, free of charge, vaccines incorporated into the routine immunization schedule to all populations through its publicly-funded SUS [25]. Managed by the Federal Government, together with States and Municipalities, decentralized and with good capillarity, achieved by>36 thousand vaccination rooms throughout 5,570 Brazilian municipalities, the PNI has historically been able to deliver massive amounts of vaccines in immunization campaigns and get to hard-to-reach populations. Assuming that Brazil is perfectly capable of rescuing unvaccinated older people, given the country's brilliant history concerning vaccination planning and implementation, acceptance by the population, and especially the capillarity of the health system, we can advance on other issues we modelled.

An important issue raised by our results is that the optimal impact of reducing the interval between doses is not (nearly) achievable given the available vaccine supply at the time of modelling (i.e., the projected number of doses to be distributed in Brazil in the following 6 months). Without increasing vaccine supply, reducing the inter-dose interval would result in a lack of dose availability to be administered as the second to a significant proportion of the eligible to receive their second dose (ie. after 8 weeks of receipt of the first dose) population. This bottleneck can result in loss to the immunization program and its credibility. The reason for not having significant difference between the scenarios studied in Fig. 4 is due to the fact that the vaccine effectiveness parameters, combined with the deployment rate of doses, are very proximate to the threshold of one strategy being better than the other, so they don't have significant difference in results. However, we see in the other results that, as soon as one increases the number of doses available, one strategy begins to be significantly more beneficial than others. These results are supported by the findings in [17].

To achieve a noticeable impact of changing the interval between doses of AZD1222, an increase of at least 50 % of the current vaccine supply, in terms of the number of available doses is required, independently of the transmission level of the epidemic. This information is particularly relevant to support vaccine procurement and purchase. For the Brazilian scenario, it also supports the necessity to improve production capacity locally, as Brazil's AZD1222 producer Fiocruz-Biomanguinhos is upgrading its factory from filling doses to *in-loco* full vaccine production. This would, in principle, enable the production of four monthly lots of doses instead of the planned three lots. Although our result suggests that increasing vaccine availability by>100 % would result in the most significant impact, we did not model such increase as we assumed it to be impracticable. Thus, one more strong recommendation based on our results can be made: decreasing the interval between doses of AZ vaccines from 12 to 8 weeks can be highly beneficial, but only if an adequate vaccine supply is available. In Brazil, this would require a 50 % increase in vaccine availability by the end of 2021.

This recommendation is important to reinforce the need for increasing and sustaining local vaccine availability and sustainable supplies, and demonstrates that the country cannot let down its guard in the fight against the pandemic. Vaccine supply and vaccination policy may change depending on vaccine effectiveness data, infection transmission, new VOC and local epidemiology, among others. This is further reinforced by the emergence of the Omicron VOC, predominant in Brazil since early 2022, against which the third dose of vaccine has been demonstrated to be required to maintain protection against severe disease [26].

Mathematical modelling has been extensively used to assist policymakers during the Covid-19 pandemic. The range of issues evaluated through modelling includes, but is not limited to, school reopening [27], the effects of lockdown and social distancing measures [28], and, of course, the impact of vaccination and identification of best vaccination strategies. Moore et al. [29] have shown

that vaccinating older age groups should be prioritized to minimize the number of future deaths or years of life lost in the UK. The same results were found by Bubar et al. [30] when considering the number of deaths as the outcome. However, assuming the use of a highly effective vaccine against infection, vaccinating younger individuals and thus the more mobile population resulted in a higher reduction of infection in the population. Some agent-based models have been used to assess the effects of delaying the second dose of mRNA-based vaccines, showing that in the context of Alpha VOC predominance, delaying up to 12 weeks would have a significant impact on reducing Covid-19 deaths [31,32].

Our results are in agreement with those reported by Silva et al. [33] who also estimated that a 8-week inter-dose interval would result in reduced ICU admissions using a hypothetical scenario on the number of vaccine doses. Our work further improves on Silva et al. by first, considering realistic and not hypothetical vaccine supply over time. Second, considering real-life national immunization strategy in which all three vaccines are modelled simultaneously, further optimizing the allocation of doses by vaccine in the ongoing vaccination program. Third, using the most up-to-date and best quality evidence from the literature as vaccine effectiveness parameters against Gamma VOC.

Ferreira et al. [17] also demonstrated that first dose efficacy and availability are essential parameters when considering the optimal interval between doses, whereas varying values of infection transmission (effective reproduction number) did not impact estimates. This was also observed in our study, supporting our choice of using various scenarios with fixed probabilities of infection over the time horizon of the study. This rendered modelling simpler and allowed for better timeliness of modelling and communication of results to decision-makers and policymakers in Brazil.

A limitation of the study was the use of constant probabilities of infection over time. This affects the magnitude of the reduction in the number of deaths, that is, we were unable to measure the number of deaths avoided by vaccination in scenarios of increased or decreased probability of infection over time. To overcome this limitation, it would be necessary to use dynamic SEIR-type models. We chose not to use this type of model as we would have to adjust case growth rates and propose future transmission scenarios for all locations in Brazil, and this would delay the delivery of results to advise policymakers, which was the main motivation of this work. Nevertheless, the result of an optimal interval between doses still holds as argued before. Finally, the results every modelling study are sensitive to the parameterization used. We addressed this by using the best available effectiveness studies regarding the Gamma variant. However, due to the lack of studies investigating different vaccine effectiveness given different intervals between doses and also the waning of immunity conferred by vaccines by the time this study was conducted, our might change in the light of new evidences.

Covid-19 vaccination strategies should be tailored to local vaccine product availability and supply over time, circulating variants of concern, and vaccine coverage in target population groups. Simpler modelling approaches can provide valuable and timely evidence to support the implementation of vaccination strategies tailored to the local context, yet following international and regional technical evidence-based guidance. These strategies should be continuously monitored and adjusted over time.

Funding and role of the funding source.

This study was funded by the Brazilian National Council for Scientific and Technological Development (CNPq) - Process # 402834/2020–8 (request for proposals MCTIC/CNPq/FNDCT/MS/SCTIE/Decit N° 07/2020).

The funding sources played no role in the study design, collection, analysis, or interpretation of the data, writing the report, or deciding to submit the paper for publication.

LSF received a master's scholarship from Coordination of Superior Level Staff Improvement (CAPES) (finance code 001). GBA received a technological and industrial scholarship from CNPq (Grant No 301796/2021–1). MEB received a technological and industrial scholarship from CNPq (grant number 315854/2020–0). LMS received a technological and industrial scholarship from CNPq (grant number 315866/2020–9). SP was supported by São Paulo State Research Support Foundation (FAPESP) (grant number: 2018/24037-4). AMB received a technological and industrial scholarship from CNPq (grant number 402834/2020-8). MQMR received a postdoctoral scholarship from CAPES (grant number 305269/2020-8). RSK has been supported by CNPq (proc. 312378/2019-0). JAFD-F has been supported by the CNPq productivity fellowship and the National Institutes for Science and Technology in Ecology, Evolution and Biodiversity Conservation (INCT-EEC), supported by MCTIC/CNPq (proc. 465610/2014-5) and FAPEG (proc. 201810267000023). RAK has been supported by CNPq (grant number: 311832/2017-2) and FAPESP (contract number: 2016/01343-7). CMT has been supported by the CNPq productivity fellowship and the National Institute of Science and Technology for Health Technology Assessment (IATS) (proc: 465518/2014-1).

Author contributions.

CMT, RAK, JAFD-F, SAC, RSK, and RMC conceptualized the study. All authors reviewed the study design and provided critical comments.

GBA, AMB, LMS, SAC, RSK, MQMR, and CMT reviewed the literature, collected and verified the underlying data, and proposed values and intervals for model parameters. All authors discussed and agreed on model parameters to be considered.

LSF, MEB, SP, and RMC were primarily responsible for model structuring, parametrization, and statistical analyses. All authors participated in the interpretation of the analyses.

LSF and GBA drafted the paper. All authors contributed to revising the paper, the tables, and the figures critically and for important intellectual content.

All authors approved the final submitted version of the paper.

All authors have full access to the data, are accountable for all aspects of the work, and will ensure that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Data Availability Statement.

The authors state that the database used in the analyses are available as a supplementary file to the paper and can be provided to interested researchers upon reasonable request.

Funding

This study was funded by the Brazilian National Council for Scientific and Technological Development (CNPq) [Process # 402834/2020–8].

Data availability

The data repository is available in the Supplementary Material.

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.

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