Universidade do Estado do Rio de Janeiro
Centro Biomédico
Instituto de Medicina Social Hesio Cordeiro

Cleber Vinicius Brito dos Santos

COVID-19 no Brasil: carga da doença, efetividade vacinal e efeitos da vacinação

Rio de Janeiro
2024

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Tese apresentada, como requisito parcial para obtenção do título de Doutor, ao Programa de Pós-Graduação em Saúde Coletiva, da Universidade do Estado do Rio de Janeiro. Área de concentração: Epidemiologia

Orientador: Prof. Dr. Cláudio José Struchiner

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Rio de Janeiro
2024

DEDICATÓRIA

Dedico esta dissertação à Célio José Alves dos Santos (*in memoriam*) e Isaura Maria de Brito (*in memoriam*).

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"*O sonho é que leva a gente para a frente. Se a gente for seguir a razão, fica aquietado, acomodado*."

-Ariano Suassuna

RESUMO

SANTOS, Cleber Vinicius Brito dos. **COVID-19 no Brasil: carga da doença, efetividade vacinal e efeitos da vacinação**. 2024. 159 f. Tese (Doutorado em Saúde Coletiva) – Instituto de Medicina Social Hesio Cordeiro, Universidade do Estado do Rio de Janeiro, Rio de Janeiro, 2024.

A pandemia de COVID-19 representou o maior desafio sanitário do século XXI. O Brasil, um dos países mais afetados, implementou um amplo programa de vacinação. Este estudo visa quantificar o impacto da COVID-19 e da vacinação no país. Através de análises de dados epidemiológicos, foram estimadas (i) a carga da doença em termos de anos de vida ajustados por incapacidade (DALYs) em 2020, (ii)a efetividade das diferentes vacinas utilizadas, (iii) o número de casos graves e óbitos evitados pela imunização e (iv) o quanto receber a vacina contra COVID-19 afetou na estadia hospitalar de pacientes com COVID-19. A COVID-19 causou um grande impacto na saúde da população brasileira, resultando em mais de 5 milhões de DALYS e, assumindo que não houve grandes mudanças no padrão de adoecimento entre 2019 a 2020, a carga da COVID-19 seria classificada como a principal causa de doenças e incapacidade no Brasil. Observamos também que o esquema primário de vacinação conferiu proteção acima de 25% e 50%, respectivamente, mesmo após 19 semanas, as doses de reforço conferiram uma maior proteção quando comparados com o esquema primário, com as doses heterólogas conferindo uma proteção maior que as doses de reforços de vacinas homólogas. A vacinação no Brasil evitou um aumento de 74% no número de casos graves (n = 875.846) de COVID-19 e um aumento de 82% no número de óbitos (n = 303.129) no primeiro ano da campanha nacional de vacinação. Por fim, observamos que o tempo médio de estadia hospitalar para os que receberam a vacina foi menor que os não vacinados e que receberem ao menos uma dose da vacina aumentou a probabilidade de alta em relação aos não vacinados. Os resultados da tese contribuem para uma melhor compreensão da dinâmica da pandemia no Brasil e podem auxiliar na formulação de políticas públicas de saúde.

Palavras-chave: vacina. pandemia; COVID-19; SARS-CoV2; Brasil; DALYS; imunização; efetividade; hospitalização.

ABSTRACT

SANTOS, Cleber Vinicius Brito dos. **COVID-19 in Brazil: burden of disease, vaccine effectiveness and vaccine effects**. 2024. 159 f. Tese (Doutorado em Saúde Coletiva) – Instituto de Medicina Social Hesio Cordeiro, Universidade do Estado do Rio de Janeiro, Rio de Janeiro, 2024.

The COVID-19 pandemic has represented one of the most significant public health challenges of the 21st century. Brazil, one of the most affected countries, has implemented a broad vaccination program. This study aims to quantify the impact of COVID-19 and vaccination in the country. Through analysis of epidemiological data, we estimated (i) the burden of disease in terms of disability-adjusted life years (DALYs) in 2020, (ii) the effectiveness of the different vaccines used, (iii) the number of severe cases and deaths averted by immunisation, and (iv) how much receiving the COVID-19 vaccine affected the hospital stay of COVID-19 patients. COVID-19 has had a significant impact on the health of the Brazilian population, resulting in more than 5 million DALYs and, assuming that there were no major changes in disease burden between 2019 and 2020, the burden of COVID-19 would be classified as the leading cause of illness and disability in Brazil. We also observed that the primary vaccination schedule provided protection above 25% and 50%, respectively; even after 19 weeks, the booster doses conferred greater protection when compared to the primary schedule, with the heterologous doses providing greater protection than the booster doses of homologous vaccines. Vaccination in Brazil prevented a 74% increase in severe cases (n = 875,846) of COVID-19 and an 82% increase in deaths (n = 303,129) in the first year of the national vaccination campaign. Finally, we observed that the average length of hospital stay for those who received the vaccine was shorter than for those who were not vaccinated and that receiving at least one dose of the vaccine increased the probability of discharge compared to those who were not vaccinated. The results of the thesis contribute to a better understanding of the dynamics of the pandemic in Brazil and can assist in formulating public health policies.

Keywords: vaccine. pandemics; COVID-19; SARS-CoV2; Brazil; DALYS; immunization; effectiveness; hospitalization.

LISTA DE ILUSTRAÇÕES

LISTA DE ABREVIATURAS E SIGLAS

CDC	*Center for Disease Control and Prevention*
CI	*Confidence Interval/Credible Interval*
CID-10	Código da Classificação Internacional de Doenças da OMS, 10ª revisão
CNPq	Conselho Nacional de Desenvolvimento Científico e Tecnológico
COVID-19	Doença do Coronavírus 2019
DALYs	*Disability-Adjusted Life Years*
DW	*Disability Weights*
EDW	*European Disability Weight*
ESPII	Emergência de Saúde Pública de Importância Internacional
ESPIN	Emergência em Saúde Pública de importância Nacional
EV	Efetividade Vacinal
FAPERJ	Fundação de Amparo a Pesquisa do Estado do Rio de Janeiro
FIOCRUZ	Fundação Oswaldo Cruz
GBD	*Global Burden of Disease Collaborative Network*
GISAID	*Global Initiative on Sharing All Influenza Data*
IBGE	Instituto Brasileiro de Geografia e Estatística
ICU	*Intensive Care Unit*
IHME	*Institute for Health Metrics and Evaluation*
OMS	Organização Mundial da Saúde
PAHO	*Pan American Health Organization*
PNI	Plano Nacional de Imunização
RLE	*Residual Life Expectancy*
rVE	*Relative Vaccine Effectiveness*
SARS-CoV-2	Coronavírus da Síndrome Respiratória Grave 2
SIM	Sistema de Informações sobre Mortalidade
SIVEP-Gripe	Sistema de Vigilância Epidemiológica da Gripe
SRAG	Síndrome Respiratória Aguda Grave
UI	*Uncertainty Interval*
UTI	Unidade de Terapia Intensiva

VAED	*Vaccine-Associated Enhanced Disease*
VE	*Absolute Vaccine Effectiveness*
VOC	*Variant of Concern*
WHO	*World Health Organization*
YLD	*Years Lived with Disability*
YLL	*Years of Life Lost due to premature mortality*

SUMÁRIO

INTRODUÇÃO

A atual pandemia da COVID-19 se apresenta, até o momento, como o maior desafio sanitário do século, sendo responsável por mais de 625 milhões de casos e 6 milhões de óbitos em todo o mundo (até 18/10/22) (RITCHIE et al., 2020). A doença foi inicialmente observada na China, no fim de 2019 e rapidamente se espalhou em todo o mundo, sendo declarada, em 30 de janeiro de 2020, pela Organização Mundial da Saúde como Emergência de Saúde Pública de Importância Internacional (ESPII) e, posteriormente (em 11/03/2020), caracterizada como pandemia (WORLD HEALTH ORGANIZATION, 2020a, 2020b, 2020c).

No Brasil, a COVID-19 foi declarada Emergência em Saúde Pública de importância Nacional (ESPIN) em 3 de fevereiro de 2020, antes mesmo da confirmação do primeiro caso, que foi notificado em 26 de fevereiro e desde então, mais de 34 milhões de casos e mais de 680 mil óbitos foram registrados, colocando o Brasil como o 5º país em número de casos e o 2º em número de óbitos (MINISTÉRIO DA SAÚDE, 2020, 2022a; RITCHIE et al., 2020).

Nesse sentido, a vacinação foi peça-chave nos programas de controle da epidemia no Brasil e no mundo. O programa de vacinação no Brasil se iniciou em 17 de janeiro de 2021, priorizando pessoas com risco relativamente alto de doença grave (idosos e pessoas com condições crônicas de saúde), populações vulneráveis (por exemplo, pessoas em situação de rua e população indígena) e profissionais de saúde e outros trabalhadores essenciais inicialmente, tendo sido estendido posteriormente a toda a população em ordem decrescente de idade. Inicialmente foram usados os imunizantes CoronaVac (Sinovac) e ChAdOx1 nCov-19 (AstraZeneca/*Oxford University*), que foram administrados em duas doses com 28 dias de intervalo e 12 semanas de intervalo, respectivamente. Em 29 de abril de 2021, a vacina BNT162b2 (Pfizer–BioNTech) foi adicionada à campanha (duas doses, com 12 semanas de intervalo) e, finalmente, em 15 de junho de 2021, a vacina Ad26.COV2.S (Janssen) foi disponibilizada (MINISTÉRIO DA SAÚDE, 2022b). Após mais de um ano do início da vacinação, mais de 80% da população brasileira completou o esquema primário da vacina contra a COVID-19 e aproximadamente 50% recebeu a dose de reforço (MINISTÉRIO DA SAÚDE, 2022b).

Ao longo da pandemia, diversos estudos foram realizados, sob diferentes perspectivas da COVID-19 no Brasil, como por exemplo, inquéritos sorológicos (HALLAL et al, 2020), aderência a uso de medidas de proteção individual (JACQUES et al., 2022), estimativas de excesso de mortalidade (AZEVEDO E SILVA; JARDIM; SANTOS, 2020), rotas de entrada

da COVID-19 no Brasil (CANDIDO et al 2020), modelagem e previsão de número de casos (BASTOS et al., 2020), estimativas de eficácia e efetividade vacinal (CERQUEIRA-SILVA et al., 2022). No entanto, algumas lacunas de conhecimento ainda necessitam ser preenchidas, sendo assim, esse projeto de tese visa contribuir com algumas dessas lacunas sobre a pandemia da COVID-19 no Brasil. Até o momento, nosso foco foi em estimar a carga da doença no primeiro ano de pandemia e os efeitos da vacinação, tanto no que se refere a efetividade, quanto aos desfechos evitados pela introdução da vacina no país e o quanto receber a vacina afetou a duração da estadia hospitalar dos casos graves de COVID-19.

Para melhor entendimento das perguntas a serem respondidas e dos processos utilizados ao longo dos trabalhos, iremos apresentar a metodologia de cada um dos artigos na seção Métodos e, posteriormente, os artigos na forma de subcapítulos na seção Resultados. O primeiro artigo (*Disability-adjusted life years associated with COVID-19 in Brazil, 2020*) compreende as nossas estimativas de carga da doença, medida em DALYs, causadas diretamente pela COVID-19 no ano de 2020. Mais adiante, o segundo artigo (*The effectiveness of COVID-19 vaccines against severe cases and deaths in Brazil from 2021 to 2022: A registry-based study*) descreve as estimativas de efetividades absoluta e relativa das vacinas de COVID-19 presentes no Brasil, para o primeiro ano de vacinação e durante períodos de dominância de variantes. O artigo 3 (*Estimated COVID-19 severe cases and deaths averted in the first year of the vaccination campaign in Brazil: a retrospective observational study*) apresenta as nossas estimativas de casos graves e óbitos de COVID-19 que foram evitados pela vacinação durante o primeiro ano da campanha de vacinação. Por fim, o quarto artigo (*The impact of vaccination on the length of stay of hospitalized COVID-19 patients in Brazil*) descreve nossas estimativas de como as vacinas de COVID-19 afetaram o tempo de estadia hospitalar e a probabilidade alta de pacientes hospitalizados com COVID-19.

1. **OBJETIVOS**

1.1 **Objetivo geral**

Fornecer estimativas da carga da COVID-19, efetividade das vacinas contra a COVID-19 e consequências da vacinação população Brasileira.

1.2 **Objetivos específicos**

a) Objetivo específico 1 – Manuscrito 1

b) Estimar a carga da doença, em DALYs, causada pela COVID-19 no Brasil durante o ano de 2020

c) Objetivo específico 2 – Manuscrito 2

d) Estimar a efetividade vacinal contra casos graves e óbitos de COVID-19 no primeiro ano de vacinação no Brasil

e) Objetivo específico 3 – Manuscrito 3

f) Estimar o número de casos graves e óbitos evitados pela vacinação de COVID-19 durante o primeiro ano de vacinação no Brasil.

g) Objetivo específico 4 – Manuscrito 4

h) Estimar o impacto da vacinação na duração da internação hospitalar por COVID-19 durante o primeiro ano de vacinação no Brasil

2. **MÉTODOS**

2.1 **Materiais e métodos referentes do manuscrito 1 - *Disability-adjusted life years associated with COVID-19 in Brazil, 2020***

2.1.1 Dados

Nós utilizamos dados de quatro bancos de dados de abrangência nacional: (i) Síndrome Gripal do E-SUS Notifica, que inclui dados individuais anonimizados sobre casos suspeitos de COVID-19 (MINISTÉRIO DA SAÚDE., 2020a, 2020b); (ii) Infecção/Doença Respiratória Aguda Grave (SRAG) do Sistema de Vigilância Epidemiológica da Gripe (SIVEP-Gripe) (MINISTÉRIO DA SAÚDE, 2021b), que contém dados individuais anonimizados sobre todos os casos graves de COVID-19 que levaram à hospitalização; (iii) o banco de dados do Sistema de Informações sobre Mortalidade (SIM) (MINISTÉRIO DA SAÚDE., 2022a), que inclui dados individuais anonimizados sobre todos os óbitos registrados no país, e (iv) o banco de dados do Instituto Brasileiro de Geografia e Estatística (IBGE) sobre estimativas populacionais específicas por sexo e idade nos níveis nacional e estadual (INSTITUTO BRASILEIRO DE GEOGRAFIA E ESTATISTICA (IBGE), 2020; INSTITUTO BRASILEIRO DE GEOGRAFIA E ESTATÍSTICA, 2021).

Filtramos os registros de casos e óbitos que continham informações completas sobre sexo, idade, estado de residência e início dos sintomas/início da hospitalização entre 26 de fevereiro de 2020 e 31 de dezembro de 2020. As mortes por COVID-19 foram aquelas em que a causa primária da morte foi codificada usando os seguintes códigos da Classificação Internacional de Doenças da OMS, 10ª revisão [CID-10]: U071 (COVID-19, vírus identificado), U072 (COVID-19, vírus não identificado), B342 (infecção por coronavírus não especificada), B972 (coronavírus como causa de doenças classificadas em outro lugar), U109 (síndrome inflamatória multissistêmica associada à COVID-19, não especificada), U972 (coronavírus como causa de doenças classificadas em outro lugar), U109 (síndrome inflamatória multissistêmica associada à COVID-19, não especificada) (WORLD HEALTH ORGANIZATION, 2016). Para estimar o YLD, os casos foram agregados por faixa etária de cinco anos, sexo e estado. Os registros de óbitos seguiram o mesmo agrupamento dos

registros de doenças, exceto que a faixa etária de menores de 5 anos foi dividida em menores de um ano e de 1 a 4 anos. A faixa etária mais velha foi definida em 95 anos ou mais.

Para comparar a carga da COVID-19 com a carga de outras causas de doenças e lesões no Brasil, usamos dados da ferramenta de resultados do GBD da *Global Burden of Disease Collaborative Network* do *Institute for Health Metrics and Evaluation* (IHME) (GBD COLLABORATIVE NETWORK, 2020a, 2020b). As estimativas da carga de doenças para 2020 ainda não estão disponíveis; portanto, usamos estimativas do DALY de 2019 para ambos os sexos, incluindo todas as idades, e agrupamos as estimativas por causas de nível 3.

As estimativas estão disponíveis no site do IHME (https://vizhub.healthdata.org/gbd-results/), e o conjunto de dados resultante é apresentado no Apêndice A.

2.1.2 Disability-Adjusted Life Year (DALY)

O DALY é uma métrica de saúde que mede os anos de vida saudável perdidos devido a uma doença. Os DALYs são estimados somando o número de anos de vida perdidos devido à mortalidade prematura (ou seja, YLLs) e o número de anos vividos com incapacidade, ajustados para a gravidade da doença (YLDs). Ao estimar os DALYs da COVID-19, consideramos todos os estados de saúde experimentados após a infecção e o desenvolvimento de sintomas, que foram classificados como "leve a moderado", "grave", "crítico", "COVID longa" e morte devido à COVID-19.

2.1.3 Years of life lost due to premature mortality (YLL)

Os YLLs foram calculados multiplicando o número de mortes em cada faixa etária e sexo pela expectativa de vida residual (*residual life expectancy* - RLE) na idade da morte:

$$YLL = Deaths\ X\ RLE$$

onde RLE corresponde à expectativa de vida restante. Por exemplo, digamos que um homem de 25 anos veio a óbito em decorrência da COVID-19 e a sua expectative de vida, dado que

chegou aos 25 anos, é de 75 anos, logo esse individuo perdeu 50 anos de vida devido a mortalidade prematura. Nós utilizamos a expectativa de vida condicional à idade definida pela tabela de vida de referência do GBD 2019 (GBD COLLABORATIVE NETWORK, 2021).

2.1.4 Years lived with disability (YLD)

Para estimar a gravidade de cada estado de saúde, utilizamos os pesos de incapacidade (*disability weights* - DWs) do estudo *Global Burden of Disease* de 2019 (2019 GBD *study*) e do *European Disability Weight* (EDWS) (SALOMON et al., 2015; DE NOORDHOUT et al., 2018; GBD COLLABORATIVE NETWORK, 2020a, 2021; WYPER et al., 2021a). O DW reflete a gravidade de um estado de saúde (ou seja, a redução na qualidade de vida). Para cada estado de saúde, combinamos dados sobre a incidência, duração e deficiência da literatura e calculamos o YLD somando o produto do número de casos, duração (em anos) e DW em todos os grupos de estados de saúde da seguinte forma:

$$YLD = Incidence\ X\ Duration\ X\ DW$$

Definimos como casos leves a moderados todos os registros com diagnóstico confirmado de COVID-19 que não levaram à hospitalização, provindos do E-SUS notifica. Casos graves foram definidos como casos hospitalizados que não exigiram cuidados intensivos, coletados do SIVEP-Gripe. Classificamos casos críticos como aqueles em que houve admissão em Unidade de Terapia Intensiva (UTI), também disponíveis no SIVEP-Gripe. Para estimar o YLD devido à COVID longa, assumimos que aproximadamente 1 em cada 7 pacientes (ou seja, 13,3%) de casos leves a moderados sofreram consequências pós-agudas por 28 dias, refletindo evidências iniciais da literatura (SUDRE et al., 2021). Definimos a duração média de casos leves a moderados como dez dias (CENTER FOR DISEASE CONTROL AND PREVENTION, 2020). Calculamos a duração de casos graves e críticos como a duração média de hospitalização e admissão na UTI. As definições de estados de saúde, DW do GBD e EDWS e as fontes de dados são mostradas na Tabela 1. Para explorar as diferenças espaciais na carga da COVID-19 em todo o país, em uma análise secundária, estimamos os DALYs para cada estado brasileiro em 2020.

2.1.5 Análise de sensibilidade e quantificação da incerteza

Seguindo estudos semelhantes, nós utilizamos simulações de Monte Carlo em uma distribuição beta PERT para amostrar valores aleatórios de intervalos de DW (MCBRIDE; MCCLELLAND, 1967; CAMERON; BALDOCK, 1998; ROSENDAL, 2020; PIRES et al., 2022). Em cada uma das 10.000 iterações, os valores da amostra DW foram usados para calcular uma estimative de YLD. A combinação de iterações resulta em uma distribuição empírica de estimativas de YLD, refletindo a incerteza conjunta nos parâmetros de entrada (ou seja, valores do intervalo DW), que foram sumarizados por seus intervalos de incerteza de 95% (95% UI). Além disso, realizamos uma análise de sensibilidade univariada para quantificar o impacto das incertezas em torno do número de casos leves a moderados, graves e críticos de COVID-19 e a proporção de casos que sofrem de COVID longa (MORAN et al., 2022; PIRES et al., 2022). A análise de sensibilidade foi baseada em dois cenários hipotéticos: um cenário de limite inferior, onde diminuímos a duração e o número de casos pela metade, e um cenário de limite superior, onde dobramos a duração do estado de saúde e o número de casos, respectivamente (Apêndice A).

Todas as análises foram realizadas no R versão 4.1.2; o código está disponível no material suplementar 2 (R CORE TEAM, 2022).

Tabela 1 Detalhes dos estados de saúde de COVID-19, respectivos pesos de incapacidade e fontes de dados

Estado de saúde	Descrição do estado do saúde	Dados	Duração (dias)	Fonte de dados	Peso da incapacidade (Intervalo de incerteza a 95%)
Leve a moderado	Caso sintomático que não leveram a hospitalização , que causa alguma dificuldade nas atividades diárias	Número de casos sintomáticos (não hospitalizado)	10	E-SUS	0.051 (0.032-0.074)
Severo	Caso sintomático que levou a hospitalização, que causa grande dificuldade nas atividades diárias	Número de casos hospitalizados (sem cuidados intensivos)	Média de estadia hospitalar	SIVEP-Gripe	0.133 (0.088-0.190)
Crítico	Casos hospitalizados que requerindo admissão em unidade de terapia intensiva com ou sem suporte respiratório.	Número de casos hospitalizados (unidade de terapia intensiva)	Média de estadia da UTI	SIVEP-Gripe	0.655 (0.579-0.727)
COVID longa (sequelas pós-agudas de COVID-19)	Sofre de problemas de saúde pós-infecção, como fadiga, labilidade emocional, insônia, etc..	Estimado na fração (13.3%) dos casos leves a moderado que evoluem para covid longa (1 a cada 7 casos)	28	E-SUS	0.219 (0.148-0.308)

UTI: Unidade de Terapia Intensiva
Fonte: O autor

2.2 **Materiais e métodos referentes do manuscrito 2 - The effectiveness of COVID-19 vaccines against severe cases and deaths in Brazil from 2021 to 2022: A registry-based study**

2.2.1 Desenho de estudo, população e banco de dados

Nosso trabalho se trata de um estudo de efetividade baseado numa coorte de registros de mais de 158 milhões de notificações, incluindo mais de dois milhões de casos graves de

COVID-19. Nós utilizamos dois bancos de dados que foram unidos pelo Ministério da Saúde: (1) os registros de vacinação do plano nacional de vacinação (PNI) (MINISTÉRIO DA SAÚDE, 2022a), que compreende dados individuais de vacinação de COVID-19; e (2) o banco de dados de Síndrome Respiratória Aguda Grave (SRAG) (MINISTÉRIO DA SAÚDE, 2021b, 2022c), que contém todos casos graves notificados no Brasil, detalhes do processo de *linkage* podem ser vistos no Apêndice B. Desse banco de dados unido, nós utilizamos os dados de indivíduos com 20 anos ou mais e que receberam pelo menos uma dose da vacina ou que tiveram um caso grave de COVID-19. Juntamente com esse banco de dados, nós também utilizamos as estimativas populacionais por idade do Instituto Brasileiro de Geografia e Estatística (IBGE) (INSTITUTO BRASILEIRO DE GEOGRAFIA E ESTATÍSTICA, 2021).

A campanha de vacinação contra a COVID-19 se iniciou em 17 de Janeiro de 2021, que corresponde ao início do nosso estudo. A exposição de interesse (esquema primário de vacinação e reforços) foram observados do início da campanha até 31 de janeiro de 2022 (semana epidemiológica 5). Os registros de vacinação no banco de dados indicam a data da aplicação da primeira e segunda dose, além do reforço e a marca da vacina recebida em cada aplicação.

2.2.2 Definição do *status* vacinal

As onbservações onde os indivíduis não apresentam nenhum registro de vacinação (primeira, segunda ou dose de reforço) foram classificadas como não vacinados. Nós considerados imunizados aqueles com (i) aqueles com o esquema vacinal primário completo, ou seja, duas doses das vacinas CoronaVac, ChAdOx1 nCov-19, e BNT162b2, ou dose única da Ad26.Cov2.S; e (ii) aqueles com o esquema vacinal primário mais uma dose de reforço, algumas vezes chamada de *booster*.

2.2.3 Desfechos de interesse

Os desfechos de interesse foram (i) casos graves de COVID-19, ou seja, casos sintomáticos de COVID-19 que levaram à hospitalização, independentemente de resultar em

óbito ou não, e (ii) óbitos por COVID-19. Os desfechos foram registrados no conjunto de dados pela data do início dos sintomas e o desfecho do caso (morte, recuperado ou ignorado). Para cada pessoa na coorte, um caso grave de COVID-19 ocorreu sempre que essa pessoa foi notificada como um caso grave de COVID-19, usando a data do início dos sintomas como referência. Portanto, caso grave de COVID-19 após a vacinação, seja com esquema vacinal primário ou com reforço, foi classificado como um caso vacinado. Indivíduos que apresentaram o desfecho (caso grave e/ou óbito) antes ou sem imunização foram classificados como casos não vacinados. A mesma classificação se aplicou aos óbitos, com indivíduos sendo classificados dependendo de seu *status* vacinal e início dos sintomas.

2.2.4 Dominância de variantes ao longo do tempo

Foram coletados dados referentes a amostras genômicas do *Global Initiative on Sharing All Influenza Data* (GISAID), que foram filtrados para o Brasil e estados brasileiros (SHU; MCCAULEY, 2017). Calculamos as proporções de variantes para cada estado e semana epidemiológica. Uma variante com frequência acima de 70% durante uma dada semana epidemiológica foi considerado como dominante, permitindo eventuais períodos de transição sem dominância de variantes (ou seja, semanas epidemiológicas sem variantes com proporção acima de 70%) (Apêndice B).

2.2.5 Modelagem estatística e análise

A efetividade absoluta da vacina (VE) é a proteção conferida contra o desfecho de interesse (casos graves ou óbitos) de indivíduos vacinados com o esquema vacinal primário, em comparação com o grupo não vacinado. A efetividade relativa (rVE) se refere a proteção contra os desfechos nos vacinados com o esquema primário e dose de reforço em comparação com o grupo de indivíduos com apenas o esquema primário.

A análise da VE (ou seja, usando o grupo de indivíduos não vacinados como ponto de comparação) foi estratificada por marca de vacina (CoronaVac, ChAdOx1 nCov-19, BNT162b2 ou Ad26.Cov2.S) quando as duas doses eram homólogas ou a vacina de dose

única (Ad26.Cov2.S). Ou seja, para esta análise, excluímos indivíduos com esquema primário de duas doses que se vacinaram com doses heterólogas. Na rVE (ou seja, usando o esquema primário como comparador), analisamos apenas as vacinas ChAdOx1 nCov-19 e BNT162b2, visto que ambas compreendiam cerca de 93% das doses de reforços administradas. Outras vacinas usadas como reforços foram excluídas (para detalhes sobre as exclusões, consulte o Apêndice B). A VE e o rVE foram avaliados em intervalos de 4 semanas e estratificados por idade em duas faixas etárias: 20-59 anos e ≥60 anos.

Na análise primária, comparamos (i) aqueles que completaram a o esquema primário de vacinação com os não vacinados (ou seja, VE), (ii) aqueles que receberam uma dose de reforço com aqueles indivíduos que receberam apenas o esquema primário (ou seja, rVE) e (iii) VE e rVE durante o domínio da variante Ômicron. Em uma análise secundária, também comparamos indivíduos com reforço com aqueles não vacinados e o VE e rVE para os períodos de domínio das variantes Delta e Gamma.

Casos graves de COVID-19 foram agrupados em dois grupos etários (20-59 anos e ≥60 anos), de acordo com o *status* vacinal (não vacinado, e os esquemas vacinais previamente descritos) e por estado de residência. O tempo foi dividido em janelas de tempo calendário *t* de tamanho *n* semanas. Indivíduos no estado de residência *l* e grupo etário *a*, se vacinados, foram classificados nessa janela de tempo como imunizados com um número *s* de semanas imunizado. Por exemplo, para *n=4* semanas, *s=1* para pessoas com 0-3 semanas após a vacinação, *s=2* para 4-7 semanas, e assim por diante. Para indivíduos não vacinados, o parâmetro *s* não varia. O número de $X_{t,s,a,l,v}$ pessoas numa janela *t* com esquema vacinal num intervalo *s* é estratificado por faixa etária *a*, estado de residência *l*, e *status* vacinal *v*. O método considera o total de pessoas-tempo $T_{t,s,a,l,v}$ o qual pessoas podem ser infectadas e desenvolver os desfechos de interesse por $T_{t,s,a,l,v} = n\ X_{t,s,a,l,v}$. Para uma combinação *i*, composta de faixa etária *a(i)*, estado *I(i)*, e *status* vacinal v_i ($v_i = 1$ para vacinados, $v_i = 0$ para não vacinados), tempo calendário t, tempo desde vacinação *s*, com desenvolver o desfecho Y_i sendo modelado como

$$Y_i \sim Poisson(\lambda_i),$$

onde $\log(\lambda_i) = \log(D_i) + \gamma_{h(i)} + \beta_{a(i),s(i)}\ v_i$, $\gamma_{h(i)}$ e $\beta_{a(i),s(i)}$ são efeitos aleatórios, em particular $\beta_{a(i),s(i)}$ é um efeito variável em função da idade, dependente do invervalo desde imunização, e *h(i)* é a combinação de tempo desde imunização, faixa etária, e estado. O termo D_i é o componente pessoa-tempo. O efeito aleatório $\gamma_{h(i)}$ indica a taxa de desfecho entre os não vacinados dado o grupo etário, estado. O efeito aleatório $\beta_{a(i),s(i)}$ indica o quanto a taxa de desfecho varia devido a vacinação.

A análise requer um mínimo de *m* de pessoas vacinadas por tempo calendário e tempo de a imunização, de modo que $X_{t,s,a,l,v} \geq m$ para evitar pequenas subamostras. Neste trabalho, m = 20. Para o grupo não vacinado, o componente pessoa-tempo requer uma avaliação do tempo total em que as pessoas não vacinadas estão em risco de casos graves dentro da janela de tempo, essa estimativa é obtida indiretamente por meio da cobertura vacinal. A proporção c_t de pessoas com pelo menos uma dose dividida pela estimativa populacional por faixa etária e estado produz a cobertura específica por idade e estado no tempo *t*. Para uma janela com limites b_1 e b_2, o componente pessoa-tempo é $nP_a(1-(c_{b1}+ c_{b2})/2)$, onde P_a é a estimativa populacional na faixa etária *a*. Sempre que a cobertura vacinal para um estado/faixa etária excedeu 95%, a população correspondente para todo o período do estudo foi redimensionada para manter a cobertura c_i limitada em 95%. Esse redimensionamento evita efeitos de pequeno números devido a incertezas nas estimativas populacionais, seguindo as estimativas de cobertura de vacinação adotadas pelo *Center for Disease Control and Prevention* (CDC) (CENTER FOR DISEASE CONTROL AND PREVENTION, 2021) .

A análise bayesiana permite a estimativa de todos os coeficientes, incluindo$\beta_{a(i),s(i)}$, os parâmetros $\gamma_{h(i)}$, entre outras estimativas. A distribuição *a priori* para os parâmetros $\gamma_{h(i)}$ e $\beta_{a(i),s(i)}$ são distribuições normais com média 0 e precisão de 0.01. A estimação dos parâmetros foi obtida por meio de uma simulação de MCMC com 3 cadeias, 6.000 iterações e *burn-in* de 4,000. Essa estimação permite obter a razão das taxas entre a taxa de R_v de casos graves de COVID-19 para os vacinados e a taxa R_u para o grupo de não vacinados, dada por $R_v/R_u = \exp(\beta_{a(i),s(i)})$. A VE é dada por $1 - R_v/R_u$. A análise bayesiana também nos permite computar diretamente os intervalos de incerteza.

2.2.6 Proteção da dose de reforço – rVE

A análise é semelhante à de VE. No entanto, a comparação é entre grupos indicados pela variável w_i, definindo combinações de doses de reforço e o esquema primário como o grupo de comparação, tal que $w_i = 1$ para pessoas vacinadas com dose de reforço *b* e série primária *p*, e $w_i = 0$ para pessoas vacinadas com apenas série primária *p*. Portanto, nesta análise, um modelo de Poisson de efeitos mistos semelhante descreve os resultados, substituindo a variável *v* pela variável *w*.

Uma análise bayesiana novamente permite a estimativa de $\beta_{a(i),s(i)}$, obtendo assim a razão de taxas, definida como a razão entre a taxa R_b de evento grave de COVID-19 para um grupo vacinado com doses de reforço e a taxa R_v para um grupo vacinado apenas com a série primária, dada por $R_b/R_v = exp(\beta_{a(i),s(i)})$. A rVE é dada por 1 - R_{vb}/R_{uv}.

2.2.7 Análise sobre períodos de dominância de variantes.

O tempo calendário e os períodos após imunização foram classificados por variantes de dominância em suas semanas iniciais. A análise estatística segue o mesmo raciocínio restringindo os intervalos a variante a ser analisada e estendendo os efeitos aleatórios para também serem ajustados pelo variante, de modo que $\beta_{a(i),s(i),u(i)}$ depende da faixa etária *a(i)*, tempo desde a imunização *s(i)*e da variante *u(i)*.

2.2.8 Análise para o desfecho óbito.

Sem perda de generalidade, essa mesma estrutura foi utilizada para analisar o óbito como o desfecho de interesse.

Nós utilizamos o R (versão 4.1.0) para análise de dados e JAGS foi usado para executar simulação MCMC (PLUMMER, 2017; R CORE TEAM, 2022) para estimar parâmetros do modelo. Seguimos as diretrizes de relatórios STROBE (Apêndice B) (VON ELM et al., 2007).

2.3 **Materiais e métodos referentes do manuscrito 3 - Estimated COVID-19 severe cases and deaths averted in the first year of the vaccination campaign in Brazil: a retrospective observational study**

2.3.1 Desenho do estudo, população e fonte de dados

Este foi um estudo ecológico usando dados observacionais para estimar o número de casos graves e óbitos por COVID-19 evitados de 17 de janeiro de 2021, data de início da campanha de vacinação em massa, até 31 de janeiro de 2022. Incluímos todos os indivíduos com idade ≥20 anos que receberam pelo menos uma dose das vacinas CoronaVac, ChAdOx1 nCov-19, BNT162b2 ou Ad26.COV2.S, ou que tiveram um caso grave deo COVID-19.

Analisamos dados selecionados de três bancos de dados nacionais: (i) Campanha de Vacinação COVID-19 (Plano Nacional de Imunização - PNI), que inclui dados individuais anônimos sobre a vacinação contra COVID-19 (MINISTÉRIO DA SAÚDE, 2022b); (ii) Doença Respiratória Aguda Grave (SRAG) do Sistema de Vigilância Epidemiológica da Gripe (SIVEP-Gripe), que contém dados sobre todos os casos graves de COVID-19 que levaram à hospitalização e óbitos por COVID-19 (MINISTÉRIO DA SAÚDE, 2022c); e (iii) dados do Instituto Brasileiro de Geografia e Estatística (IBGE) sobre estimativas populacionais específicas por idade a nível nacional, estadual e municipal (INSTITUTO BRASILEIRO DE GEOGRAFIA E ESTATISTICA (IBGE), 2020). Os dados do SI-PNI e do SIVEP-Gripe foram vinculados probabilisticamente pelo Ministério da Saúde do Brasil e mais informações são fornecidas no Apêndice C.

Excluímos indivíduos que: (i) foram vacinados, mas não tinham registro das datas de vacinação; (ii) tiveram infecção confirmada em laboratório, mas não tinham registro da data de início dos sintomas; e (iii) foram vacinados, mas tinham registros de vacinação inconsistentes, como discordância entre a primeira e a segunda vacinas ou ausência de registro da segunda dose para aqueles em um esquema de vacinação de duas doses, ou ausência de registro de qualquer uma das duas primeiras doses em indivíduos com a dose de reforço (o diagrama de fluxo que ilustra as etapas para atingir a população final é apresentado no Apêndice C).

2.3.2 Desfecho

Estimamos a carga evitada para dois desfechos: casos graves de COVID-19 e óbitos por COVID-19. Definimos casos graves de COVID-19 e óbitos em vacinados como aqueles indivíduos confirmado laboratorialmente com RT-PCR ou positividade no teste rápido de antígeno pelo menos 14 dias após a vacinação, seguindo as definições fornecidas pelo Ministério da Saúde do Brasil (detalhadas no Apêndice C). O grupo não vacinado foi definido como indivíduos com registros de doença grave ou morte, mas sem registro de vacinação, ou indivíduos com registros de vacinação cujo início dos sintomas ocorreu antes da primeira dose da vacina. Os resultados com início dos sintomas ocorrendo ≤14 dias após a data da vacinação foram excluídos da análise.

2.3.3 Grupos vacinais

Calculamos o número de casos graves de COVID-19 e mortes evitadas entre indivíduos que foram (i) "pelo menos parcialmente vacinados", definidos como aqueles que receberam pelo menos uma dose de uma vacina de duas doses (ou seja, vacinas CoronaVac, ChAdOx1 nCov-19, BNT162b2); e dois outros subconjuntos de vacinação: (ii) "totalmente vacinados", definidos como aqueles que receberam uma dose de Ad26.COV2.S ou duas doses das outras três vacinas; e (iii) "vacinados com reforço", definidos como aqueles que foram totalmente vacinados e receberam uma dose de reforço. Apenas uma dose de reforço foi aprovada no Brasil durante o período coberto por este estudo.

2.3.4 Análise estatística

Para estimar a carga evitada de COVID-19, usamos as etapas descritas por Haas (HAAS et al., 2022). Inicialmente, calculamos a população suscetível diária em categorias específicas por idade (20–29, 30–39, 40–49, 50–59, 60–69, 70–79, 80–89 e ≥90 anos) subtraindo o número de novos casos das estimativas populacionais dentro de cada faixa etária

(IBGE). Em seguida, atribuímos a população suscetível ao grupo não vacinado ou aos grupos vacinados, para cada uma das categorias de vacinação mencionadas acima. Em seguida, calculamos as taxas de incidência de desfechos diárias e específicas por idade para os grupos não vacinados e vacinados para cada desfecho (casos graves e mortes). O número de pessoas-tempo para cada grupo de vacinação foi calculado multiplicando a proporção diária da população suscetível em cada grupo de vacinação pelas estimativas populacionais por faixa etária do IBGE (INSTITUTO BRASILEIRO DE GEOGRAFIA E ESTATISTICA (IBGE), 2020; INSTITUTO BRASILEIRO DE GEOGRAFIA E ESTATÍSTICA, 2021). O número de pessoas-tempo para o grupo não vacinado foi calculado subtraindo o número de pessoas-tempo dos grupos vacinados das estimativas populacionais do IBGE. Em seguida, para cada desfecho e grupo de vacinação, calculamos as diferenças diárias de taxas específicas por idade entre os não vacinados e vacinados e seus respectivos intervalos de confiança (IC) de 95%.
Finalmente, para cada faixa etária, multiplicamos as diferenças diárias de taxas pela população suscetível (ou seja, a população sem evidência prévia de COVID-19) e pela proporção de indivíduos que receberam pelo menos uma dose da vacina. Esse processo foi repetido e somado para todos os dias de acompanhamento para cada resultado para estimar a carga de COVID-19 evitada pela vacinação em massa. As etapas acima mencionadas foram inicialmente determinadas nacionalmente e então repetidas para cada um dos 27 estados brasileiros e suas 5569 cidades.
Todas as análises foram realizadas usando o software estatístico R (versão 4.1.1) (R CORE TEAM, 2022).

2.4 **Materiais e métodos referentes do manuscrito 4 - The impact of vaccination on the length of stay of hospitalized COVID-19 patients in Brazil**

2.4.1 Desenho do estudo, população e fonte de dados

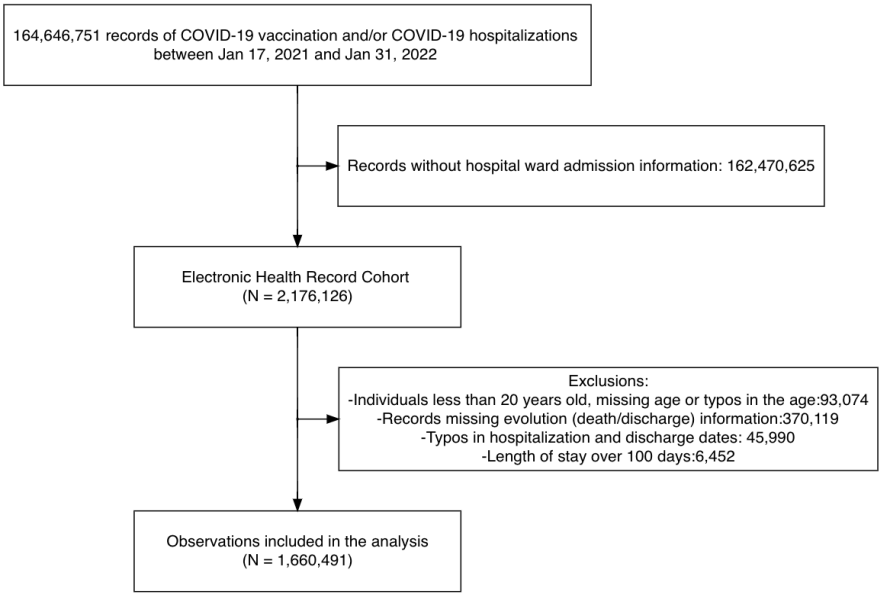
Analisamos dados de dois bancos de dados nacionais: (i) Sistema de Informação do Programa Nacional de Imunização (PNI) (MINISTÉRIO DA SAÚDE, 2021a), que inclui dados individuais anônimos sobre a vacinação contra a COVID-19; (ii) Doença Respiratória Aguda Grave (SRAG) do Sistema de Vigilância Epidemiológica da Gripe (SIVEP-Gripe)

(MINISTÉRIO DA SAÚDE, 2021b, 2022a), um banco de dados nacional que contém dados sobre todos os casos graves de COVID-19 que levaram à hospitalização. Os dados da vacinação (SI-PNI) e dos casos graves de COVID-19 (SIVEP-Gripe) foram vinculados probabilisticamente pelo Ministério da Saúde do Brasil, e os detalhes sobre a vinculação estão detalhados em SANTOS et al., 2023a. O conjunto de dados não contém informações pessoais que nos permitam identificar múltiplas internações hospitalares para a mesma pessoa.

O conjunto de dados vinculado original consistia em 164.646.751 observações, incluindo mais de 2 milhões de casos graves de COVID-19. Cada linha corresponde a um episódio de admissão hospitalar e/ou registro de vacinação, com colunas informando a data da admissão hospitalar, a data de entrada na Unidade de Terapia Intensiva (UTI), o desfecho (óbito ou alta), a data do desfecho, a idade em anos (posteriormente agrupada em 20-49 anos, 50-69 anos e 70 ou + anos), a marca da vacina e as datas de vacinação para todo o país no período entre 17 de janeiro de 2021 e 31 de janeiro de 2022.

Foram incluídas as hospitalizações com COVID-19 confirmada em laboratório (n=2.176.126). Excluímos observações: (i); com idade inferior a 20 anos, idade omitida ou apresentando erros de digitação na idade (por exemplo, valores negativos de idade) (93.074 observações), (ii) data de evolução ausente (370.119 observações), (iii) apresentaram valores aberrantes de admissão e/ou alta hospitalar (por exemplo, admissão hospitalar anterior ao início da pandemia e datas de alta anteriores à admissão - 45.990 observações), (iv) com internação hospitalar superior a 100 dias (6.452 observações), dado que internações hospitalares substancialmente longas (mesmo no caso de serem informações verdadeiras) teriam efeito desproporcional no ajuste (Figura 1).

Figura 1. Diagrama de fluxo da população de estudo



Fonte: O autor

2.4.2 Grupos vacinais

A vacinação no Brasil começou em janeiro de 2021 com as vacinas CoronaVac (Sinovac Biotech) de duas doses e ChAdOx1 nCov-19 (AstraZeneca/Universidade de Oxford). A introdução das vacinas BNT162b2 de duas doses (Pfizer–BioNTech) e Ad26.Cov2.S de dose única (Janssen) ocorreu tempo depois, em maio e junho de 2021, respectivamente. A vacinação priorizou inicialmente grupos populacionais com alto risco de doença grave (por exemplo, idosos e pessoas com condições crônicas de saúde), além de populações vulneráveis (por exemplo, indígenas) e profissionais de saúde. Posteriormente, a vacinação se estendeu a toda a população de acordo com as faixas etárias, dos mais velhos aos mais jovens (MINISTÉRIO DA SAÚDE, 2021a, 2022b).

Os indivíduos incluídos no estudo foram classificados em um dos seguintes grupos: (i) não vacinados, como aqueles sem nenhum registro de vacinação no momento da admissão hospitalar; (ii) parcialmente vacinados, aqueles que receberam apenas uma dose de uma vacina de duas doses (ou seja, vacinas CoronaVac, ChAdOx1 nCov-19, BNT162b2); (iii) totalmente vacinados, definidos como aqueles que receberam duas doses das vacinas (ou uma

dose do Ad26.COV2.S); e (iv) vacinados com reforço, definidos como aqueles que foram totalmente vacinados e receberam qualquer dose de reforço. Apenas uma dose de reforço foi aprovada no Brasil durante o período do estudo.

2.4.3 Modelo de sobrevida multi-estado

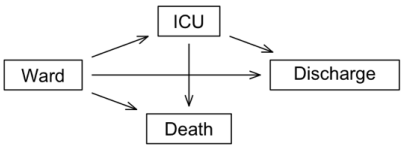
Utilizamos um modelo de sobrevida de risco competitivo específico para idade. Essa estrutura já foi utilizada anteriormente para modelar a demanda hospitalar e demonstrou produzir estimativas confiáveis do tempo de internação durante a pandemia de COVID-19 (GROSSO et al., 2021; PRESANIS et al., 2021; VEKARIA et al., 2021; JACKSON et al., 2022; TOBIN et al., 2023).

A progressão do paciente pelo hospital foi representada por um modelo multiestado, com os seguintes estados: enfermaria, UTI, alta e óbito, conforme descrito na Figura 2. No modelo, os indivíduos podem fazer a transição de enfermaria para UTI, enfermaria para alta, enfermaria para óbito, UTI para alta e UTI para óbito. Ou seja, o modelo permite apenas a enfermaria como estado de entrada e não permite o retorno entre os estados.

Nosso objetivo foi estimar o tempo para cada transição (ou seja, enfermaria para alta, enfermaria para UTI e UTI para alta) e também estimar a probabilidade dessas transições.
Essa abordagem de risco competitivo produz probabilidades de tempo para evento e transição que são mais diretas de interpretar e utilizar em trabalhos de modelagem posteriores do que a abordagem comum de riscos específicos de causa para analisar dados de sobrevivência em vários estados (LARSON, MARTIN; DINSE, 1985; JACKSON et al., 2022; TOBIN et al., 2023). Modelamos a distribuição do tempo de internação como uma distribuição *gama* condicional à faixa etária (20-49 anos, 50-69 anos e 70 ou + anos) e calculamos a estimativa de máxima verossimilhança para esse modelo em nossos dados de tempo para evento (ou seja, número de dias gastos em cada estado), produzindo distribuições preditivas e probabilidades cumulativas de sobrevivência em cada caminho.

Todas as análises foram realizadas no R versão 4.10, utilizando o pacote flexsurv (JACKSON, 2016; R CORE TEAM, 2022).

Figura 2. Modelo multi estados utilizado no estudo



Fonte: O autor

3. RESULTADOS

3.1 *Disability-adjusted life years associated with COVID-19 in Brazil, 2020* (Anos de vida ajustados por incapacidade associados com a COVID-19 no Brasil, 2020)

(*Submetido* a *PLOS One*)

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Resumo

Introdução: Este estudo objetivou quantificar a carga, a nível nacional e estadual, da COVID-19 no Brasil durante 2020 e a contrastar com a carga de outras causas de doenças.

Metodologia: Usamos dados de vigilância sobre casos de COVID-19, hospitalizações e mortes entre fevereiro/2020 e dezembro/2020. Calculamos os anos de vida ajustados por incapacidade (Disability-adjusted life Years - *DALYs*) com base no modelo de consenso da COVID-19 e métodos desenvolvidos pela *European Burden of Disease Network*, que inclui casos leves, graves, críticos, covid longa e morte prematura. Usamos estimativas de DALYs do Brasil da *Global Burden of Disease Collaborative Network* para comparar a carga da COVID-19 com a de outras causas de doenças e lesões.

Resultados: A COVID-19 levou a 5.445.785 DALYs, ou 2.567 DALYs/100.000, com >99% da carga causada por mortalidade prematura. Os estados mais populosos

apresentaram os maiores DALYs. No entanto, os DALYs por 100.000 habitantes foram maiores nos estados de Roraima, Rio de Janeiro e Amapá. Assumindo que não houve grandes mudanças na carga de doenças de outras causas de doenças e lesões de 2019 a 2020 no Brasil, a carga da COVID-19 seria classificada como a principal causa em 2020.

Conclusões: A COVID-19 impactou severamente a saúde populacional do Brasil em 2020, destacando a falta de esforços eficazes de mitigação.

Palavras-chave: SARS-CoV2, pandemia, coronavírus, Brasil, Carga de doença, YLD, YLL, DALY, saúde populacional.

Abstract

Background: We quantified the national- and state-level burden of COVID-19 in Brazil during 2020 and contrasted it to the burden from other causes of disease and injury.

Methods: We used national surveillance data on COVID-19 cases, hospitalisations and deaths between February/2020 to December/2020. We calculated disability-adjusted life years (DALYs) based on the COVID-19 consensus model and methods developed by the European Burden of Disease Network, which includes mild, severe, critical cases, long covid and premature death. We used Brazil DALYs estimates from the Global Burden of Disease Collaborative Network to compare the COVID-19 burden to that from other causes of disease and injury.

Results: COVID-19's led to 5,445,785 DALYs, or 2,567 DALYs/100,000, with >99% of the burden caused by premature mortality. Most populated states experienced the highest DALYs. However, the DALYs per 100,000 population were higher in the Roraima, Rio de Janeiro, and Amapá states. Assuming no major changes in disease burden from other causes of disease and injury from 2019 to 2020 in Brazil, COVID-19's burden would rank as the leading cause in 2020.

Conclusions: COVID-19 severely impacted Brazil's populational health in 2020, highlighting the lack of effective mitigation efforts.

Keywords: SARS-CoV2, pandemic, coronavirus, Brazil, Burden of disease, YLD, YLL, DALY, population health.

Background

In December 2019, the first outbreak caused by the severe respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified in Wuhan, China. Later in March 2020, the World Health Organization (WHO) declared the Coronavirus disease 2019 (COVID-19) a pandemic [1]. In Brazil, the first case was reported on February 26, 2020. Over that year, 7 million cases and 190,000 deaths were registered, and the inability of Brazil's federal government to develop a nationwide plan to combat the pandemic directly affected the implementation of public health measures to control the spread of the disease [2–4].

Since the start of the pandemic, many efforts have been made to measure the health impact of COVID-19 on the population, including monitoring and daily publication of new cases, hospitalisation and deaths[2]. In Brazil, the Ministry of Health is responsible for COVID-19 surveillance, including monitoring and recording case counts, hospital admission, and deaths. Additionally, a myriad of studies have been undertaken focusing on different perspectives of the disease, including national and local seroprevalence surveys [5,6], estimates of excess mortality[7], and evaluations of the impact of vaccination, social vulnerability and mobility on COVID-19 incidence and mortality[8–10]. All these studies have helped to monitor the evolution of the pandemic over space and time and quantify the effects of measures to reduce disease incidence.

Nevertheless, an overall assessment of the health burden of COVID-19, which accounts for the disease's morbidity and mortality in a single metric, can be of great use in facilitating the comparison with other countries and diseases. This can be achieved by standardising the population health loss due to both cases and deaths as a function of time, using the disability-adjusted life years (DALYs) metric [11–13]. The morbidity is translated into estimates of years lived with disability (YLD), adjusting for the severity of the disability caused by the disease or injury. The mortality is translated into years of life lost due to premature mortality (YLL), using age-conditional life tables, considering that deaths at younger ages have a more significant impact on population health[11–13].

This study aimed to estimate the direct impact of COVID-19 on the Brazilian population's health during 2020 and to contrast COVID-19's burden with that from other causes of disease and injury.

Methods

Data

We used data from four national databases: (i) Flu-like syndrome (*Síndrome Gripal*) from the E-SUS Notifica, which includes anonymised individual-level data on suspected cases of COVID-19 [14,15]; (ii) Severe Acute Respiratory Infection/Illness (SARI) from the Influenza Epidemiological Surveillance System (SIVEP-Gripe) [16], which holds anonymised individual-level data on all COVID-19 severe cases that led to hospitalisation; (iii) the Mortality Information System (*Sistema de Informações sobre Mortalidade - SIM*)[17] database, which includes anonymised individual-level data on all deaths registered in the country, and (iv) Brazilian Institute for Geography and Statistics (IBGE) database on sex and age-specific population estimates at the national and state levels[18,19].

We filtered the disease and death records which contain information on sex, age, state and symptom onset/hospitalisation onset between February 26, 2020, and December 31, 2020. The COVID-19 deaths were those where the primary cause of death was coded using the WHO International Classification of Disease 10th revision (ICD-10) codes U071 (COVID-19, Virus identified), U072 (COVID-19, Virus not identified), B342 (Coronavirus infection unspecified), B972 (Coronavirus as the cause of diseases classified elsewhere), U109 (Multisystem inflammatory syndrome associated with COVID-19, unspecified)[20]. To estimate the YLD, the disease registries were aggregated by five-year age group, sex, and state. The death registries followed the same grouping as the disease registries, except that the under-5-year age group was split into under-one-year old and 1-4 years of age. The oldest age group was set at 95 years or older.

To compare the COVID-19 burden to the burden from other causes of disease and injury in Brazil, we used data from the GBD results tool from the Global Burden of Disease Collaborative Network of the Institute for Health Metrics and Evaluation (IHME)[12,21]. Burden of disease estimates for 2020 was not available by the time of the preparation of the manuscript; hence we used 2019 DALY estimates for both sexes, including all ages and grouped the estimates by level-3 causes. The estimates are freely available on the IHME website (https://vizhub.healthdata.org/gbd-results/), and the resulting dataset is presented in Apêndice A.

Disability-Adjusted Life Year (DALY)

The DALY is a health metric measuring the healthy life years lost due to a disease. DALYs are estimated by summing the number of years of life lost due to premature mortality (i.e., YLLs) and the number of years lived with disability, adjusted for the severity of the disease (i.e., YLDs). When estimating DALYs from COVID-19, we accounted for all health states experienced upon infection and development of symptoms, which were classified as "mild to moderate", "severe", "critical", "long COVID", and death due to COVID-19.

Years of life lost due to premature mortality (YLL)

YLLs were calculated by multiplying the number of deaths in each age group and sex by the residual life expectancy at the age of death:

$$YLL = Deaths\ X\ RLE$$

where *RLE* corresponds to the remaining life expectancy. We used the age-conditional life expectancy defined by the GBD 2019 reference life table [22].

Years lived with disability (YLD)

To estimate the severity of each health state, we obtained disability weights (DWs) from the 2019 Global Burden of Disease study (2019 GBD study) and the European Disability Weight (EDWS) study [12,13,22–24]. The DW reflects the severity of a health state (i.e., the reduction in the quality of life). For each health state, we combined data on the incidence from the surveillance systems, duration and disability from the literature and calculated the YLD by summing the product of the number of cases, duration (in years) and DW across all health states groups as follows:

$$YLD = Incidence\ X\ Duration\ X\ DW$$

We defined as mild to moderate cases all the records with a confirmed diagnosis of COVID-19 that did not lead to hospitalisation. Severe cases were defined as hospitalised cases that did not require intensive care. We classified critical cases as those where intensive care was provided. To estimate the YLD due to "long COVID", we assumed that approximately 1-in-7 patients (i.e., 13.3%) of mild to moderate cases would suffer post-acute consequences for 28 days, reflecting early evidence from the literature [25]. We defined the mean duration of mild to moderate cases as ten days [26]. We calculated the duration of severe and critical cases as the mean duration of hospitalisation and ICU admission. The health states definitions, DW from the GBD

and EDWS and the data sources are shown in Table 2. To explore spatial differences in the COVID-19 burden across the country, in a secondary analysis, we estimated the DALYs for each Brazilian state in 2020.

Uncertainty and sensitivity analysis

Following similar studies, we used Monte Carlo simulations from a beta PERT distribution to sample random values from a specified uncertainty distribution of the DW range values [27–30]. In each of the 10,000 iterations, the DW sample values were used to calculate a YLD estimate. The combination of iterations results in an empirical distribution of YLD estimates, reflecting the joint uncertainty in the input parameters (i.e., DW range values), which were summarised by its 95% bootstrapped uncertainty intervals (UI). Furthermore, we used a univariate sensitivity analysis to quantify the impact of the uncertainties around the number of COVID-19 mild to moderate, severe and critical cases and the proportion of cases that suffer from long COVID [29,31]. This sensitivity analysis was based on assuming two scenarios: a lower-bound scenario, where we decrease the duration and the number of cases by half, and an upper-bound scenario, where we double the health state duration and the number of cases, respectively (Apêndice A).

All analyses were run in R version 4.1.2; the code is available in supplementary material 2 [32].

Table 2 COVID-19 health states, attributable disability weights and data sources

Health state	Health state description	Data	Duration (days)	Data source	Disability weight (95% uncertainty interval)
Mild to moderate	Non-hospitalised symptomatic case, which causes some difficulty with daily activities	Number of symptomatic cases (non-hospitalised)	10[26]	E-SUS[15]	0.051 (0.032-0.074)
Severe	Hospitalised symptomatic case, which causes great difficulty with daily activities	Number of hospitalised patients (non-intensive care)	Estimated mean duration of hospital stay	SIVEP-Gripe[16]	0.133 (0.088-0.190)
Critical	Hospitalised symptomatic case requiring intensive care unit admission with or without respiratory support.	Number of hospitalised patients (intensive care)	Estimated mean duration of ICU stay	SIVEP-Gripe[16]	0.655 (0.579-0.727)
Long COVID (Post-acute consequences)	Suffers from a symptomatic health loss post-infection, such as fatigue, emotional lability, insomnia etc.	Estimated based on the fraction (13.3%) of mild to moderate cases that evolved to long covid (1-in-7) [25]	28[25]	E-SUS[15]	0.219 (0.148-0.308)

ICU: Intensive Care Unit
Fonte: O autor

Results

From February 26, 2020, to December 31, 2020, more than 7.8 million mild to moderate, severe, and critical COVID-19 cases were notified in Brazil, and 221,012 deaths (Table 3 and Apêndice B). Based on the number of mild to moderate cases, we estimated that 942,263 persons suffered from long covid, such as fatigue and insomnia (Table 2 and Apêndice A).

The estimated COVID-19 burden in 2020 was 5,445,785 DALYs (95% uncertainty interval (UI) 5,438,752-5,458,732), corresponding to 2,567 DALYs per 100,000 population. For both sexes, more than 99% of the total DALY burden was experienced by individuals between 30 and 84 years of age, with the higher burden experienced by males between 60- and 74-year-old groups (Figure 1a and

supplementary material 3). The DALY rate showed that most of the burden was experienced by individuals aged 60 years or more (Figure 3 and Apêndice A).

A total of 37,281 years of life were lost due to disability (i.e., YLD), accounting for 0.69% of the total DALY burden. The mild cases contributed to 26.55% of the crude YLD, long covid to 42.46%, severe cases to 21.76% and critical to 9.22% (Apêndice A). Nevertheless, the YLD rate was led by severe cases (approx. 38% of the YLD rate) (Apêndice A). Deaths due to COVID-19 resulted in 5,408,504 years of life lost (YLL) due to premature mortality, with males accounting for 59% of the YLL (Table 4). The COVID-19 deaths resulted, on average, in 24 years of life lost due to premature mortality.

When comparing the estimated DALYs resulting from COVID-19 in 2020 with Brazil's leading causes of disease and injury in 2019, COVID-19's burden surpassed the burden of all diseases and injuries, suggesting that it may have been the leading cause of disease and injury in Brazil in 2020 (Figure 4). The estimated COVID-19 DALYs were considerably greater than those from interpersonal violence (3,649,901 to 3,979,773 DALYs) and ischemic heart disease (3,507,748 to 3,892,657 DALYs).

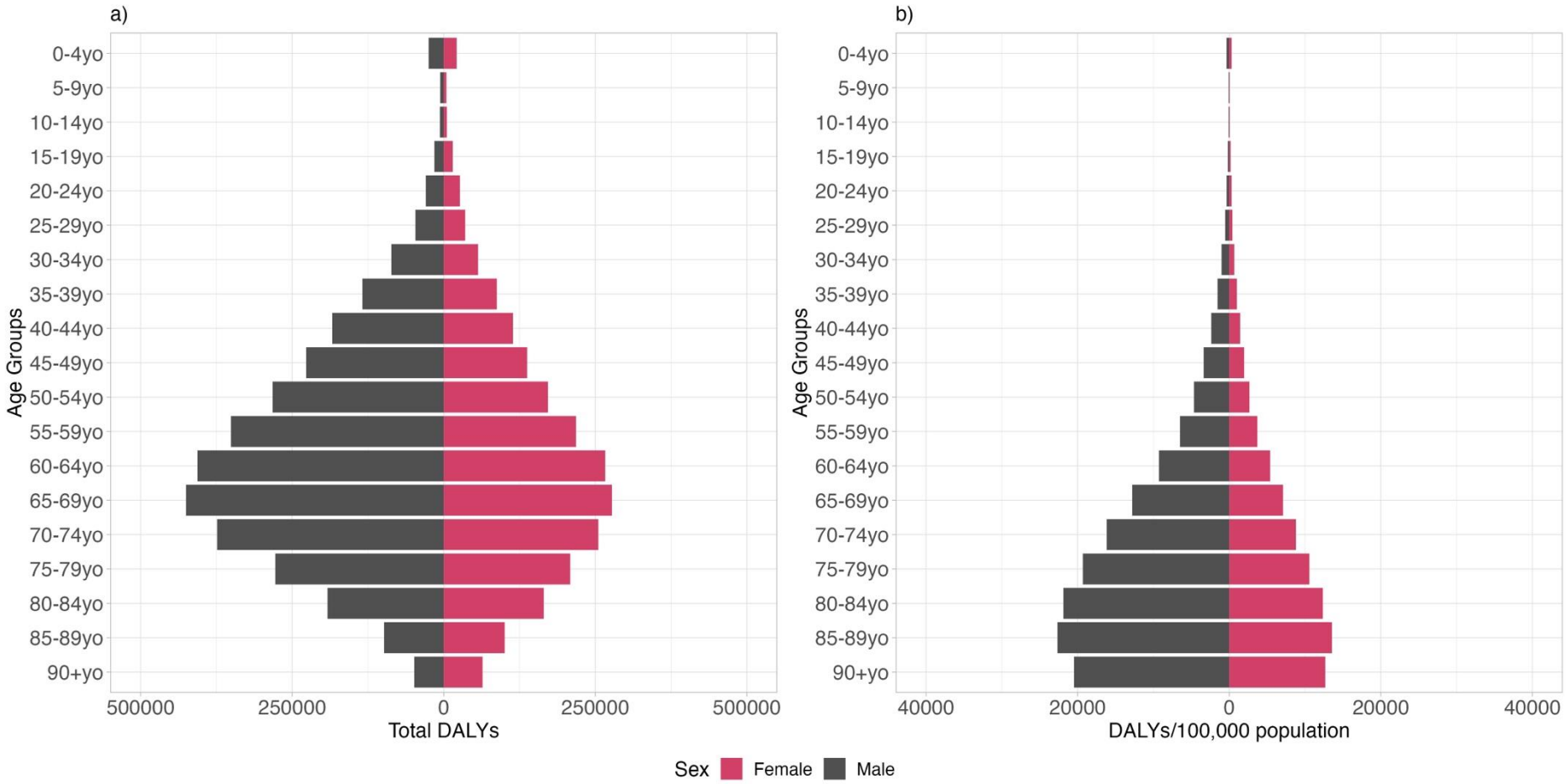
Figure 3 illustrates the distribution of DALYs due to COVID-19 in the Brazilian states in 2020. More DALYs were lost in the Southeast states of São Paulo, Rio de Janeiro, and Minas Gerais, while the states of Acre, Roraima, and Amapá presented the lowest estimates (Figure 5a). However, when accounting for the state's population size, we note that the highest COVID-19 burden was experienced in the states of the North, such as Roraima, Amapá and Amazonas, and also in the Southeast, in Rio de Janeiro (Figure 5b).

Table 3. Absolute number of observed COVID-19 mild to moderate, severe, and critical cases, and of deaths due to COVID-19, and estimated number of long covid cases in Brazil, by age group and sex, between February 26, and December 31, 2020

Age group	**Mild cases**		**Long covid**		**Severe cases**		**Critical cases**		**Deaths**	
	Female	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**
0-4 years	48571	59751	6460	7947	9973	12957	1900	2340	237	275
5-9 years	48951	65774	6510	8748	6252	8158	1007	1251	50	65
10-14 years	63810	74438	8487	9900	3369	3800	564	681	62	76
15-19 years	134577	121308	17899	16134	3806	2629	589	498	194	201
20-24 years	321839	301734	42805	40131	6938	4900	979	889	367	411
25-29 years	416798	382358	55434	50854	9014	7974	1375	1587	525	706
30-34 years	446916	415186	59440	55220	11523	12689	1855	2623	926	1431
35-39 years	473536	431249	62980	57356	14306	18163	2650	4025	1578	2435
40-44 years	444606	393178	59133	52293	15251	21948	3008	4985	2278	3690
45-49 years	353852	305690	47062	40657	16172	23905	3468	5951	3061	5072
50-54 years	293577	249889	39046	33235	18957	26327	4395	7536	4301	7087
55-59 years	239565	205887	31862	27383	21821	28815	5767	8996	6212	10012
60-64 years	164777	147879	21915	19668	23509	29061	7066	10463	8768	13389
65-69 years	108902	100710	14484	13394	23708	29287	7895	11312	10769	16515
70-74 years	66427	63031	8835	8383	22993	27033	8144	10714	11943	17524
75-79 years	37415	34914	4976	4644	20851	22187	7511	9285	12162	16210
80-84 years	18740	18350	2492	2441	19802	18672	7049	7280	12422	14445
85-89 years	9461	9415	1258	1252	15239	12129	5224	4577	10032	9821
90 or + years	5569	6056	741	805	12892	7969	3689	2520	8988	6772
Total	3697889	3386797	491819	450444	276376	318603	74135	97513	94875	126137

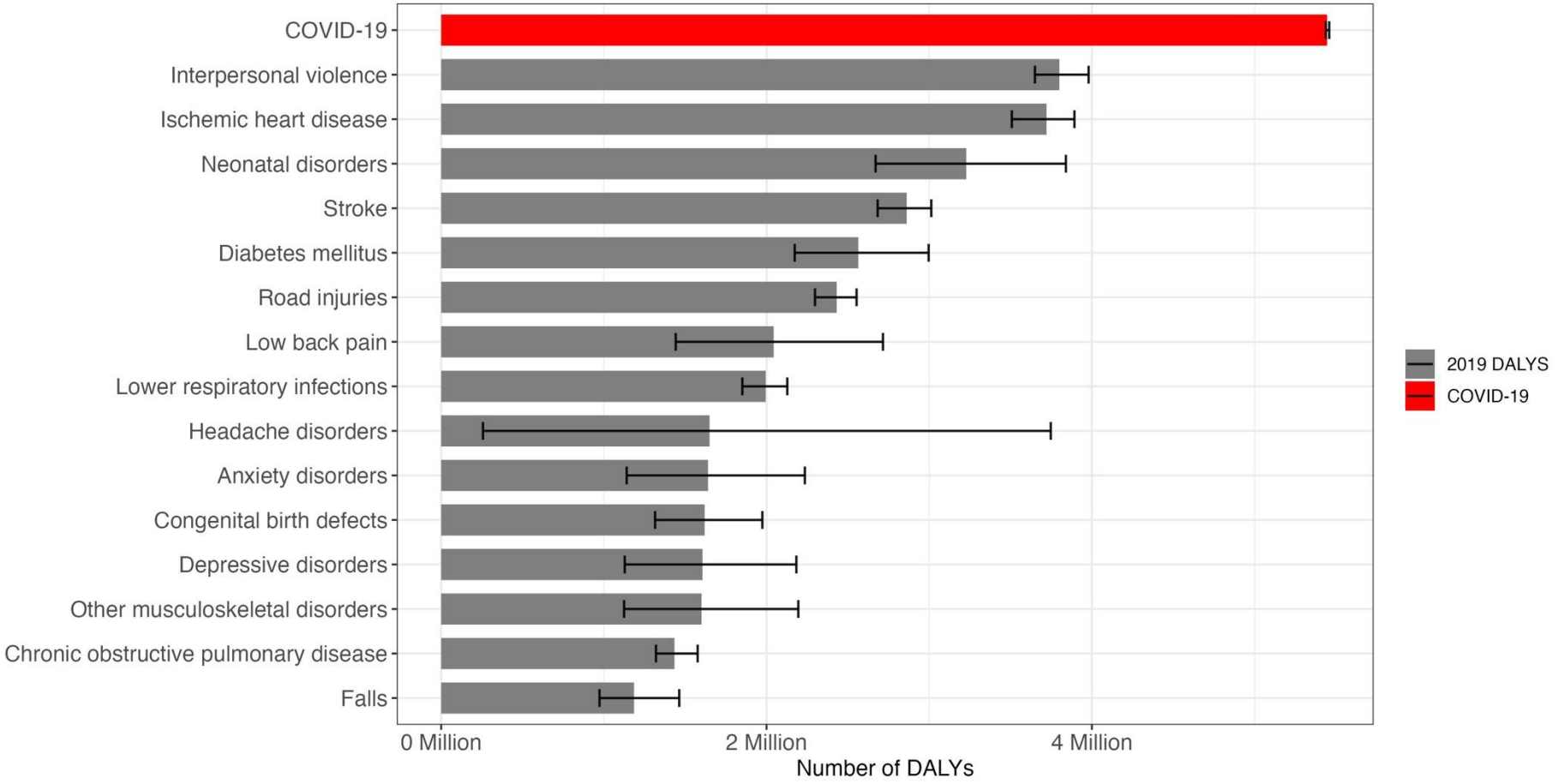
Fonte: O autor

Figure 3. Distribution of estimated (a) Disability-adjusted life years (DALY) and (b) DALY per 100,000 individuals due to COVID-19 in Brazil by age group and sex between February 26, 2020, and December 31, 2020.



Fonte: O autor

Figure 4. Estimate of the number of DALYs lost for COVID-19 in 2020 and from the pre-pandemic 15 leading causes of disease and injury in Brazil in 2019.



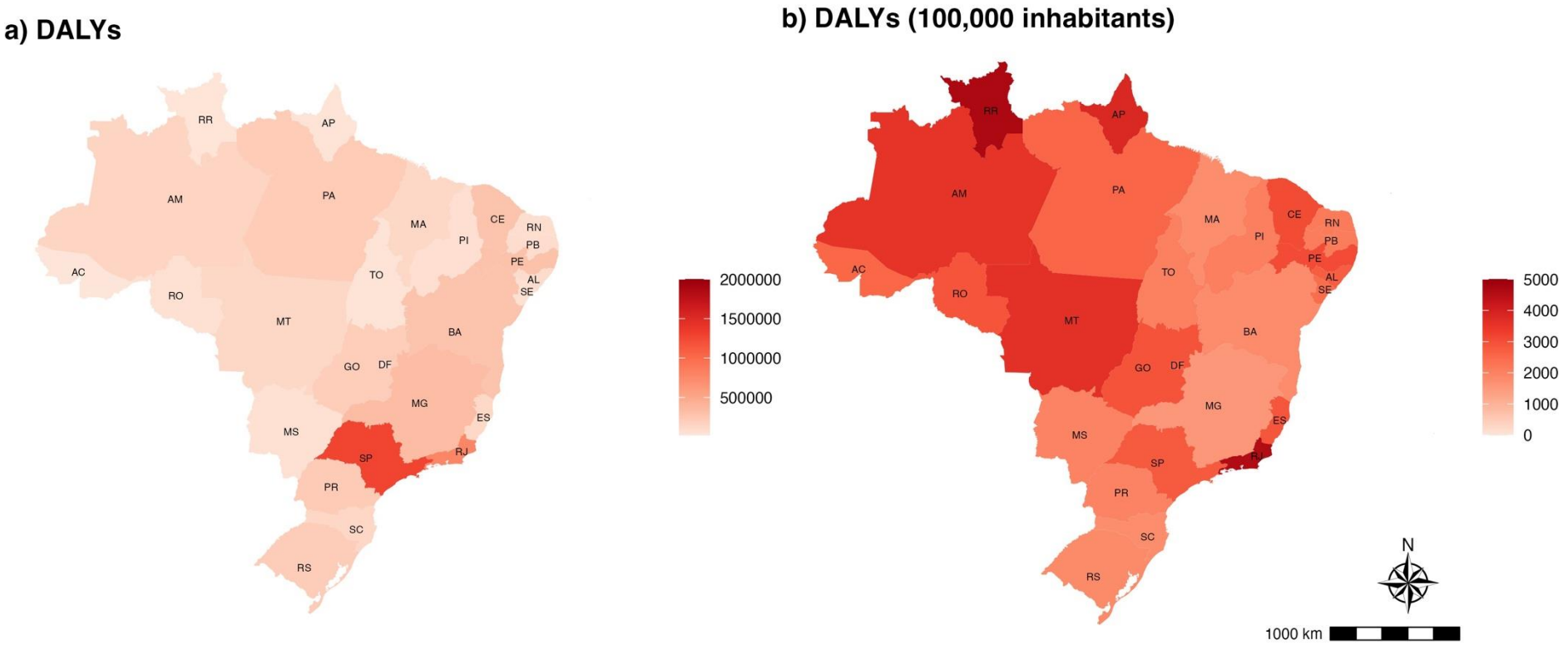
Fonte: O autor

Table 4 Total number of years of life lost due to disability (YLD) and years of life lost due to premature mortality (YLL) due to COVID-19 in Brazil by age group and sex between February 26, 2020, to December 31, 2020

Age group	YLD (95% Uncertainty interval)				YLL			
	Female		Male		Female		Male	
	Crude	Per 100,000 population	Crude	Per 100,000 population	Crude	Per 100,000 population	Crude	Per 100,000 population
0-4 years	350.46 (296.68-490.04)	5.18 (4.39-7.25)	440.57 (373.66-620.04)	6.22 (5.27-8.75)	20973.75	310.20	24356.98	343.83
5-9 years	283.21 (233.81-391.32)	3.94 (3.25-5.44)	375.19 (308.62-517.67)	4.99 (4.10-6.88)	4201.50	58.46	5461.96	72.62
10-14 years	288.98 (228.5-387.45)	3.75 (2.96-5.03)	335.80 (266.28-449.61)	4.17 (3.31-5.58)	4900.87	63.57	6007.52	74.61
15-19 years	552.44 (426.32-727.83)	6.68 (5.16-8.81)	486.38 (376.53-639.32)	5.67 (4.39-7.45)	14368.91	173.87	14887.38	173.57
20-24 years	1283.04 (989.71-1681.11)	15.25 (11.76-19.98)	1180.43 (903.46-1547.65)	13.68 (10.47-17.94)	25362.48	301.49	28403.21	329.21
25-29 years	1664.15 (1279.36-2185.46)	19.78 (15.21-25.98)	1529.13 (1176.25-2011.06)	17.94 (13.80-23.60)	33678.38	400.32	45289.41	531.37
30-34 years	1817.36 (1400.31-2396.65)	21.35 (16.45-28.15)	1733.41 (1352.16-2289.19)	20.32 (15.85-26.83)	54815.75	643.92	84709.87	992.99
35-39 years	1967.91 (1530.12-2596.88)	22.42 (17.43-29.59)	1894.48 (1491.57-2516.14)	21.78 (17.15-28.93)	85610.62	975.43	132105.11	1519.06
40-44 years	1882.91 (1467.20-2491.13)	23.78 (18.53-31.46)	1827.07 (1453.83-2436.42)	23.58 (18.77-31.45)	112345.02	1418.88	181981.18	2348.91
45-49 years	1575.09 (1240.08-2093.94)	22.56 (17.76-29.99)	1555.38 (1261.94-2098.43)	23.12 (18.76-31.20)	136010.39	1948.05	225365.80	3350.59
50-54 years	1412.74 (1124.79-1894.26)	21.99 (17.51-29.49)	1417.50 (1161.01-1923.33)	23.38 (19.15-31.72)	170469.01	2653.63	280891.39	4632.03
55-59 years	1283.13 (1041.9-1735.07)	21.84 (17.73-29.53)	1320.88 (1104.39-1804.19)	24.46 (20.45-33.41)	216891.24	3691.15	349567.79	6473.43
60-64 years	1060.56 (882.79-1447.61)	21.51 (17.90-29.36)	1142.95 (972.8-1568.26)	26.11 (22.22-35.41)	265262.15	5379.19	405063.28	9254.17
65-69 years	876.96 (748.9-1212.51)	22.43 (19.15-31.01)	991.73 (863.92-1373.64)	29.87 (26.02-41.38)	276557.56	7073.61	424119.99	12775.13
70-74 years	717.94 (630.53-1002.1)	24.79 (21.77-34.60)	812.17 (719.78-1130.21)	35.11 (31.12-48.86)	254244.97	8777.73	373054.42	16129.05
75-79 years	570.68 (512.28-803.48)	28.92 (25.96-40.72)	615.35 (555.38-858.12)	42.78 (38.61-59.65)	208012.95	10542.01	277247.97	19272.58
80-84 years	479.30 (439.52-682.54)	35.89 (32.91-51.11)	467.10 (427.42-659.36)	53.29 (48.76-75.22)	164451.44	12313.65	191233.38	21817.22
85-89 years	346.82 (322.39-497.67)	46.74 (43.45-67.07)	291.28 (267.69-414.38)	67.08 (61.65-85.42)	100221.50	13506.01	98113.57	22594.06
90 or + years	269.93 (249.99-392.83)	53.37 (49.43-77.67)	181.14 (166.58-261.31)	76.30 (70.16-110.06)	63817.72	12617.76	48447.41	20404.75
Total	18683.62 (15045.19-25109.86)	422.17 (358.72-528.22)	18597.96 (15203.26-25118.34)	519.85(450.02-720.18)	2212196.23	82848.93	3196307.63	143089.18

Fonte: O autor

Figure 5. Distribution of estimated (a) Disability-adjusted life years (DALYs) and (b) DALYs per 100,000 populations due to COVID-19 in Brazil by the state of residence between February 26, 2020, and December 31, 2020.



Fonte: O autor

Discussion

We estimated that the COVID-19 burden in Brazil reached around 5 million DALYs lost in 2020. Assuming there were no major changes in the disease burden experienced by the Brazilian population from 2019 to 2020, our results showed that COVID-19 led to enough DALYs lost to rank as the leading cause of disease and injury in the country in 2020. The COVID-19 burden was higher than all 15 leading causes of disease and injury as estimated by the GBD 2019, including interpersonal violence, ischemic heart disease, neonatal disorders, and stroke. Most of the COVID-19 health impact was due to premature mortality, representing 99.31% of the DALYs.

These effects remain consistent across all our sensitivity analyses, which intended to accommodate a range of scenarios regarding over- and under-reporting of mild, severe, and critical COVID-19 cases and the estimation of long covid cases. Even in the most conservative scenario, the burden produced by COVID-19 in 2020 remained the leading cause of DALYs lost in Brazil.

To date, several studies have estimated the COVID-19 burden in 2020 in different countries [29,31,33–43]. Unfortunately, the use of different methodologies poses barriers to the direct comparison among the estimates. With that in mind, we can still compare our results to those from six studies (India[37], Netherlands[38], Germany[40], Malta[41], Denmark[29], Scotland[43]). Results presented in these studies corroborate our findings regarding the overwhelming contribution of the YLL in the DALYs estimates, with more than 90% of the burden derived from YLL, ranging from 95% in Malta to 99,6% in India[37,41]. Furthermore, the high relative contribution of YLL in the COVID-19 disease burden is in line with what was observed in the GBD study estimates of the relative contribution of YLL from lower respiratory infections [12,21].

As expected, the crude estimates reflected the underlying countries' population, with India reporting the higher crude estimates (approximately 14 million DALYs) and Malta the lowest (5478 DALYs). In contrast, regarding the DALY rate, findings from Scotland had shown the highest per capita burden (ranging from 1770 to 1980 DALY/100,000), and those from Germany the lowest (368 DALY/100,000)[40,43]. Adding our results to this body of knowledge suggests that the COVID-19 burden in Brazil (i.e., 2,567 DALY/100,000) was higher than in any other country. Such differences between countries reflect not only how hard the epidemic hit each country but also its population structure, the age distribution of the outcomes (especially the deaths), data availability, data assumptions, and model choices.

Although comparisons in the COVID-19 DALYs can be useful to demonstrate the extent to which each country was affected, care must be sought when interpreting such results, given the difference in the timing of the peak of cases, especially regarding the absolute rate difference might not be the most informative or appropriate, given that baseline vulnerability in each country will significantly differ.

Previous studies described the local and regional differences in how COVID-19 affected the population's health. Early estimates of the COVID-19 excess deaths reported that initially, the pandemic severely affected the larger cities in Southeast Brazil, with a changing pattern later in the pandemic[44]. Another study regarding the burden averted due to vaccination showed that vaccination saved more lives in northern Brazil, where the incidence rate was higher [10].

This is the first study to provide comprehensive estimates of the COVID-19 burden of disease in Brazil. To this end, we used the best available evidence on COVID-19 cases, which were largely used in many studies from Brazil[9,10,44–56]. We also adopted a widely used protocol developed for this kind of estimation[23,29,31,37,41,43,57–59]. Nevertheless, our study has some limitations. We used the Brazilian population projections based on the 2010 census data (the most recent census information available by the time the manuscript was prepared), which does not account for changes in the population size like the migration of Venezuelans between 2017 and 2020 [60]. However, the IBGE projection is the best available estimate of the Brazilian population and is widely used in other studies[9,10,44,46–48,52,61]. When comparing the DALY estimates with pre-pandemic causes, there are some potential drawbacks to take into account, especially related to the competing risk of death. It is unlikely that all COVID-19 deaths are additional, and it is likely that at least part of those deaths replaces deaths that would have occurred due to other causes. The extent to which this is true should not be overstated [62].

Studies have shown that in 2020, there was a reduction of 8.8% in ischemic heart disease mortality compared to the previous year [61]. Nevertheless, given that the DALY difference between ischemic heart disease and COVID-19 was 32%, it is unlikely that this reduction would change our conclusions on the enormous COVID-19 burden. Our estimates are based on a published consensus method developed by the European Burden of Disease Network and the ECDC [23]. However, the estimates of the number of cases and duration of long covid remain highly uncertain [23,62–64]. Our sensitivity analyses showed that a wide range of assumptions had a minimal impact on the overall burden of COVID-19, given that YLD contributed to less than 1% of the total DALYs lost. However, as more epidemiological

information on long-COVID emerges, it should be integrated into the modelling process to increase the robustness of the YLD estimates.

We have shown that the direct impact of the COVID-19 pandemic on the Brazilian population's health has been substantial. Despite the mitigation efforts, in 2020, the disease stood out as the leading cause of DALYs relative to all other health conditions observed in the previous year. Future work should be directed towards international comparison over longer periods, incorporating the role of vaccination rollout and the upsurge of variants of concern.

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Availability of data and materials

Data supporting this manuscript comes from databases the Brazilian Ministry of Health maintains. Anonymised individual data are open and freely available at https://opendatasus.saude.gov.br

Abbreviations

COVID-19: Coronavirus Disease 2019; DALY: Disability-adjusted life year; ECDC: European Centre for Disease Prevention and Control; YLD: Years of life lost due to disability; YLL: Years of life lost due to premature mortality; ICU: Intensive care unit; GBD: Global Burden of Disease; MoH: Ministry of Health; WHO: World Health Organization.

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3.2 The effectiveness of COVID-19 vaccines against severe cases and deaths in Brazil from 2021 to 2022: A registry-based study (A efetividade das vacinas de COVID-19 contra casos graves e óbitos no Brasil em 2021 e 2022)

(Publicado no Lancet Regional Health Americas)

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Resumo

Background: O Brasil iniciou a vacinação em massa contra COVID-19 em Janeiro de 2021 com as vacinas CoronaVac e ChAdOx1, seguindo pela BNT162b2 e Ad26.COV2.S. Até o fim de 2021, mais de 317 milhoes de doses foram administradas na população adulta.

Métodos: Nós utilizamos um conjunto de dados que compreende mais de 158 milhões de registros de vacinação e casos graves de COVID-19 que foram unidos por meio de um linkage probabilístico pelo ministério da saúde e foi analisado via um modelo de Poisson de efeitos mistos, ajustado por idade, estado de residência, tempo desde a vacinação e tempo

calendário para estimar a efetividade do esquema primário e da dose de reforço. O método nos permitiu estimar a efetividade contra hospitalizações e óbitos, incluindo períodos de dominância de variantes.

Resultados: A efetividade absoluta contra casos graves e óbitos permaneceu acima de 25% e 50%, respectivamente, mesmo após 19 semanas da vacinação com o esquema primário das vacinas BNT162b2, ChAdOx1, ou CoronaVac. As doses de reforço conferiram uma maior proteção quando comparados com o esquema primário, com as doses heterólogas conferindo uma proteção maior que as doses de reforços de vacinas homólogas. A efetividade contra hospitalização durante a dominância da variante Ômicron no grupo etário de 60 anos ou mais foi 61·7% (95% IC, 26·1-86·2) para a ChAdOx1, 95·6% (95% IC, 82·4-99·9) para a CoronaVac, e 72·3% (95% IC, 51·4-87·4) para a BNT162b2.

Discussão: Nosso estudo fornece evidências da efetividade das vacinas de COVID-19 no Brasil, inclusive durante a dominância da variante Ômicron. Comparações da efetividade entre diferentes vacinas exigem cautela devido a potenciais viés relacionados a faixas etárias, picos de casos e eventuais mudanças comportamentais.

Palavras-chave: COVID-19, vacinas de COVID-19, efetividade, Brasil, América Latina, Pandemia

Summary

Background: Brazil started the COVID-19 mass vaccination in January 2021 with CoronaVac and ChAdOx1, followed by BNT162b2 and Ad26.COV2.S vaccines. By the end of 2021, more than 317 million vaccine doses were administered in the adult population.

Methods: A cohort dataset of over 158 million vaccination and severe cases records linked from official national registries was analyzed via a mixed-effects Poisson model, adjusted for age, state of residence, time after immunization, and calendar time to estimate the absolute vaccine effectiveness of the primary series of vaccination and the relative effectiveness of the booster. The method permitted analysis of effectiveness against hospitalizations and deaths, including in the periods of variant dominance.

Findings: Vaccine effectiveness against severe cases and deaths remained over 25% and 50%, respectively, after 19 weeks from primary vaccination of BNT162b2, ChAdOx1, or CoronaVac vaccines. The boosters conferred greater protection than the primary series of vaccination, with heterologous boosters providing marginally greater protection than homologous. The effectiveness against hospitalization during the Omicron dominance in the

60+ years old population started at 61·7% (95% CI, 26·1-86·2) for ChAdOx1, 95·6% (95% CI, 82·4-99·9) for CoronaVac, and 72·3% (95% CI, 51·4-87·4) for the BNT162b2 vaccine.
Interpretation: This study provides real-world evidence of the effectiveness of COVID-19 vaccination in Brazil, including during the Omicron wave, demonstrating protection even after waning effectiveness. Comparisons of the effectiveness among different vaccines require caution due to potential bias effects related to age groups, periods in the pandemic, and eventual behavioural changes.
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Keywords: COVID-19, COVID-19 vaccines, effectiveness, registry-based study, Brazil, Latin America, Pandemic

Introduction

Since the start of the current severe acute respiratory syndrome-associated coronavirus 2 (SARS-CoV-2) pandemic, more than 32 million confirmed cases and 670 thousand deaths due to coronavirus disease (COVID-19) had been reported in Brazil alone (as of July 01, 2022)[1]. One key step to ending the pandemic is the deployment of vaccines with durable effectiveness. Brazil began vaccinating the population in mid-January 2021, prioritizing people at relatively high risk of severe disease (e.g., the elderly and people with chronic health conditions), vulnerable populations (e.g., homeless and indigenous people), health care workers, and further extending to the entire population by decreasing age. Vaccination started mostly with CoronaVac (Sinovac Biotech) and ChAdOx1 nCov-19 (AstraZeneca/Oxford University) vaccines. The BNT162b2 (Pfizer–BioNTech) and Ad26.Cov2.S (Johnson & Johnson–Janssen) vaccines were incorporated later in the campaign (May and June 2021, respectively)[2,3]. However, the upsurge of Variants of Concern (VOCs) and an increase in reported breakthrough infections generated concerns about the vaccine's long-term protection.

Several observational studies have assessed the waning of the protective effect of COVID-19 vaccines over time[4–11]. However, these studies commonly estimated vaccine effectiveness (VE) for broadly defined periods or the analysis was restricted to specific vaccines and age groups/populations. Consequently, most of these studies were not adequately positioned to determine whether VE waning was due to declining protection from the primary series of vaccination or the emergence of a new VOC, or both.

Surveillance datasets in Brazil provide a substantial amount of data to assess VE in a real-world setting. Based on the surveillance data from COVID-19 severe cases and vaccination, with over 150 million records, we estimated the protection given by the four COVID-19 vaccines currently available and in use in Brazil against severe cases and deaths due to COVID-19 in the first year of mass vaccination.

Methods

Study design, population, and data source

This was a registry-based effectiveness study of a national health-record cohort with more than 158 million records, including over 2 million severe COVID-19 cases, where individual data were evaluated for tracking both the outcomes of interest (severe cases and deaths due to COVID-19) and their vaccination status over time. We used two datasets linked (please refer to Supplementary material 1 for details) by the Brazilian Ministry of Health (MoH): the National Immunization Program (NIP) records[2], which comprise all individual-level data on vaccination, and the Severe Acute Respiratory Illness (SARI) dataset[12,13], which contain all COVID-19 severe cases that lead to hospitalization and deaths. From the linked dataset, we extracted data on all individuals aged 20 years or older who had received at least one dose of CoronaVac, ChAdOx1 nCov-19, BNT162b2, or Ad26.COV2.S vaccines, or who had a severe COVID-19 illness. Along with the linked dataset, we used age-specific 2021 population estimates maintained by the MoH and the Brazilian Institute for Geography and Statistics (IBGE)[14].

The COVID-19 vaccination campaign started on January 17, 2021, which is the first epoch of the study. Vaccination events (primary series or booster doses) were observed from the start of the vaccination campaign until January 31, 2022 (Epidemiological week 05). Vaccination records indicate the date of the first, second, and booster doses and the vaccine received in each event.

Vaccination status definition

Individuals without any record of vaccination (first dose, second dose or booster) were considered unvaccinated. We considered as immunized those (i) with only the primary series of vaccination (i.e., two doses from the CoronaVac, ChAdOx1 nCov-19, and BNT162b2 vaccines or the single-dose Ad26.Cov2.S vaccine) and (ii) those with the primary series of vaccination plus a booster dose.

Outcomes of interest

The outcomes of interest were (i) COVID-19 severe cases, i.e., symptomatic COVID-19 cases leading to hospitalisation, regardless of death, and (ii) deaths due to COVID-19. The outcomes were registered in the dataset by the date of symptoms onset and the final case status (death, recovered or ignored). For each person in the cohort, an outcome of severe COVID-19 illness occurred whenever this person was notified as a severe COVID-19 case, using the date of symptoms onset as reference. Therefore, a record of severe COVID-19 illness after immunisation, either fully or booster-vaccinated, was classified as an immunised case. Individuals presenting the outcome prior to or without immunisation were classified as unvaccinated cases. The same classification applies to the death outcome, with individuals being classified depending on their vaccination status and symptoms onset. Records without a case registry in the national electronic record were assumed as not presenting the outcomes of interest.

Dominance of Variant of Concern (VOC) over time

Data on genomic samples were obtained from GISAID and filtered across Brazilian states[15]. We calculated the proportions of VOCs for each state and epidemiological week. A VOC with a frequency over 70% was considered the weekly dominating variant, allowing eventual transition periods without VOC dominance (i.e., epidemiological weeks without a VOC proportion over 70%) (Apêndice B).

Statistical modelling and analysis

Absolute vaccine effectiveness (VE) is the protection against the outcomes of interest of individuals vaccinated with the primary or booster-plus series, compared to the unvaccinated group. Relative vaccine effectiveness (rVE) is the protection against the outcomes of interest of booster-plus vaccinated compared to the risk in individuals with only the primary series of vaccination.

The analysis of the absolute VE (i.e., using the group of unvaccinated individuals as a point of comparison) was stratified by vaccine brand when the two doses were homologous (CoronaVac, ChAdOx1 nCov-19, BNT162b2 or Ad26.Cov2.S). That is, for this analysis, we excluded individuals with heterologous primary series. In the rVE (i.e., using the primary series of vaccination as a comparator), we analysed only the ChAdOx1 nCov-19 and BNT162b2 vaccines, given that both comprised almost 93% of the boosters administered. Other vaccines used as boosters were excluded (for details on the exclusions, please refer to Apêndice B). The VE and rVE were assessed in 4-week intervals and stratified by age into two age groups: 20-59 years and ≥60 years.

In the primary analysis, we compared (i) those who completed the primary series of vaccination to the unvaccinated (i.e., VE), (ii) those who had received a booster shot with those individuals who had received only the primary series of vaccination (i.e., rVE), and (iii) VE and rVE during the dominance of the Omicron variant. In a secondary analysis, we also compared individuals boosted to those unvaccinated and the VE and rVE for the periods of Delta and Gamma VOC dominance.

Cases of severe COVID-19 were aggregated into two age groups (20-59 and 60+ years old), vaccination status (unvaccinated and other combinations of vaccination schemes), and state of residency. Time was divided into calendar-time windows t of size n weeks. Individuals in a state of residency l and age group a, if vaccinated, were classified within these windows as immunized with a number s immunization weeks. For instance, for $n=4$ weeks, $s=1$ for people with 0-3 weeks after immunization, $s=2$ for 4-7 weeks, and so forth. For unvaccinated individuals, parameter s do not vary. A number of $X_{t,s,a,l,v}$ people in window t with immunization schedule in s-interval is stratified by age group a, state l, and vaccine status v (primary scheme with each vaccine or primary scheme with vaccine plus booster). The methodology considers the total person-time $T_{t,s,a,l,v}$ at which people could be infected and develop the outcomes of interest by $T_{t,s,a,l,v} = n\, X_{t,s,a,l,v}$. For a combination i, composed of age group $a(i)$, state $I(i)$, and vaccination status v_i ($v_i = 1$ for vaccinated, $v_i = 0$ for unvaccinated), calendar window t, and immunization status s, a total Y_i developing of one of the outcomes is modeled as

$$Y_i \sim Poisson(\lambda_i),$$

where $\log(\lambda_i) = \log(D_i) + \gamma_{h(i)} + \beta_{a(i),s(i)}\, v_i$, $\gamma_{h(i)}$ and $\beta_{a(i),s(i)}$ are random effects, in particular $\beta_{a(i),s(i)}$ is an age-varying effect dependent on the immunization interval, and $h(i)$ is an index unique for a combination of immunization time, age group, and state. The term D_i is the person time component obtained from the database. The random effects $\gamma_{h(i)}$ evaluates the

outcome rate for unvaccinated in a given age group, state, and immunization status. The random effect $\beta_{a(i),s(i)}$ indicates how much this outcome rate changes due to the immunization.

Since groups are potentially stratified by specific primary series or a combination of the primary scheme plus booster dose, the vaccinated status indicates this subgroup. The analysis requires a minimum m of vaccinated persons by calendar window and immunization period such that $X_{t,s,a,l,v} \geq m$ to avoid small subsamples. In this work, $m = 20$. For the unvaccinated group, the person-time component requires an assessment of the total time that unvaccinated people are at risk of severe cases within the time window, this estimate is obtained indirectly via vaccination coverage. The proportion c_t of people with at least one dose divided by the population estimate per age group and state, yields the age- and state-specific coverage of vaccination at time t. For a window with bounds b_1 and b_2, the person-time component is $nP_a(1-(c_{b1}+ c_{b2})/2)$, where P_a is the population estimate in the age group a. Whenever the final vaccine coverage for a state/age group exceeded 95%, the corresponding population for the whole study period was resized to maintain coverage c_i bounded at 95%. This resizing avoids small number effects possibly incurred due to uncertainties in the population estimates, following the estimates of vaccination coverage adopted by the Center for Disease Control and Prevention[16].

A Bayesian analysis allows the estimation of all coefficients, including $\beta_{a(i),s(i)}$, the parameters $\gamma_{h(i)}$, and other transformed quantities. The prior distribution for parameters $\gamma_{h(i)}$ and $\beta_{a(i),s(i)}$ were normal distributions with a mean equal to 0 and a precision of 0.01. Estimation of parameters is obtained with MCMC simulation with 3 chains, 6,000 iterations, and a 4,000 burn-in period. This estimation permits obtaining the rate ratio between the rate R_v of severe COVID-19 events for a vaccinated group and the rate R_u for an unvaccinated group, given by $R_v/R_u = \exp(\beta_{a(i),s(i)})$. Vaccine effectiveness (VE) is given by $1 - R_v/R_u$. The Bayesian analysis allows a direct computation of uncertainty intervals.

Protection of Booster doses - rVE

The analysis is similar to the one for VE. However, the comparison is between groups indicated by variable w_i, defining combinations of booster doses and the primary series as a comparison group, such that $w_i = 1$ for vaccinated people with booster dose b and primary series p, and $w_i = 0$ for vaccinated people with only primary series p. Hence, in this analysis, a similar mixed-effects Poisson model describes the outcomes, replacing the variable v with the variable w.

A Bayesian analysis again permits estimation of $\beta_{a(i),s(i)}$, thus obtaining the rate ratio, defined as the ratio between the rate R_b of severe COVID-19 event for a group vaccinated with booster doses and the rate R_v for a group vaccinated with only the primary series, given by $R_b/R_v = exp(\beta_{a(i),s(i)})$. The rVE is given by 1 - R_{vb}/R_{uv}.

Analysis over periods of variant dominance

Calendar windows and immunisation periods are further classified by variants of dominance in their initial weeks. The statistical analysis follows the same reasoning by restricting the intervals to the VOC to be analyzed and extending the random effects to also be adjusted by VOC, such that $\beta_{a(i),s(i),u(i)}$ depends on age group *a(i)*, immunization period *s(i)*, and the variant of concern *u(i)*.

Analysis for death outcomes

Without loss of generality, this same framework is used to analyze death as an outcome of interest. The R language (version 4.1.0) was used for data manipulation and exploratory data analysis and JAGS was used to perform MCMC simulation[17,18] to estimate model parameters. We followed the STROBE reporting guidelines (Apêndice B)[19].

Ethics statement

The study was conducted in accordance with fundamental ethical principles of the Declaration of Helsinki and the Brazilian National Health Council on research involving human beings. The Research Ethics Committee approved the study protocol of the Evandro Chagas National Institute of Infectious Diseases- Fiocruz (CAAE: 51567721.9.0000.5262).

Role of the funding source

The funders had no role in the study design, data analysis, data interpretation, or writing of the report. All the authors had final responsibility for the decision to submit for publication.

Results

Descriptive statistics and characteristics of vaccination

Brazil has had four COVID-19 epidemic waves up to February 2022. The first occurred between May and October 2020, before the immunisation campaign; the second

during February and April 2021, in the periods of dominance of the Gamma variant; the third occurred between June and August 2021, during the Delta dominance; and the last at the end of 2021, during the upsurge of the Omicron variant (Figure 6).

During the first year of the COVID-19 vaccination program, more than 377 million doses were administered. Most first doses (58·8 million) and second doses (48·1 million) were ChAdOx1 nCoV-19 vaccines. In contrast, most booster vaccines administered were BNT162b2 (33·1 million), accounting for almost 90% of booster vaccines administered (Figure 6 and Table 5). Most individuals with ChAdOx1 nCoV-19 primary series were 50-59 years old (27·5%) and 40-49 years old (22·9%). The primary series with the BNT162b2 vaccine were more frequent in the groups of 20-29 (33·0%) and 30-39 years old (28·0%). Conversely, most primary series of CoronaVac vaccine were in 20-29 (21·9%) and 70-79 (19·8%) years old individuals. Lastly, the single-dose Ad26.COV2.S vaccine was administered more frequently in the 40-49 years old group (45·5%) but corresponded to only 4% of the vaccines administered in Brazil. As expected, the Southeast region concentrated most of the doses administered in Brazil due to its population size, representing 42% of the country's population. The distribution of the first, second and booster doses of the vaccines by age group and vaccine brand over time is presented in the supplementary material (Apêndice B).

Most severe cases of COVID-19 among the individuals who completed the primary series with the ChAdOx1 nCoV-19 vaccine were in the 80+ years (31·5%) and 60-69 years (27·4%) groups, while the severe cases in the ChAdOx1 nCoV-19 booster recipients occurred more frequently in the 80+ (42·3%) and 70-79 years old (22·4%) groups. Most severe cases among the recipients of the BNT162b2 occurred in the 50-59- and 40-49-years old groups (28·9% and 23·0%, respectively), while cases in booster recipients were concentrated in the 80+ (41·5%) and 70-79 years (36·0%) old groups. Severe cases among the CoronaVac recipients occurred in the older groups (i.e., 70-79 and 80+ years old). Deaths among the recipients of the ChAdOx1 nCoV-19 vaccine were more concentrated in the 80+ years old group (31·4%, 40·0% and 34·2%, respectively). Conversely, deaths in those with the BNT162b2 primary series concentrated in the 50-59 and 80+ years old groups (30·4% and 40·0%) (Table 6). The weekly incidence of severe cases and deaths are presented in Apêndice B.

As described in the Introduction, the rollout of the first dose of a COVID-19 vaccine started in January 2020. Roll out of the second dose started in July 2021, which is also when the Gamma VOC dominance started to decline (Figure 6). Roll out of booster doses, the

majority of which were BNT162b2 vaccines, started after September 2021, reaching more than 2 million doses weekly in October 2021 and becoming more significant after January 2022.

Absolute and relative vaccine effectiveness for severe cases

The absolute effectiveness compared the groups of vaccinated and unvaccinated individuals, whereas the relative effectiveness compared vaccinated with a primary scheme plus booster and people with only the primary scheme. Variations in the primary scheme might induce different baseline risks. In individuals aged 20 to 59 years with ChAdOx1 nCoV-19 as the primary series of vaccination, absolute effectiveness against severe cases was 81·1% (95% Credible Interval - CI, 80·3-81·9) in the first four weeks after vaccination (Figure 7 and Apêndice B). The rVE in the initial weeks was 43·7% (95% CI, 18·8-63·8) for the homologous booster (i.e., ChAdOx1 nCoV-19) and 66·5% (95% CI, 62·8-70·0) for the heterologous booster with the BNT162b2 vaccine (Figure 7A). In individuals with CoronaVac as the primary vaccine series, the effectiveness was 84·7% (95% CI, 83·7-85·5) in the first four weeks. The rVE was 73·0% (95% CI, 67·8-77·6) for the BNT162b2 booster and 93·8% (95% CI, 76·1-99·7) for the ChAdOx1 nCoV-19 (Figure 7B) in the first four weeks. In the recipients of the BNT162b2 as a primary series, the VE was 90·3% (95% CI, 89·5-91·0) in the first four-week interval. The rVE of the homologous booster was 36·6% (95% CI, 21·6-50·4), and the ChAdOx1 nCoV-19 booster conferred a 39·9% (95% CI, -15·3-77·2) protection (Figure 7C). The VE of the Ad26.COV2.S peaked at 70·7% (95% CI, 66·9-74·2) after 20 weeks, with rVE of 82·4% (95% CI, 63·2-93·7) for the BNT162b2 booster (Figure 7D) in the initial weeks. The same analysis in the population aged 60 years or older gave similar results, with higher protection among the older population, except for the primary series of the CoronaVac and its ChAdOx1 nCoV-19 booster. The absolute effectiveness of the booster doses is shown in Apêndice B.

Vaccine effectiveness against death

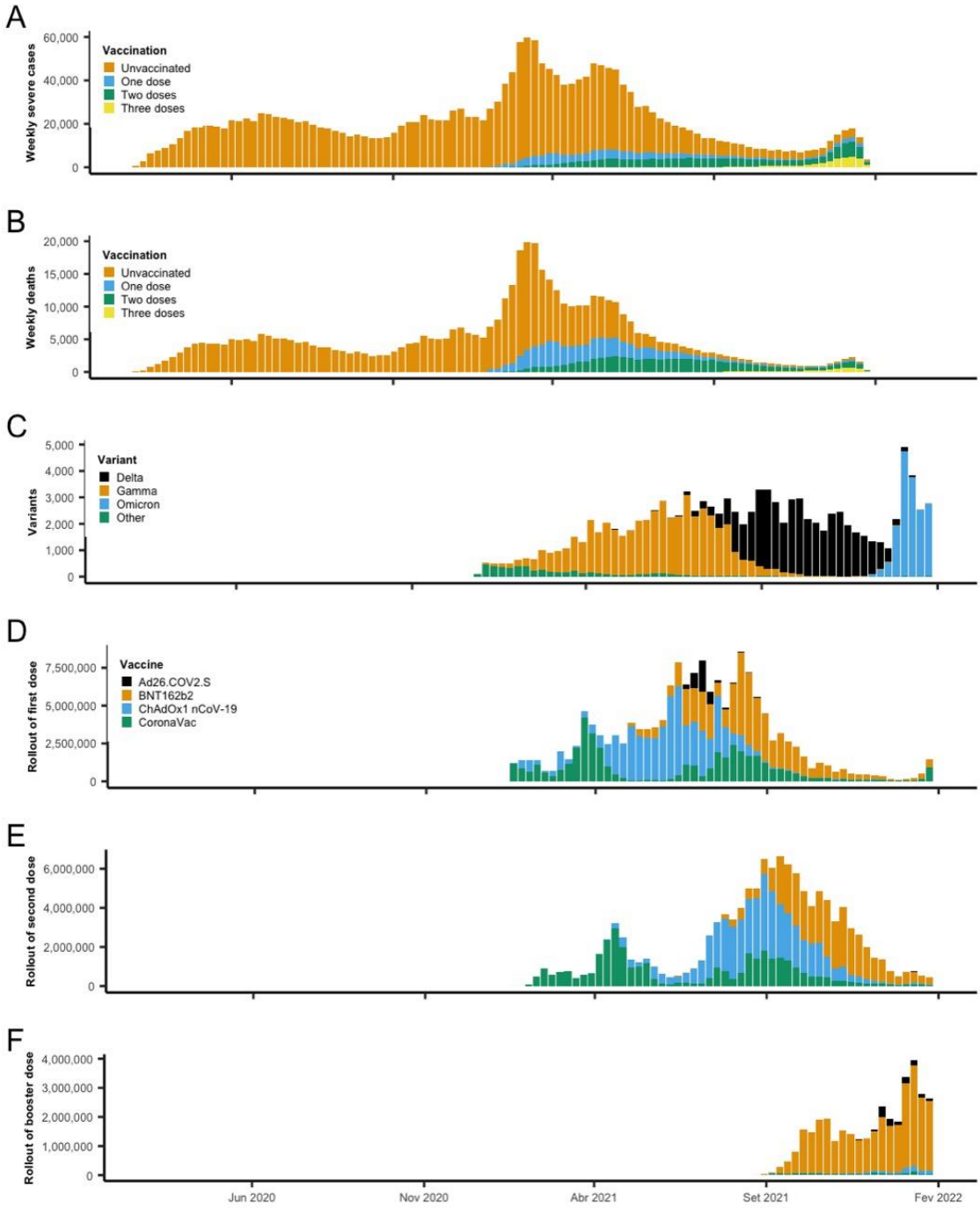
The effectiveness of COVID-19 vaccines when assuming death as the outcome showed similar patterns (Figure 8 and Apêndice B). As expected, the protection against deaths was superior to those observed against severe cases, irrespective of the vaccine dose and age group. The primary series of vaccination provided high levels of protection, with effectiveness above 50% for the timeframe up to 19 weeks for most vaccines, except for

CoronaVac among the elderly. The ChAdOx1 nCoV-19 and BNT162b2 booster vaccines conferred higher protection relative to the primary series.

Vaccine effectiveness in the periods of dominance of the Omicron variant

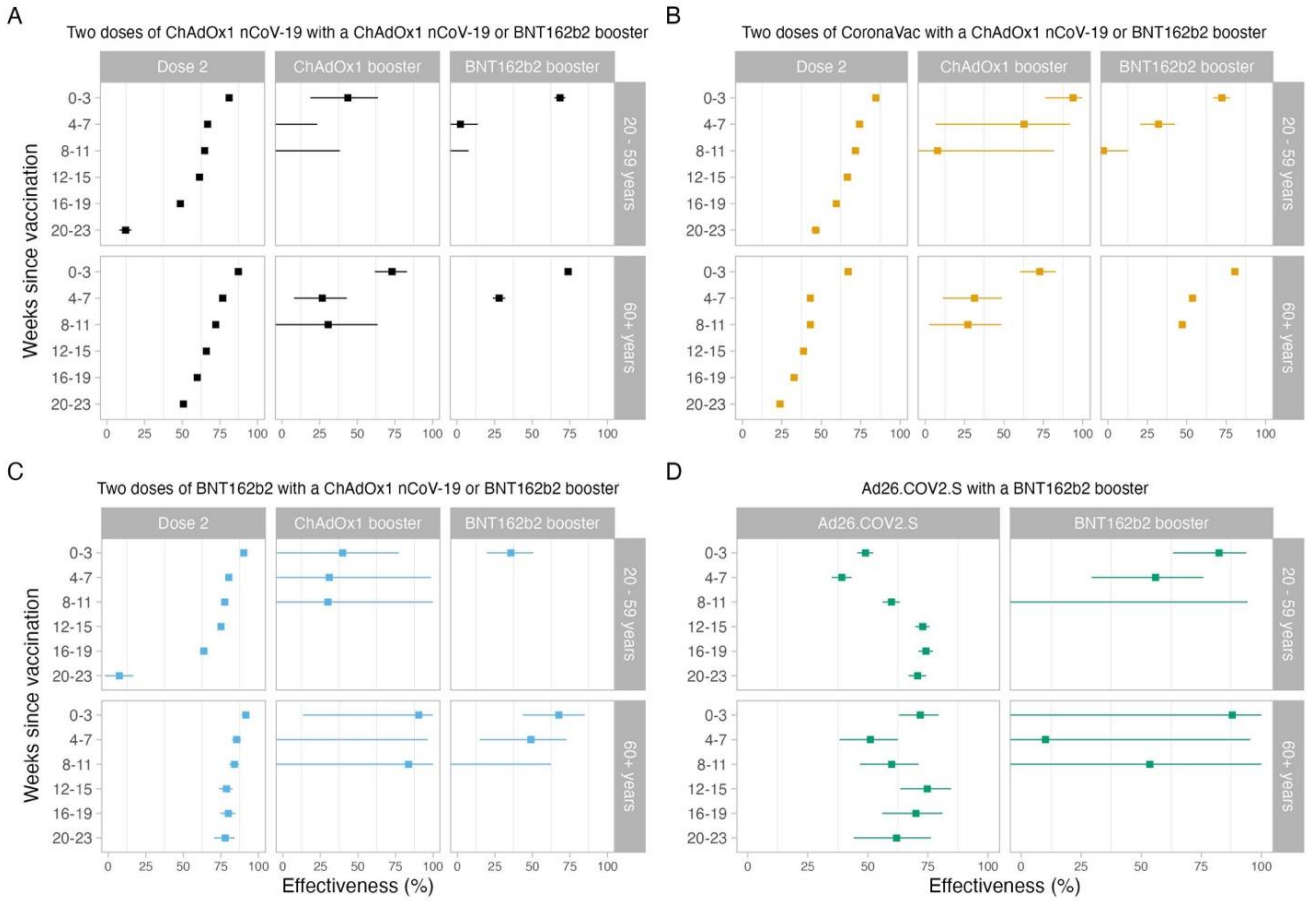
The vaccine effectiveness against severe cases in persons who received a primary series of the ChAdOx1 nCoV-19, CoronaVac, Ad26.COV2.S or BNT162b2 and after a booster dose with either ChAdOx1 nCoV-19 or BNT162b2, during the dominance of the Omicron variant, are shown in figure 9 and Apêndice B. The primary series of vaccination in the younger ranged from 83·7% (95% CI, 74·3-90·8) for CoronaVac to 96·2% (95% CI, 58·8-100·0) for the Ad26.COV2.S vaccine, and from 61·7% (95% CI, 26·1-86·2) to 95·6% (95% CI, 82·4-99·9), for ChAdOx1 nCoV-19 and CoronaVac, in the older group, respectively. Regardless of age and vaccine brand, the protection of the primary series of vaccination remained above 50% for more than 15 weeks. All booster shots were more effective than the primary series, with the relative protection lasting at least 11 weeks. The vaccine's protection in the periods of dominance of the other VOCs is presented in Apêndice B.

Figure 6. Weekly severe cases, deaths, variants and vaccine uptake from national datasets in Brazil. (A) weekly number of COVID-19 severe cases; (B) weekly number of deaths due to COVID-19; (C) weekly number of variants among sequenced SARS-CoV-2 samples; (D) vaccine uptake of the first dose; (E) vaccine uptake of the second dose; (F) vaccine uptake of the booster dose.



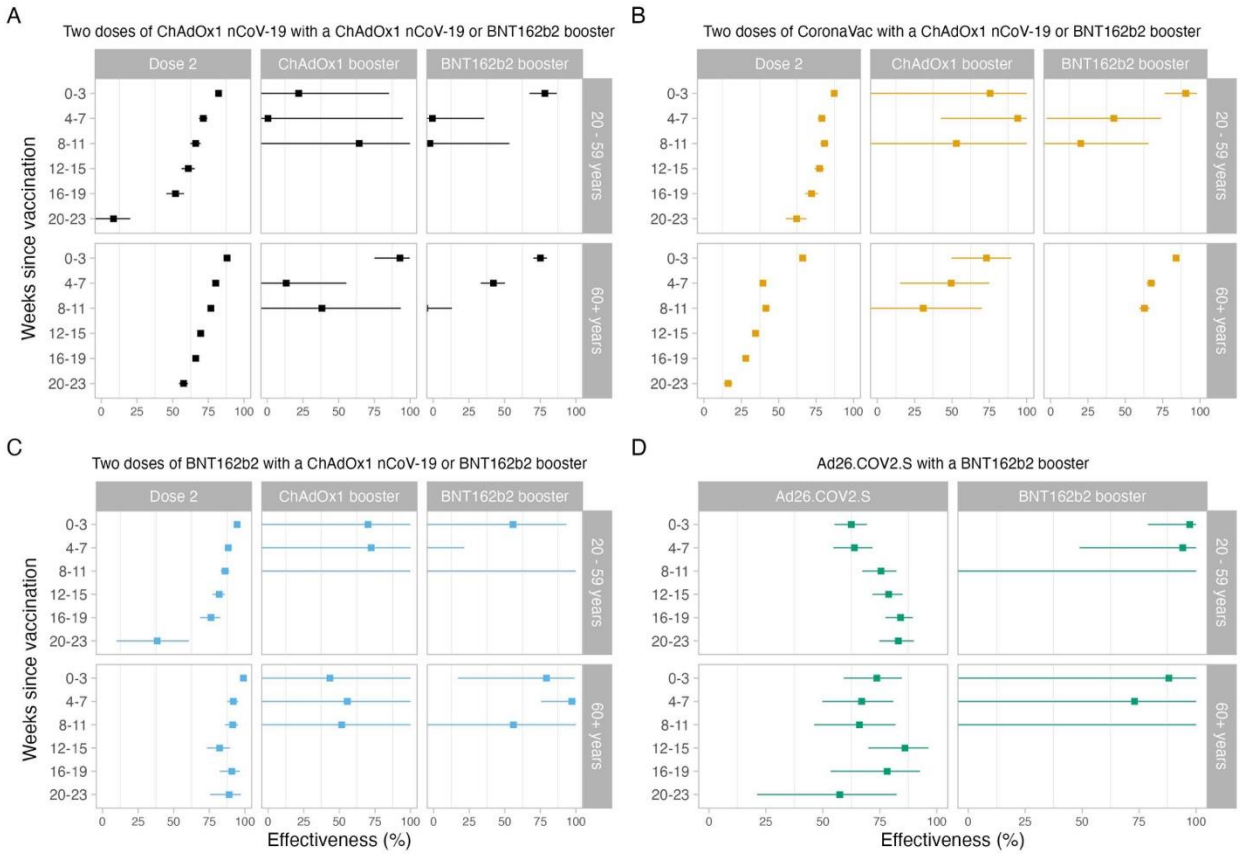
Fonte: O autor

Figure 7. Estimates of the absolute (first column in each panel) and relative (second and third columns) vaccine effectiveness against severe cases after completing the vaccine primary series and booster according to the primary series for age groups by length of the time since vaccination. (A) Effectiveness of the ChAdOx1 nCoV-19 vaccine against severe COVID-19. (B) Effectiveness of the CoronaVac vaccine against severe COVID-19. (C) Effectiveness of the BNT162b2 vaccine against severe COVID-19. (D) Effectiveness of the Ad26.COV2.S vaccine against severe COVID-19 (ChAdOx1 as booster was not significant). Panel rows correspond to age groups and columns correspond to the vaccine dose. Lines correspond to credible interval and points to the estimated mean. Missing lines and points are due to estimated values outside the graphic limits (0 to 100%).



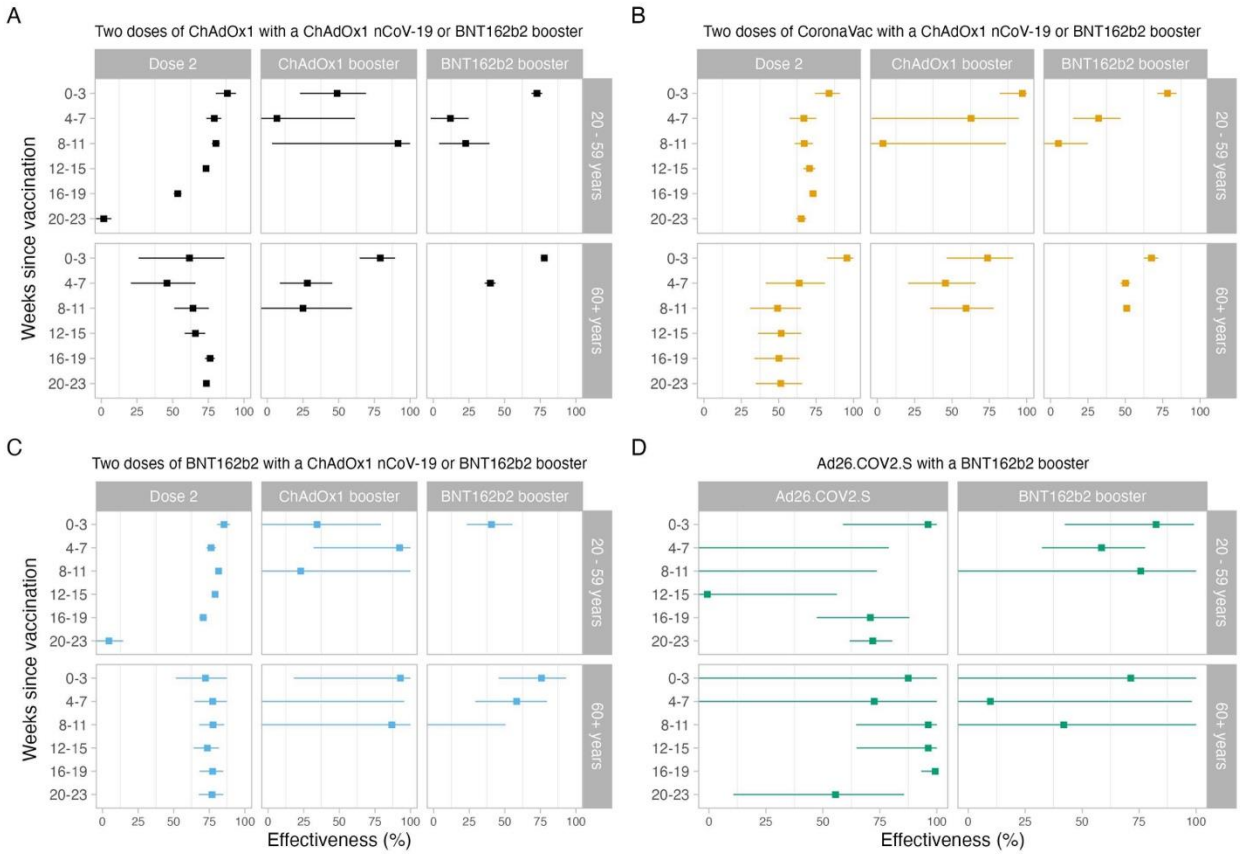
Fonte: O autor

Figure 8. Estimates of the absolute (first column in each panel) and relative (second and third columns) vaccine effectiveness against death after completing the vaccine primary series and booster according to the primary series for age groups by length of the time since vaccination. (A) Effectiveness of the ChAdOx1 nCoV-19 vaccine against severe COVID-19. (B) Effectiveness of the CoronaVac vaccine against severe COVID-19. (C) Effectiveness of the BNT162b2 vaccine against severe COVID-19. (D) Effectiveness of the Ad26.COV2.S vaccine against severe COVID-19 (ChAdOx1 as booster was not significant). Panel rows correspond to age groups and columns correspond to the vaccine dose. Lines correspond to credible interval and points to the estimated mean. Missing lines and points are due to estimated values outside the graphic limits (0 to 100%).



Fonte: O autor

Figure 9. Estimates of the absolute (first column in each panel) and relative (second and third columns) vaccine effectiveness against severe cases after completing the vaccine primary series and booster according to the primary series for age groups by the length of the time since vaccination in periods of dominance of the Omicron variant. (A) Effectiveness of the ChAdOx1 nCoV-19 vaccine against severe COVID-19. (B) Effectiveness of the CoronaVac vaccine against severe COVID-19. (C) Effectiveness of the BNT162b2 vaccine against severe COVID-19. (D) Effectiveness of the Ad26.COV2.S vaccine against severe COVID-19. Panel rows correspond to age groups, and columns correspond to the vaccine dose. Lines correspond to credible interval and points to the estimated mean. Missing lines and points are due to estimated values outside the graphic limits (0 to 100%).



Fonte: autor

Table 5. Baseline characteristics of the vaccinated individuals by vaccine type and dose in Brazil from January 17, 2021 to January 31, 2022.

		ChAdOx1nCoV-19			BNT162b2			CoronaVac			Ad26.COV2.S	
		1st dose (%)	2nd dose (%)	Booster(%)	1st dose (%)	2nd dose(%)	Booster(%)	1st dose(%)	2nd dose(%)	Booster(%)	1st dose(%)	Booster(%)
Sex	Female	30830381 (52·7)	25669514 (53·3)	6153332 (54·5)	26616219 (51·0)	20321759 (52·3)	18981352 (57·3)	23094206 (53·7)	19241380 (54·5)	6661146 (57·0)	2114175 (45·8)	708272 (48·45)
	Male	27600227 (47·3)	22499055 (46·7)	5138017 (45·5)	25530100 (49·0)	18552186 (47·7)	14122825 (42·7)	19911494 (46·3)	16062393 (45·5)	5003420 (43·0)	2504900 (54·2)	753534 (51·55)
Age group	20-29	6048079 (10·5)	4381186 (9·2)	110915 (9·9)	12773101 (3·4)	9412804 (33·0)	2388519 (7·2)	9366210 (23·7)	7398433 (21·9)	61811 (5·3)	481977 (10·5)	132506 (9·1)
	30-39	10824049 (18·8)	8440699 (17·7)	174470 (15·6)	9892566 (28·1)	7975906 (28·0)	4064154 (12·3)	7669218 (19·4)	6478403 (19·2)	96357 (8·3)	1456661 (32·0)	423332 (29·3)
	40-49	13366061 (23·2)	10822112 (22·9)	253371 (22·7)	7070063 (20·7)	6573000 (23·1)	5027590 (15·3)	4161076 (10·5)	3548816 (10·5)	119566 (10·3)	720114 (45·5)	76264 (46·7)
	50-59	15014931 (26·1)	13100899 (27·5)	296712 (26·5)	4070323 (11·9)	4063906 (14·2)	6337143 (19·3)	2400848 (6·0)	2083599 (5·1)	15579 (13·4)	482381 (10·6)	182232 (12·6)
	60-69	9596846 (16·6)	8437141 (17·7)	192365 (17·2)	4513512 (11·2)	3540912 (11·2)	7631714 (23·2)	5866500 (14·8)	5314526 (15·7)	2403699 (20·7)	411008 (9·9)	21780 (11·5)
	70-79	10364300 (11·8)	8966164 (11·9)	55611 (5·0)	7619212 (10·2)	5888700 (10·2)	5216913 (15·9)	7496631 (19·0)	6708333 (19·8)	2559449 (22·0)	96013 (10·2)	59562 (10·4)
	>80	1653190 (2·9)	1419620 (2·9)	31283 (2·8)	2944515 (10·1)	3743744 (10·1)	2161194 (6·5)	2522239 (6·3)	2211116 (6·5)	2288109 (19·8)	33318 (10·1)	31700 (10·2)
Region	North	4832851 (8·4)	4028094 (8·4)	140734 (12·5)	4439811 (8·5)	2893479 (7·5)	1770922 (5·3)	2646159 (6·2)	2110163 (6·0)	11805 (1·0)	23729813 (10·3)	556586 (3·8)
	Northeast	12773952 (22·0)	10818005 (22·5)	123674 (11·0)	12763436 (24·6)	8760300 (22·6)	6663071 (19·9)	9255961 (21·65)	7683622 (21·9)	14127 (1·2)	8223171 (17·9)	2289663 (15·7)
	Southeast	26638066 (45·8)	21528116 (42·8)	685164 (60·9)	21563899 (41·6)	17133635 (44·3)	15646672 (47·4)	21773545 (50·9)	17355368 (49·4)	10688122 (92·0)	20836012 (45·4)	6016884 (41·3)
	South	9368212 (16·1)	8384766 (17·9)	75999 (6·7)	8462171 (16·3)	6622700 (16·86)	6351667 (19·2)	5978449 (13·9)	5327704 (15·1)	57222 (4·9)	8688886 (18·9)	3810219 (26·1)
	Center-West	4444304 (7·6)	3593082 (8·26)	98844 (8·7)	4600848 (8·8)	3336888 (8·6)	2623912 (7·8)	3094223 (7·2)	2631376 (7·4)	8966 (0·8)	5293356 (11·5)	1888923 (13·0)
Total		58430725	48153645	1129141	52146446	38873993	33104252	43001824	35531003	1166468	46190883	1461808

Fonte: O autor

Table 6. Characteristics of the population with outcome registries according to vaccination in Brazil from January 17, 2021 to January 31, 2022.

Characteristic		Unvaccinated		ChAdOx1 nCoV-19						BNT162b2						CoronaVac						Ad26.COV2.S			
				≥1st dose (%)		2nd dose (%)		Booster (%)		≥1st dose (%)		2nd dose (%)		Booster (%)		≥1st dose (%)		2nd dose (%)		Booster (%)		1st dose (%)		Booster	
		Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths
Sex	Female	779908 (44·7)	164340 (43·3)	73005 (48·8)	24054 (45·8)	29210 (50·8)	7349 (46·3)	234 (53·0)	59 (40·3)	10280 (52·3)	1817 (42·4)	4235 (55·6)	651 (42·4)	12720 (54·6)	3060 (48·6)	114282 (51·0)	41552 (47·4)	83366 (51·0)	26694 (47·0)	2056 (54·0)	498 (52.8)	1130 (36.2)	223 (34.4)	34 (45.3)	29 (41.4)
	Male	963025 (55·3)	215088 (56·7)	76582 (51·2)	28421 (54·2)	28241 (49·2)	8534 (53·7)	208 (47·0)	87 (59·7)	9359 (47·7)	2469 (57·6)	3387 (44·4)	885 (57·6)	10556 (45·4)	3230 (51·4)	110076 (49·0)	46169 (52·6)	79724 (49·0)	30115 (53·0)	1751 (46·0)	445 (47.2)	1994 (63.8)	426 (65.6)	41 (54.7)	41 (58.6)
Age group	20-29	84216 (4.8)	6156 (1·6)	2957 (2·0)	346 (0·7)	1234 (2·2)	103 (0·6)	3 (0·7)	0	3189 (18·2)	224 (5·4)	1378 (19·8)	77 (5·1)	166 (0·7)	17 (0·3)	3628 (1·6)	241 (0·3)	2397 (1·5)	126 (0·2)	9 (0·2)	3 (0.3)	177 (5.7)	18 (2.8)	5 (6.7)	1 (1.4)
	30-39	201171 (11·6)	20172 (5·3)	7087 (4·7)	1342 (2·6)	2242 (3·8)	322 (2·0)	6 (1·4)	2 (1·4)	3330 (19·0)	467 (11·2)	1325 (19·0)	152 (10·1)	343 (1·5)	80 (1·3)	5106 (2·3)	566(0·6)	3238 (2·0)	253 (0·4)	11 (0·3)	3 (0.3)	716 (23.0)	98 (15.1)	11(14.7)	6 (8.6)
	40-49	297234 (17·1)	40785 (10·8)	14965 (10·0)	3823 (19·1)	4498 (7·9)	880 (5·5)	24 (5·4)	10 (6·8)	4257 (24·2)	1010 (24·1)	1603 (23·0)	326 (21·7)	388 (1·7)	229 (3·6)	5790 (2·6)	1032 (1·2)	3766 (2·3)	571 (1·0)	23 (0·6)	7 (0.7)	1410 (45.3)	239 (36.9)	24 (32.0)	20 (28.6)
	50-59	362953 (20·8)	68826 (18·1)	31862 (21·4)	10033 (19·1)	10354 (18·1)	2302 (14·5)	34 (7·7)	22 (15·1)	5113 (29·1)	1531 (36·6)	2016 (28·9)	457 (30·4)	707 (3·0)	455 (7·2)	6409 (2·9)	1587 (1·8)	4198 (2·6)	940 (1·7)	53 (1·4)	15 (1.6)	561 (18.0)	141 (21.8)	9 (12.0)	11 (15.7)
	60-69	339719 (19·5)	87697 (23·1)	43685 (29·3)	14987 (28·6)	15704 (27·4)	3858 (24·3)	89 (20·1)	28 (19·2)	1100 (6·3)	503 (12·0)	398 (5·7)	219 (14·6)	3631 (15·6)	1095 (17·4)	40282 (18·0)	14183 (16·2)	27275 (16·8)	8283 (14·6)	278 (7·3)	65 (6.9)	135 (4.3)	65 (10.0)	5 (6.7)	8 (11.4)
	70-79	260162 (14·9)	81416 (21·5)	11761 (7·9)	5457 (10·4)	5216 (9·1)	2061 (13·0)	99 (22·4)	34 (23·3)	320 (1·8)	250 (6·0)	116 (1·7)	139 (9·3)	8384 (36·0)	1897 (30·2)	91799 (41·0)	36910 (42·1)	67953 (41·7)	23029 (40·5)	834 (21·9)	167 (17.7)	79 (2.5)	44 (6.8)	15 (20.0)	16 (22.9)
	>80	197578 (11·3)	74381 (19·6)	36913 (24·7)	16452 (31·4)	18038 (31·5)	6342 (40·0)	187 (42·3)	50 (34·2)	260 (1·5)	198 (4·7)	133 (1·9)	131 (8·7)	9645 (41·5)	2512 (40·0)	70876 (31·7)	33179 (37·8)	53989 (33·2)	23593 (41·5)	2599 (68·3)	683 (72.4)	35 (1.1)	43 (6.6)	6 (8.0)	8 (11.4)
Region	North	115440 (6·6)	32733 (8·6)	8024 (5·4)	3061 (5·8)	3577 (6·2)	1086 (6·8)	49 (11·1)	22 (15·1)	944 (4·8)	203 (4·7)	330 (4·3)	83 (5·4)	733 (3·1)	272 (4·3)	7353 (3·3)	3382 (3·9)	5178 (3·2)	1919 (3·4)	5 (0·1)	0	107 (3.4)	32 (4.9)	4 (5.3)	8 (11.4)
	Northeast	234297 (13·4)	53300 (14·0)	19599 (13·1)	8192 (15·6)	7429 (12·9)	3072 (19·3)	39 (8·8)	28 (19·2)	2525 (12·9)	770 (18·0)	939 (12·3)	406 (26·4)	3204 (13·8)	1565 (24·9)	26912 (12·0)	11395 (13·0)	19084 (11·7)	7461 (13·1)	1 (0·0)	1 (0.1)	299 (9.6)	115 (17.7)	5 (6.7)	13 (18.6)
	Southeast	883939 (50·7)	181848 (48·0)	80538 (53·8)	28117 (53·6)	29565 (51·5)	7871 (49·6)	305 (69·0)	87 (59·6)	9840 (50·1)	2000 (46·7)	4151 (54·5)	717 (46·7)	12365 (53·1)	2948 (46·9)	125040 (55·7)	48040 (54·8)	87335 (53·5)	29926 (52·7)	3776 (99·2)	939 (99.6)	1528 (48.9)	276 (42.5)	32 (42.7)	29 (41.4)
	South	336562 (19·3)	73598 (19·4)	28105 (18·8)	8555 (16·3)	11851 (20·6)	2417 (15·2)	15 (3·4)	3 (2·1)	4280 (21·8)	783 (18·3)	1492 (19·6)	195 (12·7)	4868 (20·9)	988 (15·7)	44807 (20·0)	16598 (18·9)	35552 (21·8)	11679 (20·6)	19 (0·5)	3 (0.3)	813 (26.0)	131 (20.2)	16 (21.3)	10 (14.3)
	Center-West	172794 (10·0)	37954 (10·0)	13323 (8·9)	4552 (8·7)	5029 (8·8)	1438 (9·1)	34 (7·7)	6 (4·1)	2051 (10·4)	530 (12·4)	710 (9·3)	135 (8·8)	2107 (9·1)	517 (8·2)	20258 (9·0)	8309 (9·5)	15950 (9·8)	5826 (10·3)	6 (0·2)	0	377 (12.1)	95 (14.6)	18 (24.0)	10 (14.3)
Total		1743033	379433	149589	52477	57451	15884	442	146	19640	4286	7622	1536	23277	6290	224371	87725	163100	56812	3807	943	3124	649	75	70

Fonte: O autor

Discussion

The current study, based on registry data with over 158 million records compiled by the Brazilian MoH, indicates that the current vaccines were highly effective against severe cases and deaths during the first year of the vaccination campaign and in the periods of dominance of specific VOC. Our results provide evidence that the VE does not completely disappear, and 20 weeks after the primary series of vaccination the protection still reached 25% irrespective of vaccine brand or age. The booster doses significantly increased the protection offered by the primary series, with rVE remaining for at least 11 weeks after boosting. Results also show that a heterologous booster dose provided good protection against severe cases and deaths. These findings suggest that booster doses, which were mostly BNT162b2, were critical in the first months of 2022 when the entrance of the Omicron variant occurred, with high effectiveness for all adults and irrespective of primary series. During the dominance of the Omicron variant, the VE waned to about 50% after 19 weeks, except for the ChAdOx1 nCoV-19 recipients in the older group. These results are consistent with VE estimations in Brazil, the US, the UK, Italy and Sweden that reported a waning of the VE over shorter follow-up periods (between 3 and 9 months)[5,6,8–10,20–24]. Our results expand such evidence with an additional vaccine (i.e., CoronaVac), considering the VOCs, using a longer follow-up and following a larger population.

The uncertainty in estimating VE for the single-dose Ad26.COV2.S was higher than any other COVID-19 vaccine used in Brazil. This result is a function of the specific rollout of Ad26.COV2.S vaccine that occurred from June to August 2021 and reached mainly adults aged 30-39 and 40-49 years, corresponding to only 4% of the vaccines administered in Brazil. The same reasoning applies to the ChAdOx1 nCoV-19 booster, which represented only a small fraction of the booster doses administered in Brazil (approx. 3%), resulting in larger intervals for the rVE estimates. Consequently, due to the fewer observations, we could not estimate the rVE of the ChAdOx1 nCov-19 booster in recipients of the Ad26.Cov2.S. The VE of Ad26.Cov2.S exhibited a different pattern of increasing effectiveness over the evaluated time frames that could be explained by its different recommendations of a single dose in the primary series. Hence, individuals' immune response after the booster dose were similar to that of naive immunized in the initial weeks after the primary series with Ad26.Cov2.S. Unexpected findings, such as some of the rVE estimates, may occur in observational studies and should not be immediately considered evidence of a harmful effect of vaccination, such as vaccine-associated enhanced disease (sometimes called VAED).

Given that the absolute VE estimates were higher, irrespective of the vaccine brand, the lower values of rVE certainly are not VAED-related. The most reasonable explanations are differences in the comparison groups, especially differential behavioural changes (e.g., booster recipients lifting mask use), unmeasured confounding and the natural waning protection [25–27].

To the best of our knowledge, this is the first study to use data over 12 months to assess the VE of the COVID-19 vaccination for all vaccine brands used in Brazil. The methodology has advantages over the screening method described in the guidelines of the World Health Organization (WHO) due to the use of rate ratios and stratification by age groups and states, a sound approach given the variability of incidences across a large country such as Brazil. Of note is that this methodology is similar to the methods employed to measure the effectiveness of other vaccination programs such as Influenza[27,28]. In addition, the large dataset provided the most extensive and robust evidence of the durability of VE in Brazil. Nevertheless, our study has some limitations. First, like all observational studies, our results might be affected by confounding beyond those already accounted for with adjustments by age, time, and location. However, we do not have information on other key factors that may affect the risk of infection, such as sociodemographic, behavioural, and clinical factors that may differ between comparison groups.

Due to the lack of randomisation of individuals in real-world settings, observational studies are more subject to bias, which leads to systematic deviations of the estimated VE from the true VE. When compared to other observational study designs, such as the test-negative case control, our study has some limitations, including the impossibility of dealing with differences in health-seeking behaviour due to lack of behavioural information and collider bias, although such bias might also occur in test-negative studies[27,29]. However, our choice to use only severe cases instead of all symptomatic cases minimises these bias effects[27]. Furthermore, the estimates depend on the quality of surveillance registries and on the projections of the resident population by IBGE, which are based on the most recent census data of 2010. However, the databases we used correspond to the best available evidence on both COVID-19 vaccination and outcomes and were largely used in many studies in Brazil[8,9,30–37]. Still, the methodology can be adapted to changing epidemiological scenarios, and its use in permanent monitoring of the effectiveness should be pursued to investigate potential confounders.

Testing protocols varied during the current pandemic, so different collection methods and tests were used throughout the country. Thus, the sensitivity and specificity of tests also

varied, potentially causing misclassification. Beyond this, there were differences in factors such as the timing of introduction, dose interval and eligibility for all vaccines. Consequently, this should prompt some caution when comparing estimated protection levels among different vaccines, as the calendar period and interval between doses differ for each vaccine and, consequently, the baseline risk. For instance, a significant number of elderly people had CoronaVac as primary scheme early in the vaccination process. By contrast, younger people had either ChAdOx1 nCov-19 or BNT162b2 in their primary scheme a few months after vaccination started. This effect might impact the estimates of both absolute and relative effectiveness due to different risks in the baselines.

The distribution of vaccines also varied over time in the country. In October 2021, the MoH recommended shortening the interval for the primary series of the ChAdOx1 nCoV-19 vaccine (from 12 to 8 weeks), and in November, the interval between the primary series and the booster dose was also shortened (from 24 to 20 weeks) and an additional dose of Ad26.COV2.S was recommended 60 days after the first dose.

Furthermore, the states could (and did) adjust their vaccination protocols along with the MoH recommendations, making it hard to account for such differences in the vaccination protocols employed by each state. Decentralization of actions is one of the pillars of the Brazilian Health System (*Sistema Único de Saúde*, SUS). Consequently, the states and municipalities may change their protocols, such as those regarding testing requirements and immunisation schedules[38]. For example, the states of Pará and Mato Grosso do Sul introduced booster vaccines prior to the MoH recommendation. Moreover, vaccine shortages also affected rollout differentially throughout the country: in states such as Rio de Janeiro and São Paulo, a two-weeks shortage of ChAdOx1 nCoV-19 caused the replacement of the second dose to the BNT162b2.

Our findings indicate that the primary series of vaccination of the ChAdOx1 nCoV-19, CoronaVac, BNT162b2 or Ad26.COV2.S confer adequate levels of protection against severe cases and deaths, although waning of immunity does occur over time. Boosting with ChAdOx1 nCoV-19 or BNT162b2 significantly increased protection levels against severe cases and death. These findings reiterate the booster dose's public health value for minimising the risk of both severe cases and death and, thus, support advocating for maximising coverage of booster doses. Future work should further analyse the protection of the current booster vaccines for longer periods of follow-up and assess the protection given by the booster vaccines other than the ChAdOx1 nCoV-19 and BNT162b2, as well as that provided by the additional booster doses and disentangle the vaccines' direct and indirect effects.

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Contributors

DAMV and TGN conceived the idea for the study. TGN coordinated the project and secured funding. All authors contributed to the study design. DAMV, CVBdS and TGN had access to the raw data. DAMV and CVBdS conducted the analysis. DAMV, CVBdS and CJS drafted the manuscript. All authors contributed to the interpretation of the study results, critically revised the draft and approved the final version of the manuscript.

Conflict of interest

DAMV, PML, MFCG, LSB, OGC, AGP, NCMV, LPF and TGN are affiliated with Fundação Oswaldo Cruz, which manufactures the ChAdOx nCoV-19 vaccine in Brazil through a full technology transfer agreement with AstraZeneca. VBGP is a Brazilian Ministry of Health employee at the National Immunization Program (NIP), being responsible for the pharmacovigilance of the vaccines used by the NIP. All other authors declare no competing interests.

Data sharing Statement

Data supporting the manuscript were from datasets maintained by the Brazilian Ministry of Health that linked the vaccination and surveillance data. The dataset resulting from the linkage was only accessible due to specific project with Departamento de Ciência e Tecnologia, Secretaria de Ciência, Tecnologia, Inovação e Insumos Estratégicos em Saúde (Brazilian Ministry of Health). Requests for these data should be made directly to the

Brazilian Ministry of Health. Unlinked, anonymized, individual-level data are freely available at https://opendatasus.saude.gov.br

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3.3 **Estimated COVID-19 severe cases and deaths averted in the first year of the vaccination campaign in Brazil: a retrospective observational study (**Casos graves e óbitos por COVID-19 evitados no primeiro ano da campanha de vacinação em massa no Brazil**)**

(Publicado no Lancet Regional Health Americas)

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Resumo

*Contexto***:** A campanha nacional de vacinação contra o COVID-19 foi iniciada no Brasil em janeiro de 2021 com a CoronaVac (Sinovac Biotech) e ChAdOx1 nCoV-19 (AstraZeneca), seguida pelas vacinas BNT162b2 mRNA (Pfizer–BioNTech) e Ad26.COV2.S (Johnson & Johnson–Janssen). Nós produzimos estimativas do número de casos graves e óbitos por COVID-19 que foram evitados durante o primeiro ano da campanha de vacinação em massa no Brasil.

*Métodos***:** Dados sobre vacinação contra COVID-19 e casos graves e óbitos por COVID-19 foram obtidos do Ministério da Saúde e usados para estimar os efeitos diretos da campanha de vacinação no número de casos graves e mortes por COVID-19 ocorridos entre 17 de janeiro de 2021 e 31 de janeiro de 2022. Para tanto, comparamos as taxas diárias por idade entre a população não vacinada e a população "pelo menos parcialmente vacinada" (recebeu pelo menos uma dose de uma vacina de duas doses), bem como outros dois subgrupos de vacinação, populações "totalmente vacinadas" (completaram o esquema vacinal primário) e "reforçadas" (completaram esquema vacinal primário e recebeu uma dose de reforço).

*Resultados***:** Estimamos que 74% (n = 875.846; IC 95% 843.383–915.709) dos casos graves de COVID-19 que ocorreram no primeiro ano de vacinação e 82% (n = 303.129; IC 95% 284.019–321.681) do total de óbitos por COVID-19 foram evitados no primeiro ano da campanha nacional de vacinação. A carga evitada foi heterogênea entre as faixas etárias e maior nos estados mais populosos. No entanto, as diferenças nas taxas de resultados entre os grupos vacinados e não vacinados foram maiores nos estados menos populosos.

*Interpretação***:** O primeiro ano do programa de vacinação contra a COVID-19 no Brasil evitou pelo menos 303.129 óbitos. Os resultados destacam a necessidade de futuras campanhas de vacinação, incluindo aquelas necessárias na pandemia atual, para atingir rapidamente uma alta adesão, principalmente entre os idosos e moradores das regiões menos populosas.

Palavras-chave: Pandemia, SARS-CoV-2, COVID-19, Imunização, Vacina, Vacinação

Abstract

Background: A nationwide Severe Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) vaccination campaign was initiated in Brazil in January 2021 with CoronaVac (Sinovac Biotech) and ChAdOx1 nCoV-19 (AstraZeneca) followed by BNT162b2 mRNA (Pfizer–BioNTech) and Ad26.COV2.S (Johnson & Johnson–Janssen) vaccines. Here we provide estimates of the number of severe cases and deaths due to coronavirus disease (COVID-19) averted during the first year of the mass vaccination campaign in Brazil.

Methods: Data on COVID-19 vaccination and COVID-19-related illness and death were obtained from the Brazilian Ministry of Health and used to estimate the direct effects of the vaccination campaign on the number of severe cases and deaths due to COVID-19 occurring between January 17, 2021 and January 31, 2022. To this end, we compared the daily age-specific rates between the unvaccinated population and the "at least partly vaccinated" population (received at least one dose of a two-dose vaccine), as well as other two vaccination subgroups, "fully vaccinated" (completed the one- or two-dose vaccine schedule), and "boosted-vaccinated" (fully vaccinated and recipients of booster dose) populations.

Findings: We estimated that 74% (n=875,846; 95% confidence interval,CI 843,383–915,709) of total expected cases of severe COVID-19 and 82% (n=303,129; 95% CI 284,019–321,681) of total expected deaths due to COVID-19 were averted in the first year of the national vaccination campaign. The averted burden was heterogeneous between age groups and higher

in the more populous states. However, outcome rate differences between vaccinated and unvaccinated groups were higher in the less populated states.

Interpretation: The first year of the COVID-19 vaccination program in Brazil saved the lives of at least 303,129 adults. The results highlight the need for future vaccination campaigns, including those required in the current pandemic, to rapidly achieve high uptake, particularly among the elderly and residents of the least populous regions.

Funding: Ministry of Health (Brazil).

Keywords: Pandemic, SARS-CoV-2, COVID-19, Immunization, Vaccine, Serious Disease, Death

Introduction

Since the start of the current Severe Acute Respiratory Syndrome-associated Coronavirus 2 (SARS-CoV-2) pandemic, more than 631 million confirmed cases and 6.5 million deaths due to coronavirus disease (COVID-19) have been reported worldwide (as of November 02, 2022)[1,2]. In Brazil, more than 34 million COVID-19 cases and 688 thousand deaths were reported, placing Brazil as the fifth in the number of cases and second in the death toll, reaching more than 4,148 daily deaths in April 2021 [1,2].

Vaccination was a key measure in controlling the COVID-19 health burden. Brazil started a nationwide COVID-19 vaccination campaign on January 17, 2021, prioritizing people at relatively high risk of severe disease (the elderly and people with chronic health conditions), vulnerable populations (e.g., homeless and indigenous people), healthcare workers, and essential workers, and then extending to the entire population by decreasing age.

The campaign in Brazil began with CoronaVac (Sinovac) and ChAdOx1 nCov-19 (AstraZeneca/Oxford University), which were administered in two doses scheduled 28 days apart and 12 weeks apart, respectively [3,4]. On April 29, 2021, the BNT162b2 mRNA vaccine (Pfizer–BioNTech) was added to the campaign (two doses, 12 weeks apart) and, finally, on June 15, 2021, the single-dose Ad26.COV2.S (Janssen) vaccine was made available [3,4]. Thus, the introduction of the four vaccines was staggered over the first 6 months of 2021. During 2021, Brazil experienced successive waves of SARS-CoV-2 infections caused by the Gamma (P.1) variant, which predominated from January through August and peaked in May; the Delta (B.1.617.2) variant, which predominated through December 2021; and the Omicron (B.1.1.529) variant which emerged in Brazil in late November, 2021 [1,2,5].

Brazil has a population of more than 220 million people [6]. By February 18, 2022, more than 300 million doses of the vaccines had been administered, corresponding to approximately 81% of the population being partly or fully immunized [4,6]. Previous analyses have found that the vaccination campaign in Brazil was highly effective, with protection against severe cases reaching 86.4% and 61.2%, for the most used vaccines in the primary course of vaccination, ChAdOx1 nCov-19 and CoronaVac, respectively[7,8,9].These findings corroborated data from real-world effectiveness studies in other countries, such as the United Kingdom, United States, and Israel [9–12].

Despite the speed and breadth of coverage achieved by this nationwide mass vaccination campaign, the precise number of COVID-19 severe cases and deaths averted in Brazil remains unknown. The only estimates come from two studies that evaluated the early impact of vaccination among the elderly [13,14] and residents of specific Brazilian states [15,16]. Quantifying the nationwide disease burden averted by the vaccination campaign would be valuable not only to help elucidate and assess the public health benefits of vaccination but also to inform the design of mass vaccination campaigns for future pandemics and even possibly during the ongoing COVID-19 pandemic. In the present study, we estimated the COVID-19 severe cases and deaths due to COVID-19 averted during the first year of the nationwide vaccination campaign in Brazil.

Methods

Study design, population, and data source

This was an ecological study using retrospective observational data to estimate the number of severe cases and deaths from COVID-19 averted from January 17, 2021, the initiation date of the mass vaccination campaign, until January 31, 2022. We included all individuals aged ≥20 years who had received at least one dose of CoronaVac, ChAdOx1 nCov-19, BNT162b2, or Ad26.COV2.S vaccines, or who had a laboratory-confirmed SARS-CoV-2 infection.

We analyzed data curated from three national databases: (*i*) COVID-19 Vaccination Campaign (SI-PNI), which includes anonymized individual-level data on COVID-19 vaccination [17]; (*ii*) Severe Acute Respiratory Infection/Illness (SARI) from the Influenza Epidemiological Surveillance System (SIVEP-Gripe), which holds data on all COVID-19

severe cases that led to hospitalization and deaths due to COVID-19[18]; and (*iii*) Brazilian Institute for Geography and Statistics (IBGE) data on age-specific population estimates at the national, state, and municipality level [17]. Data from SI-PNI and SIVEP-Gripe were probabilistically linked by the Brazilian Ministry of Health and further information is provided in Apêndice C.

We excluded individuals who: (*i*) were vaccinated but lacked a record of the vaccination dates; (*ii*) had a laboratory-confirmed infection but lacked a record of the symptom onset date; and (*iii*) were vaccinated but had inconsistent vaccination records, such as a discordance of first and second vaccines or lack of a record for the second dose for those on a two-dose vaccine schedule, or lack of a record for the any of the two first doses in boosted individuals (flow diagram illustrating the steps to reach the final population are presented in Apêndice C).

Outcomes

We estimated the averted burden for two outcomes: severe COVID-19 cases and deaths due to COVID-19. We defined COVID-19 severe cases and deaths in vaccinated as those individuals with laboratory-confirmed RT-PCR or rapid antigen testing positivity at least 14 days after vaccination, following the definitions given by the Brazilian Ministry of Health (detailed in Apêndice C). The unvaccinated group were defined as individuals with severe disease or death records but no record of vaccination, or individuals with vaccination records whose symptom onset before the first dose of the vaccine. Outcomes with symptom onset occurring ≤14 days after the vaccination date were excluded from the analysis.

Vaccination groups

We calculated the number of severe COVID-19 cases and deaths averted (*i*) among individuals who were "at least partly vaccinated," defined as those who had received at least one dose of a two-dose vaccine (i.e., CoronaVac, ChAdOx1 nCov-19, BNT162b2 vaccines); and two other vaccination subsets: (*ii*) "fully vaccinated," defined as those who had received one dose of Ad26.COV2.S or two doses of the other three vaccines; and (*iii*) "boosted-vaccinated," defined as those who were fully vaccinated and received a booster dose. Only one booster dose was approved in Brazil during the period covered by this study.

Statistical analysis

To estimate the averted burden of COVID-19, we used the steps described by Haas [19]. Initially, we calculated the daily susceptible population in age-specific categories (20–29, 30–39, 40–49, 50–59, 60–69, 70–79, 80–89, and ≥90 years) by subtracting the number of new cases from the population estimates within each age group (IBGE). We then assigned the susceptible population into the unvaccinated group or the vaccinated groups, for each of the above-mentioned vaccination categories. Then, we calculated daily, age-specific outcome incidence rates for the unvaccinated and vaccination groups for each outcome (severe cases and deaths). The number of person-days for each vaccination group was calculated by multiplying the daily proportion of the susceptible population in each vaccination group by the IBGE age-group population estimates [6,20]. The number of person-days for the unvaccinated group was calculated by subtracting the number of person-days of the vaccinated groups from the IBGE population estimates. Next, for each outcome and vaccination group, we calculated the daily age-specific rate differences between the unvaccinated and vaccinated and their respective 95% confidence interval (CI).

Finally, for each age group, we multiplied the daily rate differences by the susceptible population (i.e., the population without previous evidence of COVID-19) and by the proportion of individuals who received at least one dose of the vaccine. This process was repeated and summed for all days of follow-up for each outcome to estimate the burden of COVID-19 averted by the mass vaccination. The abovementioned steps were initially determined nationally and then repeated for each of the 27 Brazilian states and their 5569 cities.

All analyses were performed using R statistical software (version 4.1.1) [21].

Results

By the end of the first year of the mass vaccination, more than 91% (~137 million) of the Brazilian population aged ≥20 years had received at least one dose of a COVID-19 vaccine, of whom about 129 million (85%) and about 44 million (29%) were fully vaccinated and boosted-vaccinated, respectively. The vaccination campaign in Brazil initially prioritized those at higher risk of severe disease (the elderly and those with chronic health conditions); consequently, vaccination occurred earlier and vaccine coverage was higher in the ≥60-year

age groups (Figure 8). For instance, by the end of 2021, >99% of the population aged ≥60 years received at least one dose of a COVID-19 vaccine, 98% were fully vaccinated, and 65% were boosted-vaccinated.

During 2021, a total of 1,169,972 cases of severe COVID-19 were recorded among the ≥20-year-old population, resulting in 369,034 deaths. We estimated that 875,846 severe cases and 303,129 deaths were averted in the at least partly vaccinated population, which would correspond to approximately 74% more severe COVID-19 cases and 82% more COVID-19-related deaths compared with the observed numbers (Table 7 and Figure 9). Although individuals aged ≥60 years represented only 20% (30,763,655) of the estimated susceptible population and 21% (30,130,737) of the at least partly vaccinated population, they made up nearly 45% (391,207) of averted severe COVID-19 cases and 61% (187,890) of averted deaths. A different pattern was observed in the fully vaccinated and boosted-vaccinated population groups, where the younger age groups (20–29, 30–39, 40–49, and 50–59 years) accounted for the higher proportions of averted severe cases and deaths.

As expected, the highest number of averted cases were estimated to occur in the most densely populated states of São Paulo, Minas Gerais, Rio de Janeiro, and Bahia (Table 8). Comparing the differences in outcome rates (as a proportion of the population) between the vaccinated and unvaccinated groups in the 27 Brazilian states, we observed the highest rate differences in severe COVID-19 cases and deaths were in the 20–59-year-old age group (Figure 10) in the Midwest region states and in the ≥60-year-old age groups in the North region states (Figure 11). The estimates of the averted severe cases and deaths for the 5569 Brazilian municipalities are shown in Apêndice C and are publicly available at https://github.com/epicleber.

Table 7: Estimated outcomes averted through COVID-19 mass vaccination program by the vaccination status and age group, Brazil Jan 31, 2021, to Jan 31, 2022

Age group	Population estimate	Severe COVID-19 cases averted	COVID-19 deaths averted
Individuals at least partially vaccinated*			
20-29 years	34 069 012	28 663·9 (22 183·7 to 37 654·14)	5008·9 (646·3 to 9064·2)
30-39 years	34 259 369	103 031·5 (94 904·1 to 112 048·45)	16 824·9 (12 507·5 to 20 950·4)
40-49 years	29 854 837	161 651·9 (154 595·4 to 169 433·8)	35 093·7 (31 420·9 to 38 707·5)
50-59 years	24 234 960	190 931·9 (185 403·6 to 197 265·6)	58 311·7 (55 346·5 to 61 277·0)
60-69 years	17 295 908	249 724·3 (246 192·3 to 254 204·2)	108 441·5 (106 344·1 to 110 538·9)
70-79 years	9 416 919	119 119·4 (117 944·3 to 121 547·0)	65 898·9 (64 762·37 to 67 035·4)
80-89 years	3 761 197	20 507·2 (20 323·2 to 21 479·8)	12 314·2 (11 858·9 to 12 759·5)
≥ 90 years	856 211	1856·1 (1837·1 to 2076·1)	1235·3 (1132·3 to 1338·33)
≥ 20 years	153 748 413	875 486·5 (843 383·0 to 915709·4)	303 129·4 (284 019·1 to 321 681·5)
Individuals fully vaccinated†			
20-29 years	34 069 012	44 486·3 (39 933·0 to 49 346·8)	5906·9 (3059·6 to 8583·5)
30-39 years	34 259 369	132 291·0 (128 878·3 to 138 320·0)	20 852·1 (18 088·89 to 23 629·1)
40-49 years	29 854 837	196 781·1 (195 074·2 to 203 222·8)	41 847·1 (39 778·5 to 44 560·0)
50-59 years	24 234 960	235 022·3 (234 898·4 to 241 530·5)	68 241·6 (67 241· to 71 132·8)
60-69 years	17 295 908	137 469·8 (136 689·35 to 144 380·3)	62 659·0 (60 814·0 to 65 566·6)
70-79 years	9 416 919	72 460·7 (72 369·4 to 77 411·4)	44431·1 (42 293·2 to 46 784)
80-89 years	3 761 197	19 175·0 (19 069·3 to 22 225·7)	16 469·1 (14 573·5 to 18 171·0)
≥ 90 years	856 211	3451·1 (3461·2 to 3691·7)	3731·1 (3100·3 to 4235·5)
≥ 20 years	153 748 413	841 137·68 (838 011·6 to 880 129·4)	264 138·4 (257 949·5 to 282 663·8)
Individuals boosted-vaccinated‡			
20-29 years	34 069 012	6641·0 (6107·3 to 7404·9)	802·3 (-121·2 to 2249·9)
30-39 years	34 259 369	12 951·7 (8625·9 to 19 948·3)	2116·3 (-187·7 to 2591·7)
40-49 years	29 854 837	15 155·8 (9141·4 to 18 285·1)	3744·6 (745·32 to 4144·14)
50-59 years	24 234 960	19 138·1 (12 657·7 to 23 588·6)	6456·3 (2463·6 to 10 416·0)
60-69 years	17 295 908	7486·3 (7334·6 to 7818·1)	2490·9 (1800·4 to 3181·3)
70-79 years	9 416 919	1834·7 (1809·6 to 2014·5)	755·1 (380·9 to 1129·28)
80-89 years	3 761 197	12 516·3 (6591·8 to 16 728·5)	8777·8 (5335·7 to 9635·5)
≥ 90 years	856 211	2062·8 (1344·3 to 7372·8)	2781·2 (1860·5 to 2928·3)
≥ 20 years	153 748 413	77 787·0 (51 612·8 to 97 161·27)	27 924·89 (13 717·00 to 39 558·95)

Data are the number of outcomes averted with 95% CI presented in parentheses. *Individuals at least vaccinated were those who received one or more doses of the COVID-19 vaccine. †Individuals who were fully vaccinated were those who completed the vaccine schedule; ‡ Individuals who received the booster dose (i.e., 3rd dose)
Fonte: O autor

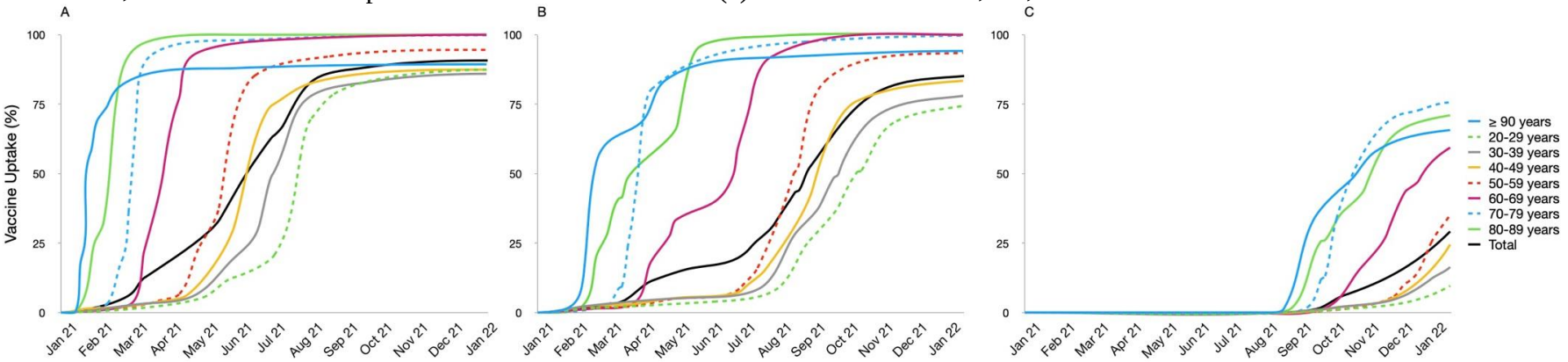
Table 8: Estimated COVID-19 outcomes averted through mass vaccination program by the vaccination status and state, Brazil Jan 31, 2021, to Jan 31, 2022

State	Estimated population	Individuals at least partially vaccinated*		Individuals fully vaccinated†		Individuals boosted-vaccinated‡	
		Averted severe cases	Averted deaths	Averted severe cases	Averted deaths	Averted severe cases	Averted deaths
Acre	559 201	3.185·7	1.103·0	3.060·7	961·1	283·0	101·6
Alagoas	2 284 354	13.013·9	4.505·9	12.503·3	3.926·3	1.156·2	415·0
Amazonas	2 672 986	15.227·9	5.272·5	14.630·5	4.594·3	1.353·0	485·7
Amapá	552 340	3.146·6	1.089·5	3.023·2	949·3	279·5	100·3
Bahia	10 669 688	60.785·1	21.046·3	58.400·3	18.339·1	5.400·7	1.938·7
Ceará	6 568 565	37.421·0	12.956·7	35.952·9	11.290·1	3.324·8	1.193·5
Distrito Federal	2 256 510	12.855·3	4.451·0	12.350·9	3.878·5	1.142·1	410·0
Espírito Santo	2 973 566	16.940·3	5.865·4	16.275·7	5.110·9	1.505·1	540·3
Goiás	5 151 411	29.347·5	10.161·3	28.196·1	8.854·2	2.607·5	936·0
Maranhão	4 680 216	26.663·1	9.231·8	25.617·0	8.044·3	2.369·0	850·4
Minas Gerais	15 977 820	91.025·5	31.516·7	87.454·2	27.462·8	8.087·6	2.903·3
Mato Grosso do Sul	2 017 276	11.492·4	3.979·1	11.041·5	3.467·3	1.021·1	366·5
Mato Grosso	2 475 387	14.102·2	4.882·7	13.548·9	4.254·7	1.252·9	449·7
Pará	5 758 306	32.805·0	11.358·4	31.517·9	9.897·4	2.914·7	1.046·3
Paraíba	2 883 545	16.427·5	5.687·8	15.783·0	4.956·2	1.459·5	523·9
Pernambuco	6 805 645	38.771·7	13.424·3	37.250·5	11.697·6	3.444·8	1.236·6
Piauí	2 288 668	13.038·5	4.514·4	12.526·9	3.933·7	1.158·4	415·8
Paraná	8 397 724	47.841·8	16.564·7	45.964·7	14.434·0	4.250·7	1.525·9
Rio de Janeiro	13 066 646	74.440·6	25.774·3	71.520·0	22.459·0	6.614·0	2.374·3
Rio Grande do Norte	2 557 213	14.568·4	5.044·1	13.996·8	4.395·3	1.294·4	464·6
Rondônia	1 256 434	7.157·9	2.478·3	6.877·0	2.159·5	635·9	228·3

Roraima	427 856	2.437·0	843·0	2.341·0	735·0	216·0	77·0
Rio Grande do Sul	8 655 734	49.311·6	17.073·7	47.376·9	14.877·5	4.381·3	1.572·8
Santa Catarina	5 466 747	31.144·0	10.783·3	29.922·1	9.396·2	2.767·1	993·3
Sergipe	1 637 385	9.328·1	3.229·7	8.962·1	2.814·3	828·8	297·5
São Paulo	34 544 205	196.798·2	68.139·5	189.077·0	59.374·9	17.485·5	6.276·9
Tocantins	1 089 560	6.207·2	2.149·1	5.963·6	1.872·7	551·5	197·9

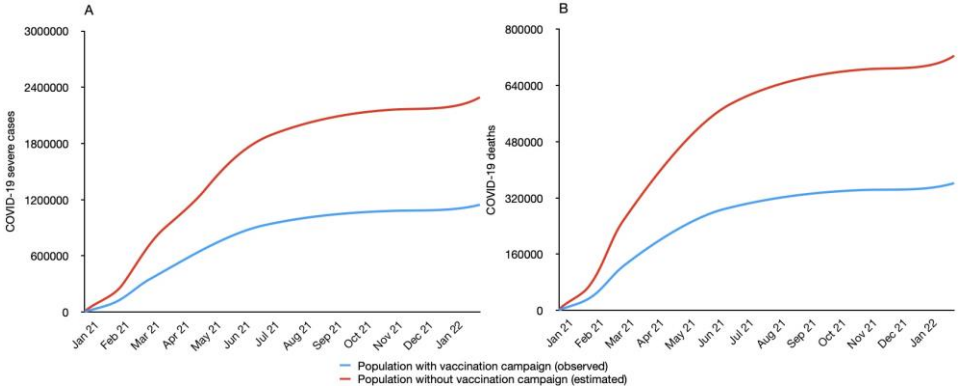
*Individuals at least partially vaccinated were those who received one or more doses of the COVID-19 vaccine. †Individuals who were fully vaccinated were those who completed the vaccine schedule. ‡ Individuals who received the booster dose (i.e., 3rd dose).
Fonte: O autor

Figure 8: Cumulative vaccine uptake for receiving any vaccine in Brazil, stratified by age group, Jan 2021 to Jan 2022 (a) Cumulative proportion of the population of individuals at least partially vaccinated, i.e., those who received at least one dose of the COVID-19 vaccine. (b) fully vaccinated, individuals that complete the vaccination schedule. (c) Boosted-vaccinated, i.e., individuals who received the booster dose.



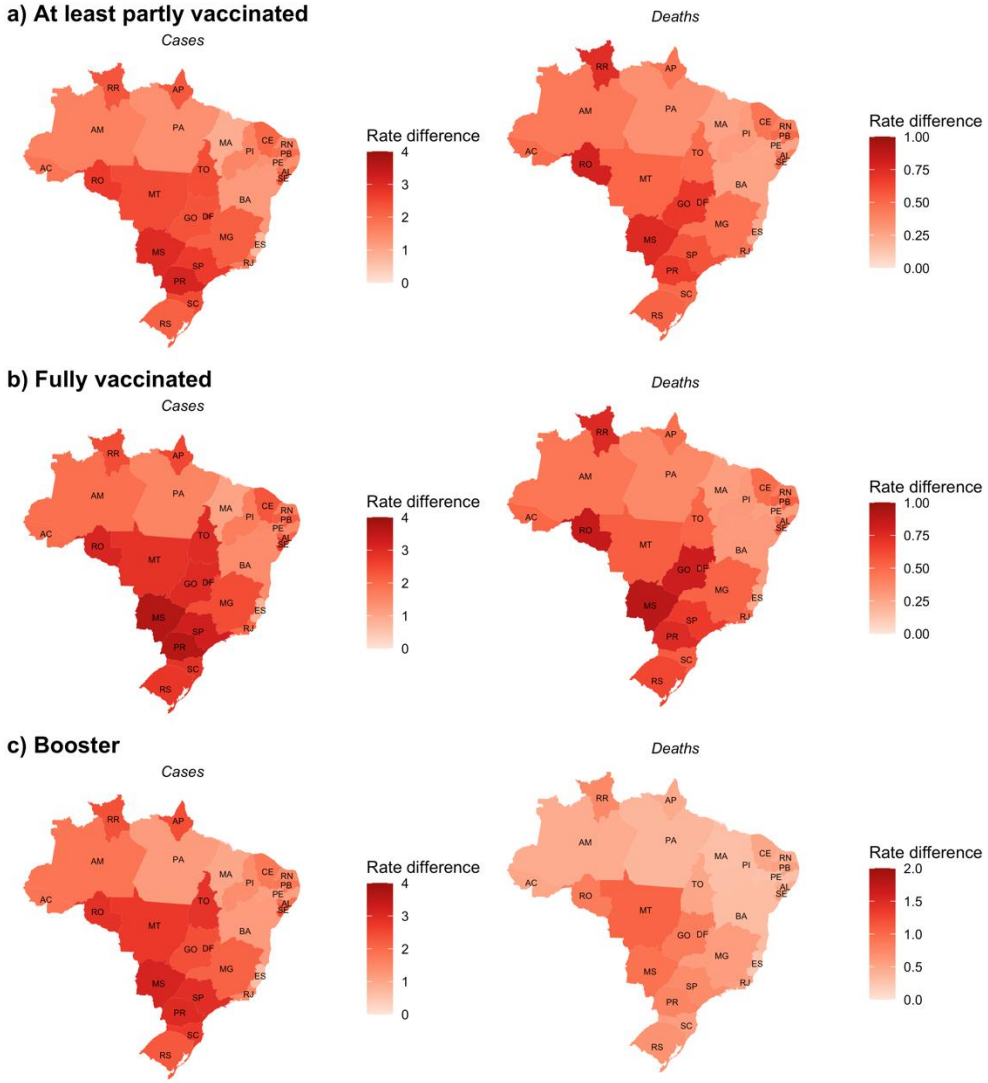
Fonte: O autor

Figure 9: Comparison of cumulative COVID-19 outcomes observed in the presence of vaccination campaign (in blue) and predicted COVID-19 outcomes in the absence of vaccination (in red) in Brazil· Jan 2021 to Jan 2022 (a) COVID-19 severe cases; (b) COVID-19 deaths



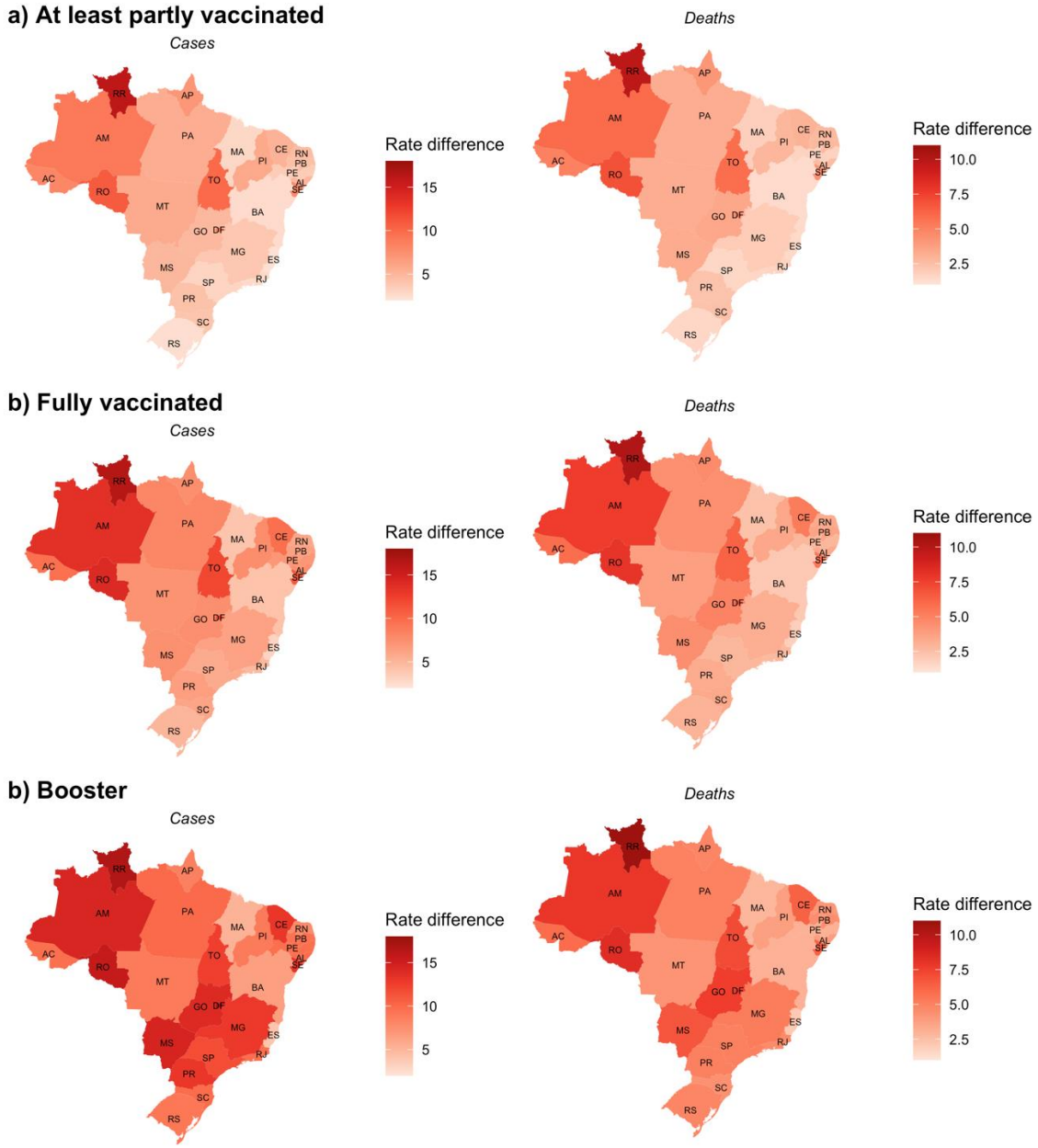
Fonte: O autor

Figure 10: Rate difference of averted COVID-19 severe cases and deaths between vaccinated and unvaccinated individuals in Brazilian states in the population between 20-59 years, from Jan 31, 2021, to Jan 31, 2022. Data are the mean daily rate difference per 100 000 population. a) Individuals at least partially vaccinated were those who received one or more doses of the COVID-19 vaccine. b) Individuals who were fully vaccinated were those who completed the vaccine schedule. c) individuals who received the booster shot.



Fonte: O autor

Figure 11: Rate difference of averted COVID-19 severe cases and deaths between vaccinated and unvaccinated individuals in Brazilian states in the population ≥ 60 years, from Jan 31, 2021, to Jan 31, 2022. Data are the mean daily rate difference per 100 000 population. a) Individuals at least partially vaccinated were those who received one or more doses of the COVID-19 vaccine. b) Individuals who were fully vaccinated were those who completed the vaccine schedule. c) individuals who received the booster shot



Fonte: O autor

Discussion

Between January 17, 2021, and the end of January 2022, nearly 23 million doses of COVID-19 vaccines were administered per month in Brazil. Brazil is recognized worldwide for the efficiency of its vaccination programs and has a successful history of inclusive governmental vaccination policies, sustained through effective communication strategies and excellent geographical coverage of the Unified Health System (*Sistema Único de Saúde* - SUS), and good population adherence [22,23]. For instance, during the 2009 H1N1 influenza pandemic, Brazil vaccinated nearly 90 million people within 3 months. Nevertheless, despite the high level of vaccine uptake in the first year of the COVID-19 campaign, Brazil has not been able to surpass the pace of vaccination observed during the 2009 H1N1 influenza pandemic. The relatively slow pace of COVID-19 vaccination could be due to a variety of factors, such as the underfunding of SUS over the past several years, the delay in vaccine acquisition and, consequently, the vaccine supply shortages, and the widespread dissemination of misinformation regarding the disease severity, the effectiveness of non-pharmaceutical interventions and the vaccine safety, especially by the federal government [14,24–26].

From the first recorded case of COVID-19 (February 26, 2020) through January 31, 2022, a total of 2,021,646 cases of severe COVID-19 and 636,873 deaths due to COVID-19 were recorded in Brazil, which was the third and second-highest number of cases and deaths due to COVID-19, respectively, by country [1,2]. Nearly 57% of the outcomes occurred during the study period examined here: from January 17, 2021 to January 31, 2022, and we estimated that an additional 875,846 severe cases and 303,129 deaths were averted by the vaccination campaign over the same period. Our estimates indicated that the decision to prioritize vaccination of the older population had important effects on averting the outcomes. Thus, although the population aged ≥60 years represented only 20% of the estimated susceptible population, they comprised almost 45% of severe cases and 61% of deaths averted by the vaccination campaign.

We estimated that the vaccination campaign averted both severe COVID-19 cases and deaths at higher numbers in the more populated states of Brazil. Interestingly, however, the rate differences between vaccinated and unvaccinated (per 100,000 inhabitants) were higher in the states with higher COVID-19 incidence rates, specifically in the 20–59-year-old group in the states from the Midwest and South regions and in the ≥60-year-old group in the states from the North region [3].

To the best of our knowledge, this is the first study to provide comprehensive estimates of the number of severe cases and deaths averted by the COVID-19 vaccination campaign in Brazil. Nevertheless, our study has some limitations. First, there is an inherent limitation in using secondary data, and the rate differences between the unvaccinated and vaccinated populations rely on observational data. To control for confounding, we stratified the data by date and age. However, we do not have information on other variables, such as socioeconomic variables, comorbidities, COVID-19 testing rate and positivity, health-seeking behaviour, and adoption of preventive strategies (e.g., social distancing, mask use) that may differ between the comparison groups. However, the databases we used are the best available evidence on both COVID-19 outcomes and vaccination and were largely used in many studies during the pandemic in Brazil[7,8,25,27–33]. The analysis here does not consider stratification by sex for two main reasons, first, given the absence of difference observed in the interim analysis, and second, previous ecological studies with similar methodology in other countries did not choose to sex-stratify [19]. A second methodological limitation is that our analysis does not incorporate the indirect effects of the vaccination campaign that might have benefited the unvaccinated individuals due to the reduction of transmission rates. Vaccines can affect not only an individual's susceptibility to infection but also reduce symptomatic infection, the likelihood of progression to severe disease and death, and may also decrease the transmissibility potential [34–36]. Given the preliminary evidence for the transmission-blocking effects of the current COVID-19 vaccines, our results may have underestimated the effects of vaccination on averting severe cases and deaths from COVID-19[37]. Still, they do provide a lower bound of the disease burden averted by the mass vaccination campaign [37–40].

Furthermore, we did not assess the effects of infection with specific SARS-CoV-2 variants, mainly because genomic surveillance is not widely adopted or regularly performed in Brazil, or of the impact of lockdowns, which were not uniformly recommended and did not occur with any geographic or temporal consistency throughout Brazil. Future work should disentangle the direct and indirect effects of vaccination on other crucial outcomes, such as the economic benefits and the number of disability-adjusted life years averted.

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3.4 *The impact of vaccination on the length of stay of hospitalized COVID-19 patients in Brazil* (O impacto da vacinação da duração da estadia hospitalar em pacientes com COVID-19 no Brasil)

(Submetido ao *Vaccine*)

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Resumo

Contexto: A duração que os casos graves de COVID-19 ocupam leitos hospitalares é um fator chave na determinação de como os casos se traduzem em um peso para o sistema de saúde. Está bem estabelecido que a vacinação com as vacinas atuais contra a COVID-19 foi eficaz contra casos graves de COVID-19. No entanto, o efeito do status vacinal no curso da COVID-19 a partir da hospitalização em diante permanece mal definido. Nesse estudo, nós estimamos o impacto da vacinação na duração da estadia de casos hospitalizados de COVID-19 no Brasil.

Métodos: Usando dados de internações hospitalares devido à COVID-19 e o status de vacinação de mais de 1,6 milhão de indivíduos que testaram positivo para COVID-19, realizamos uma análise de sobrevivência de risco competitivo da progressão hospitalar da COVID-19 entre 17 de janeiro de 2021 e 31 de janeiro de 2022.

Resultados: Observamos que o tempo médio de internação para aqueles que receberam alta diretamente da enfermaria do hospital (enfermaria para alta) para o grupo de 50-69 anos

diminuiu de 12,51 (IC de 95%, 12,39-12,63) nos não vacinados para 11,02 dias (IC de 95%, 10,98-11,07) naqueles que receberam a dose de reforço. Resultados semelhantes foram observados nas faixas etárias de 20-49 e 70 ou mais anos. O tempo médio entre a admissão hospitalar e a entrada na UTI foi menor nos não vacinados para todas as faixas etárias. O intervalo médio entre a UTI e a alta nos 50-69 anos foi de 19,29 dias (IC de 95%, 18,95-19,64) nos não vacinados e 16,92 dias (IC de 95%, 16,78-17,07) nos receptores de reforço, com uma tendência semelhante nas outras faixas etárias. As probabilidades de sobrevivência cumulativa indicaram maiores probabilidades de alta entre os indivíduos vacinados, incluindo as vias do hospital para a alta e da UTI para a alta.

Interpretação: A vacinação reduziu as admissões hospitalares e as estadias hospitalares nas vias do hospital para a alta e da UTI para a alta, contribuindo para uma menor carga do sistema de saúde. Nossos resultados demonstram que, mesmo quando as vacinas não protegem contra casos graves que levam a hospitalizações, elas reduzem a duração das estadias hospitalares dos indivíduos.

Palavras-chave: COVID-19, Hospitalização, Tempo de internação, Riscos competitivos, Análise de sobrevivência

Abstract

Background: The duration that COVID-19 severe cases occupy hospital beds is a key factor in determining how caseloads translate into a burden to the health system. It has been well established that vaccination with the current COVID-19 vaccines was effective against severe COVID-19 cases. However, the effect of vaccination status on the course of COVID-19 from the point of hospitalization onward remains ill-defined. Here, we estimated the impact of vaccination on the length of stay of hospitalized COVID-19 cases in Brazil.

Methods: Using data from hospital stays due to COVID-19 and the vaccination status of more than 1.6 million individuals who tested positive for COVID-19, we performed a competing-risk survival analysis of COVID-19 in-hospital progression between January 17, 2021, and January 31, 2022.

Findings: We found that the mean length of stay for those who were discharged directly from the hospital ward (ward-to-discharge) for the 50-69-year-olds decreased from 12.51 (95% CI, 12.39-12.63) in the unvaccinated to 11.02 days (95% CI, 10.98-11.07) in booster recipients. Similar results were observed in the 20-49 and 70 or + years age groups. The average time between hospital admission and ICU entrance was shorter in the unvaccinated for all the age groups. The average interval between ICU and discharge in the 50-69 years was 19.29 days (95% CI, 18.95-19.64) in the unvaccinated and 16.92 days (95% CI, 16.78-17.07) in the

booster recipients, with a similar trend in the other age groups. Cumulative survival probabilities indicated higher discharge probabilities among vaccinated individuals including hospital-to-discharge and ICU-to-discharge pathways.
Interpretation: Vaccination reduced hospital admissions and hospital stays across the hospital-to-discharge and ICU-to-discharge pathways, contributing to a lessened health system burden. Our results demonstrate that even when vaccines fail to protect against severe cases that lead to hospitalizations, they reduce the duration of individuals' hospital stays.

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Keywords: COVID-19, Hospitalization, Length of stay, Breakthrough infections, Competing risks, Survival analysis, Multi-state model

Introduction

The COVID-19 pandemic has posed unprecedented challenges to public health systems across the globe, placing immense pressure on healthcare infrastructures and urging rapid responses to mitigate its impact. Vaccination has emerged as a cornerstone of global efforts to curb transmission rates and reduce the severity of illness among populations (1,2). Numerous studies have demonstrated the effectiveness of COVID-19 vaccines in mitigating the risk of severe cases and fatalities among those vaccinated (2–5). However, breakthrough cases are still expected, and healthcare systems may still face considerable pressure in the future due to the looming threat of emerging variants and waning immunity (5–7). Therefore, it is important to assess the protective effects of vaccines beyond preventing severe disease and death (8).

The impact of vaccination on the course of COVID-19 from the point of hospitalization onwards is still not well established (8,9). It is crucial to understand the factors that impact hospital stay for COVID-19 admissions (10). The duration of hospitalization represents a critical metric in evaluating the burden imposed by COVID-19 on healthcare systems. It encompasses factors such as bed occupancy, medical staffing levels, and the availability of essential resources like ventilators and intensive care units and costs associated with the hospitalization. By unravelling the determinants influencing hospital stay

for COVID-19 patients, we gain insights into the dynamics shaping healthcare utilization during an upsurge in cases. Such insights not only inform resource allocation strategies but also facilitate proactive measures to avert potential crises and ensure optimal patient care delivery (11,12).

Surveillance datasets in Brazil offer a substantial amount of data to evaluate the impact of the COVID-19 vaccines in a real-world setting. Based on the surveillance data from COVID-19 severe cases and vaccination, with over 160 million records, we estimated the impact of COVID-19 vaccination on the hospital stay of COVID-19 cases in Brazil from January 17, 2021, to January 31, 2022.

Methods

Study design, population, and data source

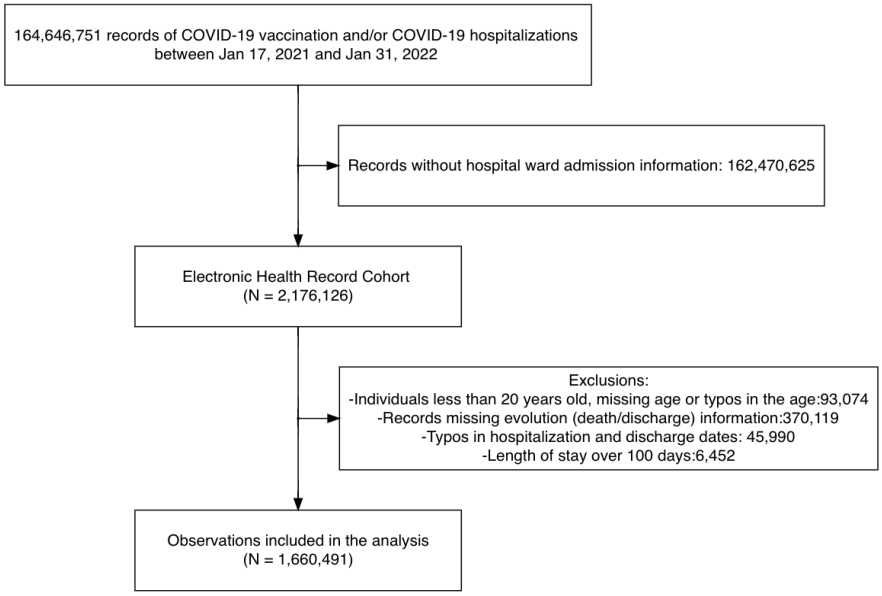
We analysed data curated from two national databases: (i) Brazilian National Immunization Information Program System (SI-PNI) (13), which includes anonymized individual-level data on COVID-19 vaccination; (ii) Severe Acute Respiratory Infection/Illness (SARI) from the Influenza Epidemiological Surveillance System (SIVEP-Gripe) (14,15), a national database which holds data on all COVID-19 severe cases that led to hospitalization. Data from vaccination (SI-PNI) and from COVID-19 severe cases (SIVEP-Gripe) were probabilistically linked by the Brazilian Ministry of Health, and details about the linkage are presented elsewhere (3). The dataset does not contain personal information that allows us to identify multiple hospital admissions for the same person.

The original linked dataset consisted of 164,646,751 observations, including over 2 million severe COVID-19 cases. Each line corresponds to a singular episode of hospital admission and/or vaccination record, with columns informing the date of hospital admission, the date of Intensive Care Unit (ICU) entrance, the outcome (either death or discharge), the date of the outcome, the age in years (later grouped into 20-49 years old, 50-69 years old, and 70 or + years), the vaccine brand and vaccination dates for the entire country for the period between January 17, 2021 and January 31, 2022.

Hospitalizations with laboratory-confirmed COVID-19 were included (n=2,176,126). We excluded observations: (i); with age under 20 years, missing age or presenting typos in their age (e.g., negative values of age) (93,074 observations), (ii) missing evolution date (370,119 observations),(iii) had aberrant values of hospitalization admission and/or discharge

(e.g., hospital admission prior to the start of the pandemic and discharge dates prior to admission - 45,990 observations), (iv) with a hospital stay greater than 100 days (6,452 observations), given that substantial long hospital stays (even in the case of them being true information) would have disproportionate effect in the fitting (Figure 12).

Figure 12. Flow diagram of the study population



Fonte: O autor

Vaccination groups

Vaccination in Brazil started in mid-January 2021 with the two-dose CoronaVac (Sinovac Biotech) and ChAdOx1 nCov-19 (AstraZeneca/Oxford University) vaccines. The introduction of the two-dose BNT162b2 (Pfizer–BioNTech) and a single-dose Ad26.Cov2.S (Janssen) vaccines occurred a few moments later, in May and June 2021, respectively. The vaccination initially prioritized population groups at high risk of severe disease (e.g., the elderly and people with chronic health conditions), in addition to vulnerable populations (e.g., indigenous people), and health care workers. Subsequently, the vaccination extended to the entire population according to age groups, from older to younger individuals (13,16).

Individuals included in the study were classified into one of the following groups: (i) unvaccinated, as those without any vaccination record at the time of hospital ward admission; (ii) partly vaccinated, those who had received only one dose of a two-dose vaccine (i.e.,

CoronaVac, ChAdOx1 nCov-19, BNT162b2 vaccines); (iii) fully vaccinated, defined as those who had received two doses of the vaccines (or one dose of the Ad26.COV2.S); and (iv) boosted-vaccinated, defined as those who were fully vaccinated and received any booster dose. Only one booster dose was approved in Brazil during the study period.

Multi-state survival model

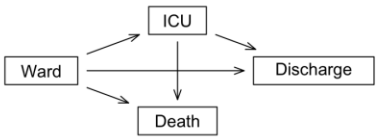
We performed an age-specific competing-risk survival model. This framework has already been used in previous studies to characterize hospital demand and has been shown to produce reliable estimates of length of stay during the COVID-19 pandemic (17–21).

The patient progression through the hospital was represented by a multi-state model, with the following states: hospital ward, ICU, discharge, and death, as described in Figure 13. In the model, individuals can transition from ward-to-ICU, ward-to-discharge, ward-to-death, ICU-to-discharge, and ICU-to-death. That is, the model only allows the ward as the entry state and does not permit return between the states.

We aimed to estimate the time for each transition (i.e., ward-to-discharge, ward-to-ICU and ICU-to-discharge) and also to estimate the probability of these transitions. This competing risk approach produces time-to-event and transition probabilities that are more straightforward to interpret and utilize in further modelling work than the common cause-specific hazards approach to analyzing multi-state survival data (17,21,22). We model the distribution of length of stay as a gamma distribution conditional on the age group (20-49 years old, 50-69 years old, and 70 or + years) and compute the maximum likelihood estimate for this model over our time-to-event data (i.e., number of days spent in each state), producing both predictive distributions and cumulative survival probabilities across each pathway.

All analyses were carried out in R version 4.10, using the *flexsurv* package (23,24).

Figure 13. The multi-state model used in the study



Fonte: O autor

Results

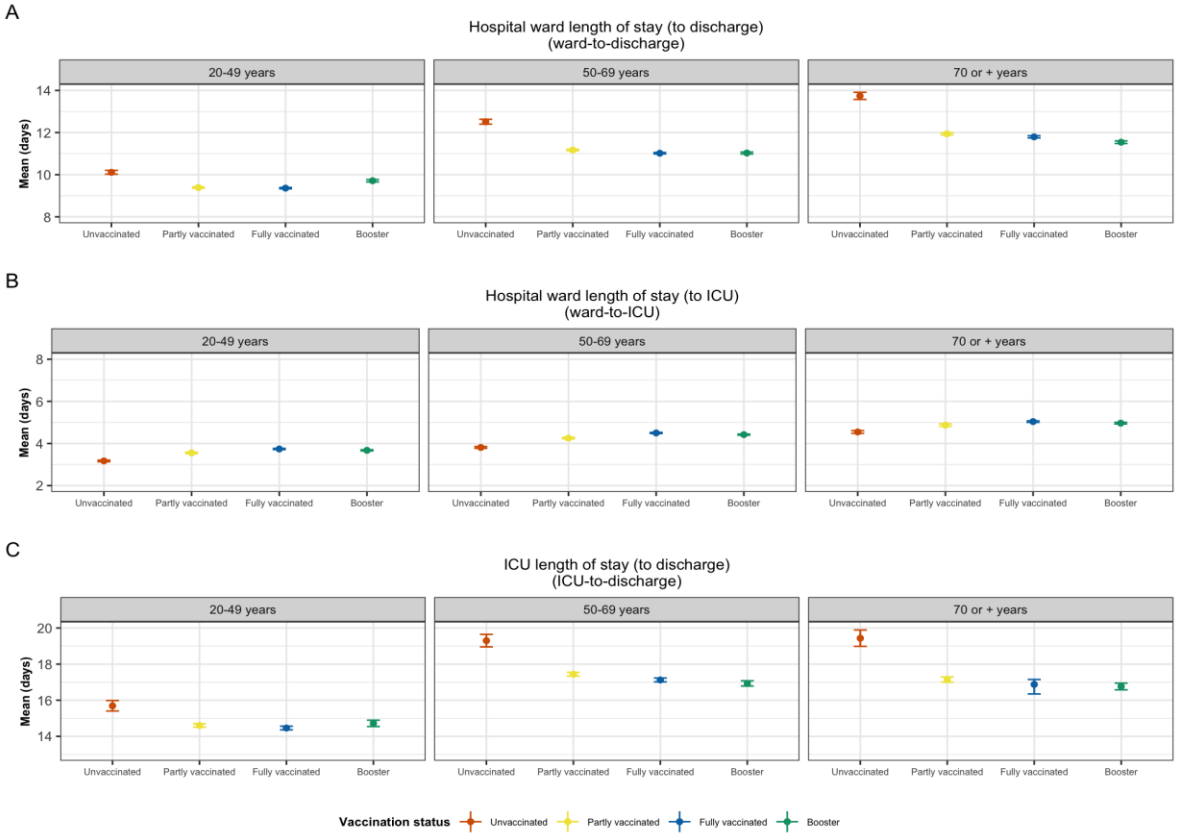
A total of 1,660,491 COVID-19 hospitalizations occurred between January 17, 2021 and January 31, 2022. The individuals admitted to the hospital had, on average, 57 years of age. The mean length of stay was 11·61 days, ICU admission was observed in 411,841 (24·80 %) hospitalizations, and 239,039 hospitalizations ended in death (14·39%). More than half (51·25%, 850,991) of hospital ward admissions and 43·63% (179,692) of ICU entrances occurred among the unvaccinated. The partly vaccinated group had 20·43% (339,316) hospital admissions and 23·59% (97,169) ICU entrances. The fully vaccinated group had 17·35% (288,061) hospital admissions and 20·75% (85,463) ICU admissions. Lastly, the booster-vaccinated group had 10·97% (182,123) hospital admissions and 12·03% (49,517) ICU admissions.

Vaccination resulted in notable decay in the ward stays, particularly among the 50-69 years and 70 or + years groups. Among the 50-69 years age group, the length of stay in the ward-to-discharge pathway decreased from 12·51 days (95% CI, 12·39-12·63) in the unvaccinated group to 11·02 days (95% CI, 10·98-11·07) in the booster-vaccinated group (Figure 14A and Table 8). Similarly, in the 70 or + years group, the length of stay decreased from 13·73 days (95% CI, 13·57-13·90) in the unvaccinated group to 11·54 days (95% CI, 11·48-11·60) in the booster group (Figure 14A and Table 8).

Regarding the time interval between hospital ward admission and ICU admission, the unvaccinated group exhibited a shorter mean compared to their vaccinated age-stratified counterparts (Figure 14B and Table 8). Furthermore, the length of stay of the ICU-to-

discharge pathway was longer for the unvaccinated group across all age groups. In the 50-69 years age group, those in the unvaccinated group spent on average 19·29 days (95% CI, 18·95-19·64) in the ICU, whereas the booster-vaccinated group spent 16·92 days (95% CI, 16·78-17·07) in the ICU before being discharged. A similar pattern was observed also in the 70 or more years age group (Figure 14C and Table 8).

Figure 14. Modelled mean length of stays and 95% confidence intervals for the (A) hospital ward to discharge, (B) Hospital ward to ICU, and (C) ICU to discharge across the 20-49 years, 50-69 years and 70 or more years old groups. The y-axis differs between the three outcome panels.



Fonte: O autor

Figure 15 shows the cumulative survival probabilities from ward-to-discharge, ward-to-ICU, and ICU-to-discharge vary as a function time since hospital admission by age group and receipt/doses of a vaccine. Figure 15A indicates that the probability of moving from ward to discharge was lowest in the unvaccinated group, with an upward trend in the discharge probabilities for partially vaccinated, fully vaccinated and booster-vaccinated groups, across all age groups. The opposite is observed for the hospital ward to ICU pathway, where the unvaccinated group exhibited the highest probability of transition compared to those vaccinated, with no change in transition probabilities from day 9 after hospital admission

(Figure 15B). Finally, those who got the vaccine were more likely to be discharged than the unvaccinated group during their ICU stay, especially in the 50-69 years and 70 or + years groups, with the booster-vaccinated group having twice the probability of discharge (0·67 and 0·60) compared to the unvaccinated (0·37 and 0·31) (Figure 15C).

Figure 15. Cumulative survival probabilities of individuals for the (A) hospital ward to discharge, (B) hospital ward to ICU, and (C) ICU to discharge across the 20-49 years, 50-69 years and 70 or more years old groups. Shaded regions represent the 95% confidence intervals. Note the y-axis differs between the three outcome panels.

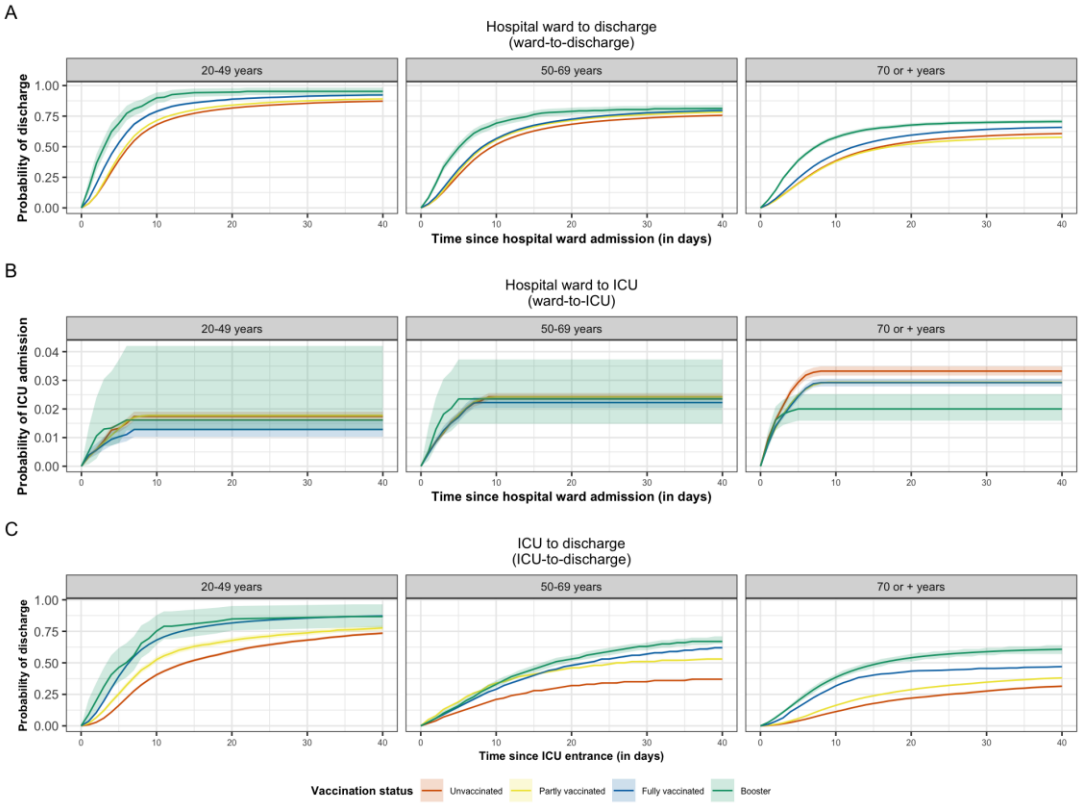


Table 9. Modelled mean length of stays and 95% confidence intervals for each hospital pathway, vaccination status and age groups.

Pathway	Vaccination status	Age group	Mean (95%CI)
Ward to discharge			
	Unvaccinated	20-49	10·11(10·02-10·20)
		50-69	12·51(12·39-12·63)
		70 or +	13·73(13·57-13·90)
	Partly vaccinated	20-49	9·38 (9·36-9·41)
		50-69	11·17 (11·14-11·20)
		70 or +	11·93 (11·88-11·99)
	Fully vaccinated	20-49	9·36 (9·33-9·39)
		50-69	11·01 (10·98-11·05)
		70 or +	11·79 (11·74-11·84)
	Booster	20-49	9·71 (9·65-9·76)
		50-69	11·02 (10·98-11·07)
		70 or +	11·54 (11·48-11·60)
Ward to ICU			
	Unvaccinated	20-49	3·17 (3·13-3·20)
		50-69	3·81 (3·77-3·85)
		70 or +	4·54 (4·48-4·61)
	Partly vaccinated	20-49	3·55 (3·52-3·58)
		50-69	4.25 (4·22-4·28)
		70 or +	4·87 (4·81-4·92)
	Fully vaccinated	20-49	3·73 (3·71-3·76)
		50-69	4·49 (4·47-4·52)
		70 or +	5·03 (5·00-5·07)
	Booster	20-49	3·67 (3·64-3·70)
		50-69	4·41 (4·39-4·44)
		70 or +	4·96 (4·92-5·00)
ICU to discharge			
	Unvaccinated	20-49	15·68 (15·40-15·98)
		50-69	19·29 (18·95-19·64)
		70 or +	19·43 (18·98-19·88)
	Partly vaccinated	20-49	14·60 (14·51-14·69)
		50-69	17·44 (17·33-17·54)
		70 or +	17·14 (16·99-17·29)
	Fully vaccinated	20-49	14·46 (14·36-14·56)
		50-69	17·12 (17·01-17·22)
		70 or +	16·87 (16·34-17·14)
	Booster	20-49	14·71 (14·54-14·89)
		50-69	16·92 (16·78-17·07)
		70 or +	16·76 (16·57-16·94)

ICU: Intensive Care Unit; CI: Confidence interval
Fonte: O autor

Discussion

Our study used real-world data from the largest government-run public healthcare system in the world (*Sistema Único de Saúde*) to demonstrate that the vaccination benefits of the current COVID-19 vaccines extend beyond the protection of severe cases. The COVID-19 vaccines were designed to protect against severe cases and deaths, but even when they failed to protect against it, we observed that they conferred a shorter hospital stay in

breakthrough COVID-19 infections when compared to those in the unvaccinated group. Moreover, we found a dose-response relationship between the number of doses and the hospital length of stay. Also, hospital stays for the booster-vaccinated group were shorter than that for partly or fully vaccinated groups. This trend argues for the importance of booster doses in bolstering vaccine effectiveness but also suggests how ongoing immunity waning or the emergence of new variants may act as potential factors influencing disease severity and hospital outcomes (7).

The reduction in the hospital length of stay estimates we have observed is in line with other studies (2,25–30). For instance, a study of 1,860 patients at a hospital in England found that vaccination was associated with a shorter length of stay (1·89 days) (27). Similarly, a study in the Netherlands found that vaccinated individuals stayed in the hospital for an average of two days less than unvaccinated individuals (28). In the US, two studies showed that fully vaccinated patients had shorter hospital stays (2·13 and 2·45 days), were less likely to be admitted to the ICU, and had lower hospitalization costs (29,30). It is worth noting that the hospital stays for COVID-19 patients in Brazil were longer than those observed in other countries (25,27–30).

Consistent with global evidence, our study confirms that advanced age remains a significant predictor of both prolonged hospitalization and a lower probability of discharge among COVID-19 patients, regardless of vaccination status. This demographic pattern highlights the increased vulnerability of older adults to severe disease outcomes and emphasizes the need for targeted interventions to protect this at-risk population segment, such as the primary series of vaccinations and booster doses. (5,17,31).

By using a comprehensive vaccination and hospitalization dataset and robust analytical frameworks, our results show the benefits of vaccination in mitigating disease severity and optimizing healthcare resource allocation. However, our study is subject to some limitations. First, given the nature of our data, the results might be affected by variables beyond those accounted for in the analysis, such as socio-demographic (e.g., socioeconomic status, healthcare access), racial/ethnical, behavioural (e.g., health-seeking behaviour), and clinical factors (e.g., comorbidities and improvement in the management of patients) that may differ between vaccination statuses, outcomes and age groups (32–36). We also were unable to incorporate the potential effects of variants in our estimates as no data was available in this regard. If data on variants at the individual level were available, this could be included as an additional stratification alongside age group. Furthermore, our estimates are directly dependent on the quality of surveillance registries. However, the databases we used

correspond to the best available evidence on both COVID-19 vaccination and outcomes and were largely used in various studies in Brazil (4,37–43).

Our findings addressed a gap in our understanding of the interplay between vaccination status and hospital stay among COVID-19 patients in Brazil. These findings reiterate the public health value of vaccination, contributing to the effective management of COVID-19 and its associated healthcare challenges. The hospital length of stay is key to characterising the healthcare burden (e.g., how many hospital beds are required and how much hospital personnel is needed per day) during an epidemic. Future work should further analyse the added protection of the second booster and the role of other factors that may affect the length of stay, such as the variants, the socioeconomic and clinical factors and the comorbidities.

Data sharing statement

The authors do not have permission to share the data. The data supporting the manuscript were from datasets maintained by the Brazilian Ministry of Health that linked the vaccination and surveillance data. The dataset resulting from the linkage was only accessible due to a specific project with Departamento de Ciência e Tecnologia, Secretaria de Ciência, Tecnologia, Inovação e Insumos Estratégicos em Saúde (Brazilian Ministry of Health). Requests for these data should be made directly to the Brazilian Ministry of Health. Unlinked, anonymized, individual-level data are freely available at https://opendatasus.saude.gov.br.

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CONSIDERAÇÕES FINAIS

Esta tese teve como objetivo quantificar a carga da COVID-19 no Brasil em DALYs, estimar a efetividade das vacinas de COVID-19, o impacto da vacinação na duração das internações hospitalares e o número de casos graves e óbitos evitados pela vacinação. Por meio de uma série de análises, demonstramos o impacto significativo da COVID-19 na população brasileira e como a introdução da vacina foi ponto chave no combate a pandemia.

Nossos achados indicam que a COVID-19 impôs uma carga substancial na saúde populacional no Brasil em 2020, conforme observado pelos anos de vida ajustados por incapacidade. Considerando que não houveram grandes mudanças no padrão de adoecimento e incapacidade no Brasil entre 2019 e 2020, a COVID-19 foi a principal causa de doenças e lesões no país, superando doenças e agravos, como violência interpessoal, infarto agudo do miocárdio, distúrbios neonatais e derrame. Sendo a maior parte do impacto da COVID-19 na saúde foi devido à mortalidade prematura. Futuros trabalhos devem ser direcionados a permitir a comparações entre países por períodos de tempo maiores, incorporando o papel da introdução das campanhas de vacinação e o surgimento de variantes do SARS-CoV2.

A campanha de vacinação se mostrou altamente efetiva na prevenção de casos graves, e óbitos. O esquema primário de vacinação com as vacinas ChAdOx1 nCoV-19, CoronaVac, BNT162b2 e Ad26.COV2.S conferiu adequada proteção contra os desfechos de interesse, inclusive durante períodos de dominância de variantes. Como esperado, também foi evidente uma queda na proteção ao longo do tempo pós vacinação. As doses de reforço da ChAdOx1 nCoV-19 e BNT162b2 aumentaram significativamente a os níveis de proteção, com reforço heterólogo conferindo uma maior proteção. Além disso, pudemos observar que a introdução das vacinas de COVID-19 evitou um aumento substancial no número de casos e óbitos. Futuros trabalhos devem avaliar a efetividade das vacinas a por períodos mais longos e para as diferentes doses de reforço, bem como tentar separar os efeitos direto e indireto da vacinação, bem como estimar os benefícios econômicos da introdução das vacinas na população.

Por fim, as vacinas contra a COVID-19 foram projetadas para proteger contra casos graves e mortes, mas mesmo quando a proteção falhou, observamos que elas resultaram numa diminuição nas estadias hospitalares quando comparadas com grupo de não vacinados, com uma relação dose-resposta entre o número de doses e o tempo de internação hospitalar. Os futuros trabalhos devem analisar os efeitos das futuras doses de reforço e incluir fatores que

possam vir a afetar a duração da estadia e/ou gravidade do caso, como variantes e fatores socioeconômicos e clínicos, como comorbidades.

Um ponto forte desta tese está na utilização de grandes conjuntos de dados populacionais e que são de acesso aberto. Isso nos permitiu conduzir análises robustas e gerar estimativas nacionais representativas. Além disso, nosso estudo se beneficia da natureza longitudinal dos dados, permitindo-nos observar variações e mudanças ao longo do tempo e avaliar o impacto da vacinação.

As descobertas desta tese têm implicações importantes para as políticas de saúde pública. Nossos resultados ressaltam o papel crítico da vacinação no controle da pandemia de COVID-19 e na redução de sua pressão sobre os sistemas de saúde, além de informar o quanto a doença afetou a saúde populacional no país. Os resultados apresentados aqui ajudaram a melhorar a nossa compreensão deste desafio global de saúde e podem informar futuras campanhas de vacinação e a otimizar a alocação de recursos.

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APÊNDICE A – Material suplementar do manuscrito Disability adjusted life years associated with COVID-19 in Brazil, 2020

Supplementary material for

Disability adjusted life years associated with COVID-19 in Brazil, 2020

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TABLE OF CONTENTS

COVID-19 DALYs in Brazil

Cleber V. B. dos Santos

2022-10-04

```
library(devtools)
library(geobr)
library(covid19br)
library(freedom)
library(rgdal)
library(ggplot2)
library(gridExtra)
library(grid)
library(ggplot2)
library(lattice)
library(stringr)
library(dplyr)
##
## Attaching package: 'dplyr'
## The following object is masked from 'package:gridExtra':
##
##     combine
## The following objects are masked from 'package:stats':
##
##     filter, lag
## The following objects are masked from 'package:base':
##
##     intersect, setdiff, setequal, union
library(ggpubr)
library(forcats)
library(data.table)
##
## Attaching package: 'data.table'
## The following objects are masked from 'package:dplyr':
##
##     between, first, last
library(foreach)
```

Note that the echo = FALSE parameter was added to the code chunk to prevent printing of the R code that generated the plot.

```
# Severe cases COVID-19 ---------------------------------------------
-
```

```
sari <- fread("/Users/cleber/Downloads/2_sub/srag/srag2020.csv",sep = ";",
select = c("DT_SIN_PRI", "CS_SEXO","SG_UF_NOT", "UTI","DT_INTERNA",
```

```
"DT_ENCERRA", "NU_IDADE_N", "DT_ENTUTI" , "DT_SAIDUTI")) #Lendo os csv e sele

as.Date("01/01/2021", "%d/%m/%Y") - as.Date("25/02/2020", "%d/%m/%Y")
## Time difference of 311 days


sari <- sari %>%
  mutate(duration_hosp = as.numeric(difftime(as.Date(DT_ENCERRA,
"%d/%m/%Y"), as.Date(DT_INTERNA, "%d/%m/%Y"), units = "days")),
      duration_hosp = replace(duration_hosp, duration_hosp > 311, 311),
      duration_ICU = as.numeric(difftime(as.Date(DT_SAIDUTI, "%d/%m/%Y"),
as.Date(DT_ENTUTI, "%d/%m/%Y"), units = "days")),
      duration_ICU = replace(duration_ICU, duration_ICU > 311, 311),
      age_group = case_when(NU_IDADE_N >=95 ~'95+ yo',
                    NU_IDADE_N >89 & NU_IDADE_N <95 ~'90-94yo',
                    NU_IDADE_N >84 & NU_IDADE_N <90 ~'85-89yo',
                    NU_IDADE_N >79 & NU_IDADE_N <85 ~'80-84yo',
                    NU_IDADE_N >74 & NU_IDADE_N <80 ~'75-79yo',
                    NU_IDADE_N >69 & NU_IDADE_N <75 ~'70-74yo',
                    NU_IDADE_N >64 & NU_IDADE_N <70 ~'65-69yo',
                    NU_IDADE_N >59 & NU_IDADE_N <65 ~'60-64yo',
                    NU_IDADE_N >54 & NU_IDADE_N <60 ~'55-59yo',
                    NU_IDADE_N >49 & NU_IDADE_N <55 ~'50-54yo',
                    NU_IDADE_N >44 & NU_IDADE_N <50 ~'45-49yo',
                    NU_IDADE_N >39 & NU_IDADE_N <45 ~'40-44yo',
                    NU_IDADE_N >34 & NU_IDADE_N <40 ~'35-39yo',
                    NU_IDADE_N >29 & NU_IDADE_N <35 ~'30-34yo',
                    NU_IDADE_N >24 & NU_IDADE_N <30 ~'25-29yo',
                    NU_IDADE_N >19 & NU_IDADE_N <25 ~'20-24yo',
                    NU_IDADE_N >14 & NU_IDADE_N <20 ~'15-19yo',
                    NU_IDADE_N >9 & NU_IDADE_N <15 ~'10-14yo',
                    NU_IDADE_N >4 & NU_IDADE_N <10 ~'5-9yo',
                    NU_IDADE_N >=1 & NU_IDADE_N <5 ~'1-4yo',
                    NU_IDADE_N < 1 ~'<1yo'),
      count=1) %>%
  filter(as.Date(DT_INTERNA, "%d/%m/%Y") > as.Date("25/02/2020", "%d/%m/%Y") &
as.Date(DT_INTERNA, "%d/%m/%Y") < as.Date("01/01/2021", "%d/%m/%Y"),
      CS_SEXO=="F" | CS_SEXO=="M",
      NU_IDADE_N >= 0 & NU_IDADE_N < 120) %>%
  rename(Sex=CS_SEXO)

#mean time of hospitalization of non-ICU patients
sari %>%
  filter(UTI!=1,
      DT_INTERNA != "" & DT_ENCERRA != "",
      duration_hosp > 0) %>%
  summarise(mean(duration_hosp))
##   mean(duration_hosp)
## 1            37.43466
```

```
severe_covid_grouped <- sari %>%
 filter(UTI!=1,
      duration_hosp > 0) %>%
 group_by( Sex, age_group) %>%
 summarise(severe_cases = sum(count)) %>%
 mutate(Duration = 37.43 / 365, # the mean time of hospitalization in person-
year
      DW = 0.133,
      severe_YLD = severe_cases * Duration* DW)
## `summarise()` has grouped output by 'Sex'. You can override using the `.groups`
## argument.
severe_covid_grouped <- severe_covid_grouped %>%
 mutate(Sex=case_when(Sex=="F" ~ "Female",
              Sex=="M" ~ "Male"))


# Critical (UCI COVID-19) ----------------------------------------------
------------

#mean time hospitalization UCI:
sari %>%
 filter(UTI==1,
      duration_ICU > 0) %>%
 summarise(mean(duration_ICU))
##   mean(duration_ICU)
## 1         11.16314

#grouping...
critical_covid_grouped <- sari %>%
 filter(UTI==1,
      duration_ICU > 0) %>% #filtering the cases transferred to UCI
 group_by(Sex, age_group) %>%
 summarise( uci_cases = sum(count)) %>%
 mutate(Duration = 11.16 / 365, # the mean time of hospitalization in person-
year
      DW = 0.655,
      critical_YLD = uci_cases * Duration* DW)
## `summarise()` has grouped output by 'Sex'. You can override using the `.groups`
## argument.
critical_covid_grouped <- critical_covid_grouped %>%
 mutate(Sex=case_when(Sex=="F" ~ "Female",
              Sex=="M" ~ "Male"))

sum(critical_covid_grouped$uci_cases)
## [1] 171648

sum(critical_covid_grouped$YLD)
## Warning: Unknown or uninitialised column: `YLD`.
```

```
## [1] 0

#rm(sari)

# Mild cases COVID-19 ------------------------------------------------
-

library(foreach)

#Get sheets
setwd("/Users/cleber/Downloads/2_sub/sg/2020")
temp = list.files(pattern="*.csv") #criando um arquivo temporario com todos
arquivos csv do diretório
for (i in 1:length(temp)) assign(temp[i], fread(temp[i], sep = ";", select =
c("dataInicioSintomas","idade", "classificacaoFinal", "sexo"))) #lendo os csv
e sele
flu_like <- rbind(ac.csv,
                  al.csv,
                  am.csv, ap.csv,
ba1.csv,ba2.csv,ce.csv,df.csv,es.csv,go1.csv,go2.csv,ma.csv,mg1.csv,mg2.csv,mg3.csv,
                  ms.csv,mt.csv,pa.csv,pb.csv,pe.csv,pi.csv,pr1.csv,
pr2.csv,rj1.csv,rj2.csv,rn.csv,ro.csv,rr.csv,
                  rs1.csv,rs2.csv,rs3.csv,sc1.csv,sc2.csv,sc3.csv,se.csv,
sp1.csv,sp2.csv,sp3.csv,sp4.csv,sp5.csv,sp6.csv,sp7.csv,
                  to.csv)

rm(ac.csv,
  al.csv,
  am.csv, ap.csv,
ba1.csv,ba2.csv,ce.csv,df.csv,es.csv,go1.csv,go2.csv,ma.csv,mg1.csv,mg2.csv,mg3.csv,
  ms.csv,mt.csv,pa.csv,pb.csv,pe.csv,pi.csv,pr1.csv,
pr2.csv,rj1.csv,rj2.csv,rn.csv,ro.csv,rr.csv,
  rs1.csv,rs2.csv,rs3.csv,sc1.csv,sc2.csv,sc3.csv,se.csv,
sp1.csv,sp2.csv,sp3.csv,sp4.csv,sp5.csv,sp6.csv,sp7.csv,
  to.csv, XX.csv, ni.csv,i,temp)

mild_covid <- flu_like %>%
 filter(dataInicioSintomas > as.Date("2020-02-25") & dataInicioSintomas <
as.Date("2021-01-01"), #filtering the cases with symptom between the first
cases of COVID-19 notified in BR and the end of 2020
      sexo=="Feminino" | sexo=="Masculino", #excluding the records without
gender classification
      idade >= 0 & idade < 120, #excluding the records with age with negative
values or >120yo
      complete.cases(idade)) %>%
 mutate(classif = case_when(
  str_detect(classificacaoFinal,
        pattern = "Confir") ~ "Confirmed",
  classificacaoFinal== "Descartado" ~"Discarted",
  classificacaoFinal== "Suspeito" ~ "Suspect",
```

```
  classificacaoFinal== "" ~ "NA",
  TRUE~"Other"
 )) %>%
 mutate(
  age_group = case_when(idade >=95 ~'95+ yo', #creating age-groups
                idade >89 & idade <95 ~'90-94yo',
                idade >84 & idade <90 ~'85-89yo',
                idade >79 & idade <85 ~'80-84yo',
                idade >74 & idade <80 ~'75-79yo',
                idade >69 & idade <75 ~'70-74yo',
                idade >64 & idade <70 ~'65-69yo',
                idade >59 & idade <65 ~'60-64yo',
                idade >54 & idade <60 ~'55-59yo',
                idade >49 & idade <55 ~'50-54yo',
                idade >44 & idade <50 ~'45-49yo',
                idade >39 & idade <45 ~'40-44yo',
                idade >34 & idade <40 ~'35-39yo',
                idade >29 & idade <35 ~'30-34yo',
                idade >24 & idade <30 ~'25-29yo',
                idade >19 & idade <25 ~'20-24yo',
                idade >14 & idade <20 ~'15-19yo',
                idade >9 & idade <15 ~'10-14yo',
                idade >4 & idade <10 ~'5-9yo',
                idade >=1 & idade <5 ~'1-4yo',
                idade < 1 ~'<1yo'))

mild_covid_grouped <- mild_covid %>%
 mutate(count=1) %>%
 group_by(sexo, age_group) %>% #grouping by sex and age
 rename(Sex = sexo) %>%
 summarise(symp_cases = sum(count)) %>%
 mutate(Sex=case_when(Sex=="Feminino" ~ "Female",
                Sex=="Masculino" ~ "Male"))#%>%
## `summarise()` has grouped output by 'Sex'. You can override using the `.groups`
## argument.

rm(flu_like)

severe_covid_grouped <- severe_covid_grouped %>%
 mutate(Sex=case_when(Sex=="F" ~ "Female",
                Sex=="M" ~ "Male"))


mild_correct <- mild_covid_grouped %>% right_join(severe_covid_grouped)

## Joining, by = c("Sex", "age_group")
mild_correct <- mild_correct %>%
 mutate(correct_mild = symp_cases - severe_cases)
```

```
mild <- mild_correct %>%
  select(Sex, age_group,correct_mild) %>%
  mutate(Duration = 10/365, #10 days divided into 365 (i.e., person-year)
      DW = 0.051,
      mild_YLD = correct_mild* Duration* DW) %>%
  select(Sex, age_group, correct_mild, mild_YLD) %>%
  rename(mild_cases = correct_mild)



# Long COVID ------------------------------------------------------------
-


long <- mild_correct %>%
  select(Sex, age_group, correct_mild) %>%
  mutate(long_cases = correct_mild*0.133,
      Duration = 28/365,
      DW = 0.219,
      long_YLD = long_cases* Duration* DW)  %>%
  select(Sex, age_group,long_cases, long_YLD)

# Deaths due to COVID-19 ------------------------------------------------
-


mortality<-
fread("/Users/cleber/Downloads/2_sub/sim/sim_preliminar_2020.csv", sep=";",
select = c("CAUSABAS", "CAUSABAS_O", "IDADE", "SEXO", "CODMUNRES"))

mortality_covid <- mortality %>%
  filter(complete.cases(IDADE) & (SEXO==1 | SEXO==2)) %>%
  filter(str_detect(CAUSABAS, pattern = "U071")|str_detect(CAUSABAS,
pattern = "U072")| str_detect(CAUSABAS, pattern = "U090")|
       str_detect(CAUSABAS, pattern = "U109")|str_detect(CAUSABAS, pattern
= "B342")| str_detect(CAUSABAS, pattern = "B972")|
       str_detect(CAUSABAS_O, pattern = "U071")|str_detect(CAUSABAS_O,
pattern = "U072")| str_detect(CAUSABAS_O, pattern = "U090")|
       str_detect(CAUSABAS_O, pattern = "U109")| str_detect(CAUSABAS_O,
pattern = "B342")| str_detect(CAUSABAS_O, pattern = "B972")) %>%
  mutate(UF = substr(CODMUNRES, 1, 2),
      UF = case_when(UF == 11 ~"RO",
                UF == 12 ~"AC",
                UF == 13 ~"AM",
                UF == 14 ~"RR",
                UF == 15 ~"PA",
                UF == 16 ~"AP",
                UF == 17 ~"TO",
                UF == 21 ~"MA",
                UF == 22 ~"PI",
```

```
                UF == 23 ~"CE",
                UF == 24 ~"RN",
                UF == 25 ~"PB",
                UF == 26 ~"PE",
                UF == 27 ~"AL",
                UF == 28 ~"SE",
                UF == 29 ~"BA",
                UF == 31 ~"MG",
                UF == 32 ~"ES",
                UF == 33 ~"RJ",
                UF == 35 ~"SP",
                UF == 41 ~"PR",
                UF == 42 ~"SC",
                UF == 43 ~"RS",
                UF == 50 ~"MS",
                UF == 51 ~"MT",
                UF == 52 ~"GO",
                UF == 53 ~"DF"),
      age_group = case_when(IDADE < 401 ~'0-1yo',
                IDADE >=495 ~'95+ yo',
                IDADE >=490 & IDADE <=494 ~'90-94yo',
                IDADE >=485 & IDADE <=489 ~'85-89yo',
                IDADE >=480 & IDADE <=484 ~'80-84yo',
                IDADE >=475 & IDADE <=479 ~'75-79yo',
                IDADE >=470 & IDADE <=474 ~'70-74yo',
                IDADE >=465 & IDADE <=469 ~'65-69yo',
                IDADE >=460 & IDADE <=465 ~'60-64yo',
                IDADE >=455 & IDADE <=459 ~'55-59yo',
                IDADE >=450 & IDADE <=454 ~'50-54yo',
                IDADE >=445 & IDADE <=449 ~'45-49yo',
                IDADE >=440 & IDADE <=444 ~'40-44yo',
                IDADE >=435 & IDADE <=439 ~'35-39yo',
                IDADE >=430 & IDADE <=434 ~'30-34yo',
                IDADE >=425 & IDADE <=429 ~'25-29yo',
                IDADE >=420 & IDADE <=424 ~'20-24yo',
                IDADE >=415 & IDADE <=419 ~'15-19yo',
                IDADE >=410 & IDADE <=414 ~'10-14yo',
                IDADE >=405 & IDADE <=409 ~'5-9yo',
                IDADE >=401 & IDADE <=404 ~'1-4yo'))
rm(mortality)
yll <- mortality_covid %>%
 mutate(count=1) %>%
 group_by(age_group,SEXO) %>%
 summarise(deaths = sum(count)) %>%
 mutate(GBD_lifetable = case_when(
  age_group =='0-1yo' ~ 88.8718951,
  age_group =='1-4yo' ~ 88.00051053,
  age_group =='5-9yo' ~ 84.03008056,
  age_group =='10-14yo' ~ 79.04633476,
```

```
    age_group =='15-19yo' ~ 74.0665492,
    age_group =='20-24yo' ~ 69.10756792,
    age_group =='25-29yo' ~ 64.14930031,
    age_group =='30-34yo' ~ 59.1962771,
    age_group =='35-39yo' ~ 54.25261364,
    age_group =='40-44yo' ~ 49.31739311,
    age_group =='45-49yo' ~ 44.43332057,
    age_group =='50-54yo' ~ 39.63473787,
    age_group =='55-59yo' ~ 34.91488095,
    age_group =='60-64yo' ~ 30.25343822,
    age_group =='65-69yo' ~ 25.68089534,
    age_group =='70-74yo' ~ 21.28820012,
    age_group =='75-79yo' ~ 17.10351469,
    age_group =='80-84yo' ~ 13.23872477,
    age_group =='85-89yo' ~ 9.990181244,
    age_group =='90-94yo' ~ 7.617724915,
    age_group =='95+ yo' ~ 5.922359078),
    yll=deaths*GBD_lifetable
  )
## `summarise()` has grouped output by 'age_group'. You can override using the
## `.groups` argument.
sum(yll$yll)
## [1] 5408504



# Mergin the results ------------------------------------------------
-

deaths <- yll %>%
  mutate(Sex=case_when(SEXO==2 ~ "Female",
                       SEXO==1 ~ "Male")) %>%
  select(age_group, Sex, deaths, yll)

severe <- severe_covid_grouped %>%
  select(age_group,Sex,severe_cases, severe_YLD)

critical <- critical_covid_grouped %>%
  select(age_group, Sex, uci_cases, critical_YLD) %>%
  rename(critical_cases = uci_cases)

daly1 <- merge(critical, severe, by=c("Sex", "age_group"))

daly <- mild %>% right_join(daly1)
## Joining, by = c("Sex", "age_group")
daly <- long %>% right_join(daly)
## Joining, by = c("Sex", "age_group")
daly <- deaths %>% right_join(daly)
## Joining, by = c("age_group", "Sex")
```

```
daly[is.na(daly)]<-0

daly <- daly %>%
 mutate(long_cases = replace(long_cases, long_cases<0, 0),
     long_YLD = replace(long_YLD, long_YLD<0, 0),
     mild_cases = replace(mild_cases, mild_cases<0, 0),
     mild_YLD = replace(mild_YLD, mild_YLD<0, 0))

daly <- daly %>%
 mutate(Daly = mild_YLD+severe_YLD+critical_YLD+long_YLD+yll)

# Calculating uncertainty intervals ------------------------------------
---


mild_covid_ <- mild_covid %>%
 select(age_group, sexo)

Incidence_mild <- table(mild_covid_$age_group, mild_covid_$sexo)
Incidence_mild <-as.data.frame(Incidence_mild)

Incidence_mild_female <- Incidence_mild %>% filter( Incidence_mild$Var2 ==
"Feminino")
Incidence_mild_male <- Incidence_mild %>% filter( Incidence_mild$Var2 ==
"Masculino")


Incidence_mild <- rbind.data.frame(Incidence_mild_female,Incidence_mild_male)

Duration = 10 / 365

DW = 0.051

mean_median_ci <- function(x) {
 c(mean = mean(x),
  median = median(x),
  quantile(x, probs = c(0.025, 0.975)))
}

YLDmildUncertainty <- foreach(i = 1:nrow(Incidence_mild),.combine = rbind) %do% {
 Mean <- Incidence_mild[i,3]
 DW <- sample(x = rpert(n= 10000, x.min= 0.032, x.mode= 0.051, x.max= 0.074),
size = 10000,replace = TRUE)
 mean_median_ci(Mean * DW * Duration) }

colSums(YLDmildUncertainty)
##      mean    median      2.5%     97.5%
## 10871.375 10837.277  7851.139 14076.304
YLDmildUncertainty <- as.data.frame(YLDmildUncertainty)
```

```
long_covid <- mild_covid %>%
  select(age_group, sexo)

Incidence_long <- table(long_covid$age_group, long_covid$sexo)
Incidence_long <-as.data.frame(Incidence_long)

Incidence_long$long_cases <- Incidence_long$Freq*0.133

Incidence_long_female <- Incidence_long %>% filter( Incidence_long$Var2 ==
"Feminino")
Incidence_long_male <- Incidence_long %>% filter( Incidence_long$Var2 ==
"Masculino")


Incidence_long <- rbind.data.frame(Incidence_long_female,Incidence_long_male)

Duration = 28 / 365

DW = 0.219

YLDlongUncertainty <- foreach(i = 1:nrow(Incidence_long),.combine = rbind) %do% {
  Mean <- Incidence_long[i,4]
  DW <- sample(x = rpert(n= 10000, x.min= 0.148, x.mode= 0.219, x.max= 0.308),
size = 10000,replace = TRUE)
  mean_median_ci(Mean * DW * Duration) }

colSums(YLDlongUncertainty)
##     mean   median     2.5%    97.5%
## 17394.29 17344.28 13108.60 21966.77
YLDlongUncertainty <- as.data.frame(YLDlongUncertainty)

sari_ <- sari %>%
  filter(UTI!=1,
         DT_INTERNA != "" & DT_ENCERRA != "",
         duration_hosp > 0) %>%
  select(age_group, Sex, count)

Incidence_hosp <- table(sari_$age_group, sari_$Sex,sari_$count)
Incidence_hosp <-as.data.frame(Incidence_hosp)

Incidence_hosp_female <- Incidence_hosp %>% filter( Incidence_hosp$Var2 == "F")
Incidence_hosp_male <- Incidence_hosp %>% filter( Incidence_hosp$Var2 == "M")

Incidence_hosp3 <- rbind.data.frame(Incidence_hosp_female,Incidence_hosp_male)

Duration = 37.43 / 365

DW = 0.133

mean_median_ci <- function(x) {
```

```
 c(mean = mean(x),
   median = median(x),
   quantile(x, probs = c(0.025, 0.975)))
}

YLDhospUncertainty <- foreach(i = 1:nrow(Incidence_hosp3),.combine = rbind) %do% {
 Mean1 <- Incidence_hosp3[i,4]
 DW <- sample(x = rpert(n= 10000, x.min= 0.088, x.mode= 0.133, x.max= 0.190),
size = 10000,replace = TRUE)
 mean_median_ci(Mean1 * DW * Duration) }

colSums(YLDhospUncertainty)
##     mean    median      2.5%     97.5%
##  8236.606  8204.707  6124.039 10501.927
YLDhospUncertainty <- as.data.frame(YLDhospUncertainty)

# Sensitivity ------------------------------------------------------------
-

#here i'll
mild_sens_double_cases <- mild_correct %>%
 select(Sex, age_group,correct_mild) %>%
 mutate(Duration = 10/365,
     DW = 0.051,
     mild = (correct_mild*2)* Duration* DW) %>%
 select(Sex, age_group,mild)
sum(mild_sens_double_cases$mild)
#19798.3

long_sens_double_cases <- mild_correct %>%
 select(Sex, age_group, correct_mild) %>%
 mutate(long_cases = (correct_mild*2)*0.133,
     Duration = 28/365,
     DW = 0.219,
     long = long_cases* Duration* DW)  %>%
 select(Sex, age_group,long)
sum(long_sens_double_cases$long)
## [1] NA
#31660.04


mild_sens_half_cases <- mild_correct %>%
 select(Sex, age_group,correct_mild) %>%
 mutate(Duration = 10/365, #10 days divided into 365 (i.e., person-year)
     DW = 0.051,
     mild = (correct_mild/2)* Duration* DW) %>%
 select(Sex, age_group,mild)
sum(mild_sens_half_cases$mild)
## [1] NA
```

```
#4949.575

long_sens_half_cases <- mild_correct %>%
  select(Sex, age_group, correct_mild) %>%
  mutate(long_cases = (correct_mild/2)*0.133,
      Duration = 28/365,
      DW = 0.219,
      long = long_cases* Duration* DW)  %>%
  select(Sex, age_group,long)
sum(long_sens_half_cases$long)
## [1] NA
#7915.011
```

Table S1. Morbidity sensitivity analyses: impact on COVID-19 YLD, Brazil, 2020

Impacted health states	Sensitivity	Total YLD
Mild to moderate cases	Decrease moderate cases by 50%	4,949.57
	Double moderate cases	19,798.30
Post-acute consequences	Decrease post-acute consequences by 50%	7,915.01
	Double post-acute consequences	31,660.04
Combination of scenarios that minimise YLD impact [a]		**12,864.59**
Combination of scenarios that maximise YLD impact [b]		**51,458.34**

a Combined criteria used: decrease in the number of both moderate cases and post-acute consequences;

b Combined criteria used: increase in the number of moderate cases and post-acute consequences by 50%.

Table S1. Summary of Disability-Adjusted Life Years of the 2019 GBD results for Brazil according to the cause. Available at https://vizhub.healthdata.org/gbd-results/

measure_id	measure_name	location_id	location_name	sex_id	sex_name	age_id	age_name	cause_id	cause_name	metric_id	metric_name	year	val	upper	lower
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	387	Protein-energy malnutrition	1	Number	2019	234582.05856062743	261251.48035658323	207999.14662085605
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	388	Iodine deficiency	1	Number	2019	2583.8105458575424	4972.80913686506	1148.8152833644424
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	389	Vitamin A deficiency	1	Number	2019	18072.25162585565	26646.48261649007	11056.565425928065
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	390	Dietary iron deficiency	1	Number	2019	659743.0313082277	1011720.443781015	424385.7067777086
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	391	Other nutritional deficiencies	1	Number	2019	27677.945136299604	36330.505881169374	21571.04135807696
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	393	Sexually transmitted infections excluding HIV	1	Number	2019	69729.49466205647	110940.35582042411	47597.87540351133
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	400	Acute hepatitis	1	Number	2019	21594.159012802465	27522.933292457652	17149.636314300074
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	405	Leprosy	1	Number	2019	2514.62430617550 26	3715.02500836511 67	1598.45640313765 67
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	408	Other unspecified infectious diseases	1	Number	2019	108570.48583819282	149236.4283096354	86236.55235645702
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	515	Asthma	1	Number	2019	448965.3970649907	661635.6781391872	310381.4920426175
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	516	Interstitial lung disease and pulmonary sarcoidosis	1	Number	2019	73306.04561488303	88621.33508084709	47761.2723410374
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	520	Other chronic respiratory diseases	1	Number	2019	66565.39014134654	77148.04844973101	56922.70774256178
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	521	Cirrhosis and other chronic liver diseases	1	Number	2019	1170623.4306604452	1238023.584805878	1113984.9992971169
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	718	Self-harm	1	Number	2019	626719.5755263034	682680.3157763474	594617.8013324933
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	724	Interpersonal violence	1	Number	2019	3799992.1088724015	3979773.1764879986	3649901.7111265394
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	729	Exposure to forces of nature	1	Number	2019	3167.9132166958893	4075.524075197417	2517.0942352995194

2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	842	Environmental heat and cold exposure	1	Number	2019	105988.62251542149	152789.57393983952	69533.75421468247
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	843	Ebola	1	Number	2019	0.0	0.0	0.0
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	630	Low back pain	1	Number	2019	2044102.3335921352	2715670.0489839525	1441813.5374309267
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	631	Neck pain	1	Number	2019	542596.5167578775	792398.1854230537	356801.6318433749
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	632	Gout	1	Number	2019	19550.6607715423	28144.978359007106	12433.5130863034 28
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	639	Other musculoskeletal disorders	1	Number	2019	1600235.5253439571	2195213.8481951742	1124478.7223276002
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	641	Congenital birth defects	1	Number	2019	1619653.8168811353	1974399.0475665892	1314928.7156885008
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	716	Other unintentional injuries	1	Number	2019	242136.55680485748	279349.45549032866	211359.1858333827
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	338	Diphtheria	1	Number	2019	110.855830539 11412	152.64442798078986	82.102566866934 08
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	339	Whooping cough	1	Number	2019	8179.9418560319 56	11161.983075938499	5890.616509615 98
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	340	Tetanus	1	Number	2019	4130.272460780992	10851.533084507813	2764.7388447657404
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	341	Measles	1	Number	2019	66.18629233612604	108.522094123585 79	49.3706435002900 65
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	411	Esophageal cancer	1	Number	2019	323233.2571911268	340083.85491740744	306838.13952648477
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	414	Stomach cancer	1	Number	2019	545219.2359096949	568478.4945809729	519168.1577913597
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	417	Liver cancer	1	Number	2019	139930.43347273007	147341.30774208912	132617.60506465824
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	423	Larynx cancer	1	Number	2019	146503.07029315343	153963.2905853141	138630.09397477887
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	426	Tracheal, bronchus, and lung cancer	1	Number	2019	866748.9304611183	906754.520746419	824500.8678500055

2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	1022	Other malignant neoplasms	1	Number	2019	388650.352683842	419576.8905049676	365380.3954373924
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	1023	Other cardiovascular and circulatory diseases	1	Number	2019	293877.3304039161	323538.2812394983	268964.4652352467
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	529	Appendicitis	1	Number	2019	47947.471110332	56548.60264096979	36292.34338771591
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	530	Paralytic ileus and intestinal obstruction	1	Number	2019	175523.93493341957	195209.8728150531	146394.13854217678
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	531	Inguinal, femoral, and abdominal hernia	1	Number	2019	153769.20006026153	196532.97701761752	119238.87647589402
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	532	Inflammatory bowel disease	1	Number	2019	46349.59919362761	54190.49827224871	39647.058057770024
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	533	Vascular intestinal disorders	1	Number	2019	89266.65842071164	96308.73550847203	82617.837163337186
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	534	Gallbladder and biliary diseases	1	Number	2019	339869.1651266341	436556.5890696655	265834.5593248367
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	535	Pancreatitis	1	Number	2019	172622.08638568	185958.969100009126	153155.2111428051
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	619	Endocrine, metabolic, blood, and immune disorders	1	Number	2019	531395.3049454737	638577.2962763697	401818.75219737354
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	627	Rheumatoid arthritis	1	Number	2019	103504.867308888	133453.7900765186	75336.61944832184
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	628	Osteoarthritis	1	Number	2019	497542.53737190366	985231.3739572625	249691.8197123114
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	297	Tuberculosis	1	Number	2019	213105.26705559008	227018.34393998983	200796.92787784542
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	298	HIV/AIDS	1	Number	2019	807432.7042503263	849402.5665427356	773530.5753850581
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	302	Diarrheal diseases	1	Number	2019	565446.014935547	683841.2887416611	468026.2268654036
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	321	Other intestinal infectious diseases	1	Number	2019	1226.1867528835137	1943.0997750385575	675.4465484899882
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	322	Lower respiratory infections	1	Number	2019	1994790.0108112518	2127570.6090563494	1851232.561746713

2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	328	Upper respiratory infections	1	Number	2019	230934.93604442215	359653.16783655185	141602.31330491856
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	329	Otitis media	1	Number	2019	59849.819711779186	97455.24470788451	35440.79787689351
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	332	Meningitis	1	Number	2019	129800.01661433573	145349.80547612556	114468.24148970917
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	337	Encephalitis	1	Number	2019	27246.293182188376	31609.680076488672	20267.89821030364
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	364	Food-borne trematodiases	1	Number	2019	0.0	0.0	0.0
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	365	Other neglected tropical diseases	1	Number	2019	51342.86937014688	72466.74108800195	34243.73399672275
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	366	Maternal disorders	1	Number	2019	130803.15596251882	140839.12150293926	121016.18324467364
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	429	Breast cancer	1	Number	2019	598058.7447726616	636738.9304932614	563114.2783994399
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	432	Cervical cancer	1	Number	2019	348416.2536160296	404298.3808616996	324215.10040369886
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	435	Uterine cancer	1	Number	2019	74322.142068717	79212.04087847899	69589.60697801026
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	438	Prostate cancer	1	Number	2019	413225.1886873036	605638.5953097729	359721.3260855095
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	441	Colon and rectum cancer	1	Number	2019	644732.2504714219	672419.4198270678	611425.9615737835
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	444	Lip and oral cavity cancer	1	Number	2019	148871.92349832004	157204.7166435582	141013.9021338604
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	447	Nasopharynx cancer	1	Number	2019	18249.4267227175	19339.822884608195	17075.063229832744
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	450	Other pharynx cancer	1	Number	2019	109752.96794941707	117179.92693370876	102718.4402106868
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	541	Other digestive diseases	1	Number	2019	131268.78778671002	169138.56680228756	95652.62353742278
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	543	Alzheimer's disease and other dementias	1	Number	2019	855327.6514646594	1874372.874799152	377333.1253174232

2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	544	Parkinson's disease	1	Number	2019	159998.24812870624	173337.43011335985	145339.4958632942
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	545	Idiopathic epilepsy	1	Number	2019	404151.5433089046	549563.1036406613	287850.0066736286
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	546	Multiple sclerosis	1	Number	2019	24794.756487326107	31459.440766283948	19863.57294936732
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	342	Varicella and herpes zoster	1	Number	2019	21686.22184558426	29505.478869269034	15177.04198318113
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	345	Malaria	1	Number	2019	11097.042138762356	22964.825473702058	5413.0968955500839
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	346	Chagas disease	1	Number	2019	174194.2242029733	302974.3817183899	109039.60418755852
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	347	Leishmaniasis	1	Number	2019	67617.83450630598	266026.3240235446	2870.27288551281
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	350	African trypanosomiasis	1	Number	2019	0.0	0.0	0.0
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	380	Neonatal disorders	1	Number	2019	3227621.9515293366	3840013.8518732428	2670497.9301191354
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	493	Ischemic heart disease	1	Number	2019	3721023.4544533067	3892657.2285360475	3507748.043631261
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	494	Stroke	1	Number	2019	2861723.2406806713	3012805.91798038	2683069.8825876014
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	498	Hypertensive heart disease	1	Number	2019	558147.3630457986	769792.9470385057	502264.9515933891
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	499	Cardiomyopathy and myocarditis	1	Number	2019	545772.4025089525	621356.7525456359	484988.71270660765
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	500	Atrial fibrillation and flutter	1	Number	2019	230116.28937971775	279885.89947355114	189167.01024767716
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	554	Motor neuron disease	1	Number	2019	43968.35832636242	46922.62958930152	40197.573334657085
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	557	Other neurological disorders	1	Number	2019	140842.80214724535	172541.1166931995	114756.52927059708
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	559	Schizophrenia	1	Number	2019	431051.70887983096	547015.259264056	313386.82771435555

2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	560	Alcohol use disorders	1	Number	2019	1051583.0262254274	1337046.8849659949	831634.6604850595
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	561	Drug use disorders	1	Number	2019	467981.9459190504	619187.0331036766	336020.82108711463
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	654	Dermatitis	1	Number	2019	282390.20230380597	440372.9706626824	169181.34178468125
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	501	Aortic aneurysm	1	Number	2019	231484.29319789313	245471.0611702248	216550.5087578073
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	502	Peripheral artery disease	1	Number	2019	54103.231028389935	92661.80924332066	29178.66896367352
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	503	Endocarditis	1	Number	2019	77155.36132857612	92952.81323205176	58867.27425067627
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	504	Non-rheumatic valvular heart disease	1	Number	2019	103773.7694791369	110719.99769803298	96149.31340739889
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	509	Chronic obstructive pulmonary disease	1	Number	2019	1434008.7060512628	1576595.4206850396	1320384.7570499734
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	510	Pneumoconiosis	1	Number	2019	19338.35357611467	22689.918219180596	16723.97621983232
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	594	Urinary diseases and male infertility	1	Number	2019	467097.99367524916	517309.5272215422	343967.8542967998
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	351	Schistosomiasis	1	Number	2019	68482.08483341704	111077.89955477891	42318.819919410256
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	352	Cysticercosis	1	Number	2019	82940.27211321458	124414.31122835567	51677.211658392895
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	353	Cystic echinococcosis	1	Number	2019	317.861032060771	453.19621349566603	193.75421317949426
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	354	Lymphatic filariasis	1	Number	2019	6899.536840284492	10341.38730096891	4416.520015832443
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	355	Onchocerciasis	1	Number	2019	0.0	0.0	0.0
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	356	Trachoma	1	Number	2019	121.76387708353211	199.62821500399755	69.60587520686919
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	357	Dengue	1	Number	2019	40600.26081353127	50448.819078768465	27017.685550875325

2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	358	Yellow fever	1	Number	2019	266.5561584750066	619.1216358101663	94.81405774418437
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	359	Rabies	1	Number	2019	76.11448898816029	91.6788750583807	64.322827162710O3
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	360	Intestinal nematode infections	1	Number	2019	23911.071584782305	38907.07992797718	13799.149979774564
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	453	Gallbladder and biliary tract cancer	1	Number	2019	119382.47268703078	137705.40873721457	103997.56464964313
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	456	Pancreatic cancer	1	Number	2019	339640.9287075585	358273.90454937646	318056.226066387l4
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	459	Malignant skin melanoma	1	Number	2019	69529.99257046377	102738.31474373385	57882.86983172882
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	462	Non-melanoma skin cancer	1	Number	2019	52194.92329567882	55221.366502837554	47105.490040316836
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	655	Psoriasis	1	Number	2019	152913.86255285243	201484.67892111622	108428.90491496662
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	658	Scabies	1	Number	2019	243672.89161035736	385832.5630450454	135745.01328953504
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	659	Fungal skin diseases	1	Number	2019	100254.32927249909	209874.267942275l8	40455.761808981646
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	660	Viral skin diseases	1	Number	2019	89859.20418004938	134381.24744126888	57550.48405588331
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	661	Acne vulgaris	1	Number	2019	85565.914426536O4	138064.8124070577	51880.41247180435
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	662	Alopecia areata	1	Number	2019	16568.072284319805	24457.41286006575	10492.023085605l
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	663	Pruritus	1	Number	2019	20627.271669586804	36857.97003755061	9870.944673201202
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	664	Urticaria	1	Number	2019	103529.62717924714	149034.29360992106	67672.03790801256
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	665	Decubitus ulcer	1	Number	2019	33550.7079784717	43404.76218791138	16556.15339908274
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	668	Other skin and subcutaneous diseases	1	Number	2019	117657.54753880178	209098.4233846312	59926.97313489101

2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	854	Executions and police conflict	1	Number	2019	70181.58973609358	90602.48351118006	49421.09536509048
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	935	Zika virus	1	Number	2019	92.37676982892964	139.20064298851582	56.1614005320122 16
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	936	Guinea worm disease	1	Number	2019	0.0	0.0	0.0
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	945	Conflict and terrorism	1	Number	2019	251.941538946197 57	412.4405087321522	157.7948716120282
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	603	Gynecological diseases	1	Number	2019	740661.3216003797	1036025.3097278355	509349.9377924529
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	613	Hemoglobinopathies and hemolytic anemias	1	Number	2019	174195.14954804795	222334.6475540035	140207.8222781778
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	695	Other transport injuries	1	Number	2019	90285.57926538092	95607.87070020013	84592.47780294144
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	697	Falls	1	Number	2019	1185461.1364943713	1463438.2039067405	973367.0010282937
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	698	Drowning	1	Number	2019	347221.11798888486	370316.1721748674	322317.4618871036
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	699	Fire, heat, and hot substances	1	Number	2019	140710.84078678858	191618.91874224992	106379.31892404404
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	700	Poisonings	1	Number	2019	14867.173487134256	17172.437089642593	12908.755743976704
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	704	Exposure to mechanical forces	1	Number	2019	263249.8794019479	325173.29596113676	217115.12293279546
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	708	Adverse effects of medical treatment	1	Number	2019	87980.44904404019	95855.74051960585	73209.15284976117
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	709	Animal contact	1	Number	2019	34186.948167399445	41480.720018169	29121.95098990557
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	712	Foreign body	1	Number	2019	230239.96919437422	263996.2268414257	199331.8529069933
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	980	Bacterial skin diseases	1	Number	2019	139272.23884671362	178352.73475194775	70739.77970530563
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	981	Blindness and vision loss	1	Number	2019	700376.728553627	950927.9798751222	490549.93816533516

2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	992	Upper digestive system diseases	1	Number	2019	488715.04932539567	739876.352950235	329458.09373301954
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	465	Ovarian cancer	1	Number	2019	150453.52234241	163533.06304772856	138189.26598279134
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	468	Testicular cancer	1	Number	2019	23191.507006918808	25914.223345788185	21516.97544236407
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	471	Kidney cancer	1	Number	2019	124141.0590143296	130542.36951187854	117594.37285171935
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	474	Bladder cancer	1	Number	2019	107756.97261264105	114563.36393598215	99750.28057181
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	477	Brain and central nervous system cancer	1	Number	2019	373186.94954039867	423714.96231683216	250314.8613896384
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	480	Thyroid cancer	1	Number	2019	30147.413408880282	34681.44923948814	28235.523143822324
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	483	Mesothelioma	1	Number	2019	27150.575510782634	31520.59250258649	23145.246818044227
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	484	Hodgkin lymphoma	1	Number	2019	26688.226578781345	33171.09543186858	23365.670642980742
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	485	Non-Hodgkin lymphoma	1	Number	2019	184737.13899070618	194056.62553230577	175931.06567941696
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	486	Multiple myeloma	1	Number	2019	95394.46113104426	104213.83006559599	83617.5144875994
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	487	Leukemia	1	Number	2019	312188.1218419523	330198.8875577887	294027.89333270973
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	490	Other neoplasms	1	Number	2019	32886.09407996156	37700.022170040975	23510.37606694146
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	492	Rheumatic heart disease	1	Number	2019	184224.8105900875	238145.94133204297	143687.28083481264
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	567	Depressive disorders	1	Number	2019	1606200.1060032342	2183261.418197973	1128433.2339183583
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	570	Bipolar disorder	1	Number	2019	560746.6417763463	863274.5302939996	344727.9253954897
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	571	Anxiety disorders	1	Number	2019	1640282.276806073	2235690.03439169	1140302.6663526746

2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	572	Eating disorders	1	Number	2019	111577.63624441753	166250.93991236165	70643.35105135657
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	575	Autism spectrum disorders	1	Number	2019	113726.96609472959	164758.9937986317	74291.22683672752
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	578	Attention-deficit/hyperactivity disorder	1	Number	2019	47953.07915168324	83607.90952347431	26961.62766951483
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	579	Conduct disorder	1	Number	2019	128397.79235378384	204189.6598921387	71282.73772179394
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	582	Idiopathic developmental intellectual disability	1	Number	2019	34649.15127495471	62322.929554071205	12433.799834474295
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	585	Other mental disorders	1	Number	2019	241992.75685516954	367917.2957925287	155387.44700703857
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	587	Diabetes mellitus	1	Number	2019	2564212.667497648	2996547.819842529	2173111.0039907345
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	588	Acute glomerulonephritis	1	Number	2019	2404.2123428903255	2649.1618913404873	2176.540270872074
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	589	Chronic kidney disease	1	Number	2019	1184118.1273818228	1274555.0568420228	1093951.4233026316
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	674	Age-related and other hearing loss	1	Number	2019	1095613.7821147854	1585939.3202882975	720912.4810932735
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	679	Other sense organ diseases	1	Number	2019	99656.20970095783	153713.8384571698	59350.81853975275
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	680	Oral disorders	1	Number	2019	972705.4267380488	1481505.7294827788	600806.2060890334
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	686	Sudden infant death syndrome	1	Number	2019	21391.476831710075	27415.072183315606	16461.313607019594
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	689	Road injuries	1	Number	2019	2431395.629322869	2553712.411408228	2297711.291956654
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	958	Typhoid and paratyphoid	1	Number	2019	365.1909649474692	656.6235135431874	191.80890007258702
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	959	Invasive Non-typhoidal Salmonella (iNTS)	1	Number	2019	2642.4976643387245	4122.949522841808	1530.0588290879693
2	DALYs (Disability-Adjusted Life Years)	135	Brazil	3	Both	22	All ages	972	Headache disorders	1	Number	2019	1649717.1590034852	3747117.047268994	256902.55292963076

Table S2. Total number of years of life lost due to disability (YLD) and years of life lost due to premature mortality (YLL) due to COVID-19 in Brazil by age group and sex between February 26, 2020, to December 31, 2020

Age group	YLD*				YLL				DALYs*			
	Female		Male		Female		Male		Female		Male	
	Crude	Per 100,000 population	Crude	Per 100,000 population	Crude	Per 100,000 population	Crude	Per 100,000 population	Crude	Per 100,000 population	Crude	Per 100,000 population
0-4	350.46 (296.68-490.04)	5.18 (4.39-7.25)	440.57 (373.66-620.04)	6.22 (5.27-8.75)	20,973.75	310.20	24,356.98	343.83	21,324.22 (21,270.43-21,463.80)	315.39 (314.59-317.45)	24,797.57(24,730.65-24,977.03)	350.05 (349.10-352.58)
5-9	283.21 (233.81-391.32)	3.94 (3.25-5.44)	375.19 (308.62-517.67)	4.99 (4.10-6.88)	4,201.50	58.46	5,461.96	72.62	4,484.71 (4,435.31-4,592.81)	62.4 (61.71-63.90)	5,837.14 (5,770.58-5,979.62)	77.61 (76.72-79.50)
10-14	288.98 (228.5-387.45)	3.75 (2.96-5.03)	335.80 (266.28-449.61)	4.17 (3.31-5.58)	4,900.87	63.57	6,007.52	74.61	5,189.85 (5,129.37-5288,32)	67.32 (66.53-68.60)	6,343.32 (6,273.79-6,457.13)	78.78 (77.92-80.19)
15-19	552.44 (426.32-727.83)	6.68 (5.16-8.81)	486.38 (376.53-639.32)	5.67 (4.39-7.45)	14,368.91	173.87	14,887.38	173.57	14,921.35 (14,795.22-15,906.74)	180.55 (179.03-182.68)	15,373.76 (15,263.91-15,526.70)	179.24 (177.96-181.02)
20-24	1,283.04 (989.71-1,681.11)	15.25 (11.76-19.98)	1,180.43 (903.46-1,547.65)	13.68 (10.47-17.94)	25,362.48	301.49	28,403.21	329.21	26,645.52 (26,352.19-15096.74)	316.74 (313.25-321.47)	29,583.64 (29,306.66-29,950.85)	342.89 (339.68-347.15)
25-29	1,664.15 (1,279.36-2,185.46)	19.78 (15.21-25.98)	1,529.13 (1,176.25-2,011.06)	17.94 (13.80-23.60)	33,678.38	400.32	45,289.41	531.37	35,342.53 (34,957.73-35,863.83)	420.1 (415.53-426.30)	46,818.54 (46,465.66-47,300.47)	549.31 (545.17-554.97)
30-34	1,817.36 (1,400.31-2,396.65)	21.35 (16.45-28.15)	1,733.41 (1,352.16-2,289.19)	20.32 (15.85-26.83)	54,815.75	643.92	84,709.87	992.99	56,633.11 (56,216.05-57,212.39)	665.27 (660.37-672.07)	86,443.28 (86,062.02-86,999.06)	1,013.31 (1,008.84-1,019.82)
35-39	1,967.91 (1,530.12-2,596.88)	22.42 (17.43-29.59)	1,894.48 (1,491.57-2,516.14)	21.78 (17.15-28.93)	85,610.62	975.43	132,105.11	1,519.06	87,578.54 (87,140.73-88,207.49)	997.85 (992.86-1,000.02)	133,999.6 (133,596.68-134,621.25)	1,540.84 (1,536.21-1,547.99)
40-44	1,882.91 (1,467.20-2,491.13)	23.78 (18.53-31.46)	1,827.07 (1,453.83-2,436.42)	23.58 (18.77-31.45)	112,345.02	1,418.88	181,981.18	2,348.91	114,227.93 (113,812.21-114,836.14)	1,442.66 (1,437.41-1,450.34)	183,808.25 (183,435.00-184,417.59)	2,372.5 (2,367.68-2,380.36)
45-49	1,575.09 (1,240.08-2,093.94)	22.56 (17.76-29.99)	1,555.38 (1,261.94-2,098.43)	23.12 (18.76-31.20)	136,010.39	1,948.05	225,365.80	3,350.59	137,585.49 (137,250.47-138,104.32)	1,970.61 (1,965.81-1,978.04)	226,921.18 (226,627.73-227,464.22)	3,373.71 (3,369.35-3,381.79)
50-54	1,412.74 (1,124.79-1,894.26)	21.99 (17.51-29.49)	1,417.50 (1,161.01-1,923.33)	23.38 (19.15-31.72)	170,469.01	2,653.63	280,891.39	4,632.03	171,881.75 (171,593.80-172,363.26)	2,675.62 (2,671.14-2,683.12)	282,308.89 (282,052.39-282,814.72)	4,655.41 (4,651.18-4,663.75)
55-59	1,283.13 (1,041.9-1,735.07)	21.84 (17.73-29.53)	1,320.88 (1,104.39-1,804.19)	24.46 (20.45-33.41)	216,891.24	3,691.15	349,567.79	6,473.43	218,174.37 (217,933.13-218,626.30)	3,712.99 (3,708.88-3,720.68)	350,888.67 (350,672.18-351,371.98)	6,497.89 (6,493.88-6,506.84)
60-64	1,060.56 (882.79-1,447.61)	21.51 (17.90-29.36)	1,142.95 (972.8-1,568.26)	26.11 (22.22-35.41)	265,262.15	5,379.19	405,063.28	9,254.17	266,322.71 (266,144.94-266,709.75)	5,400.69 (5,397.09-5,408.55)	406,206.23 (406,036.07-406,631.53)	9,280.29 (9,276.39-9,290.00)
65-69	876.96 (748.9-1,212.51)	22.43 (19.15-31.01)	991.73 (863.92-1,373.64)	29.87 (26.02-41.38)	276,557.56	7,073.61	424,119.99	12,775.13	277,434.52 (277,306.46-277,770.06)	7,096.04 (7,092.76-7,104.62)	425,111.72 (424,983.91-425,493.63)	12,805.00 (12,801.15-12,816.51)
70-74	717.94 (630.53-1,002.1)	24.79 (21.77-34.60)	812.17 (719.78-1,130.21)	35.11 (31.12-48.86)	254,244.97	8,777.73	373,054.42	16,129.05	254,962.91 (254,875.50-255,247.07)	8,802.51 (8,799.50-8,812.33)	373,866.59 (373,774.20-374,184.62)	16,164.16 (16,160.17-16,177.91)
75-79	570.68 (512.28-803.48)	28.92 (25.96-40.72)	615.35 (555.38-858.12)	42.78 (38.61-59.65)	208,012.95	10,542.01	277,247.97	19,272.58	208,583.63 (208,525.23-208,816.43)	10,570.93 (10,567.97-10,582.73)	277,863.32 (277,803.35-278,106.09)	19,315.35 (19,311.19-19,332.23)
80-84	479.30 (439.52-682.54)	35.89 (32.91-51.11)	467.10 (427.42-659.36)	53.29 (48.76-75.22)	164,451.44	12,313.65	191,233.38	21,817.22	164,930.74 (164,890.95-165,133.97)	12,349.54 (12,346.56-12,364.76)	191,700.48 (191,660.79-191,892.73)	21,870.51 (21,865.98-21,892.44)
85-89	346.82 (322.39-497.67)	46.74 (43.45-67.07)	291.28 (267.69-414.38)	67.08 (61.65-85.42)	100,221.50	13,506.01	98,113.57	22,594.06	100,568.32 (100,543.88-100,719.16)	13,552.75 (13,549.46-13,573.08)	98,404.85 (98,381.26-98,527.94)	22,661.14 (22,665.71-22,689.48)
90+	269.93 (249.99-392.83)	53.37 (49.43-77.67)	181.14 (166.58-261.31)	76.30 (70.16-110.06)	63,817.72	12,617.76	48,447.41	20,404.75	64,087.66 (64,067.71-64,210.55)	12,671.13 (12,667.19-12,695.43)	48,628.56 (48,614.00-48,708.73)	20,481.05 (20,474.92-20,514.82)
Total	18,683.62 (15,045.19-25,109.86)	422.17 (358.72-528.22)	18,597.96 (15,203.26-25,118.34)	519.85(450.02-720.18)	2,212,196.23	82,848.93	3,196,307.63	143,089.18	2,230,879.86 (2,227,241.41-2,237,306.08)	83,271.09 (83,207.64-83,431.17)	3,214,905.59 (3,211,510.90-3,221,425.98)	143,609.04 (143,539.20-143,809.35)

*Estimated mean (95% Uncertainty Interval)

APÊNDICE B – Material suplementar do manuscrito The effectiveness of COVID-19 vaccines against severe cases and deaths in Brazil from 2021 to 2022: a registry-based study

Supplementary material for

The effectiveness of COVID-19 vaccines against severe cases and deaths in Brazil from 2021 to 2022: a registry-based study

TABLE OF CONTENTS

Table S1. STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	STROBE items	The location where the items are reported
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Abstract
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Background, 1st and 2nd paragraphs
Objectives	3	State specific objectives, including any prespecified hypotheses	Background, last paragraph
Methods			
Study design	4	Present key elements of study design early in the paper	Methods, study design, population and data source sections
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Methods, study design, population and data source sections and Supplementary material
Participants	6	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Methods, study design, population and data source, vaccination status definition, outcomes, and variant dominance sections

Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Methods, population and data source, vaccination status definition, outcomes, and variant dominance sections
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Methods, population and data source section and Supplementary material
Bias	9	Describe any efforts to address potential sources of bias	Methods, statistical modelling and analysis section and Supplementary material
Study size	10	Explain how the study size was arrived at	STROBE flowchart (and Supplementary material Figure SX)
Quantitative Variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Methods, population and data source, vaccination status definition, outcomes, and variant dominance sections
Statistical Methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	Methods, statistical modelling and analysis section and Supplementary material
Results			

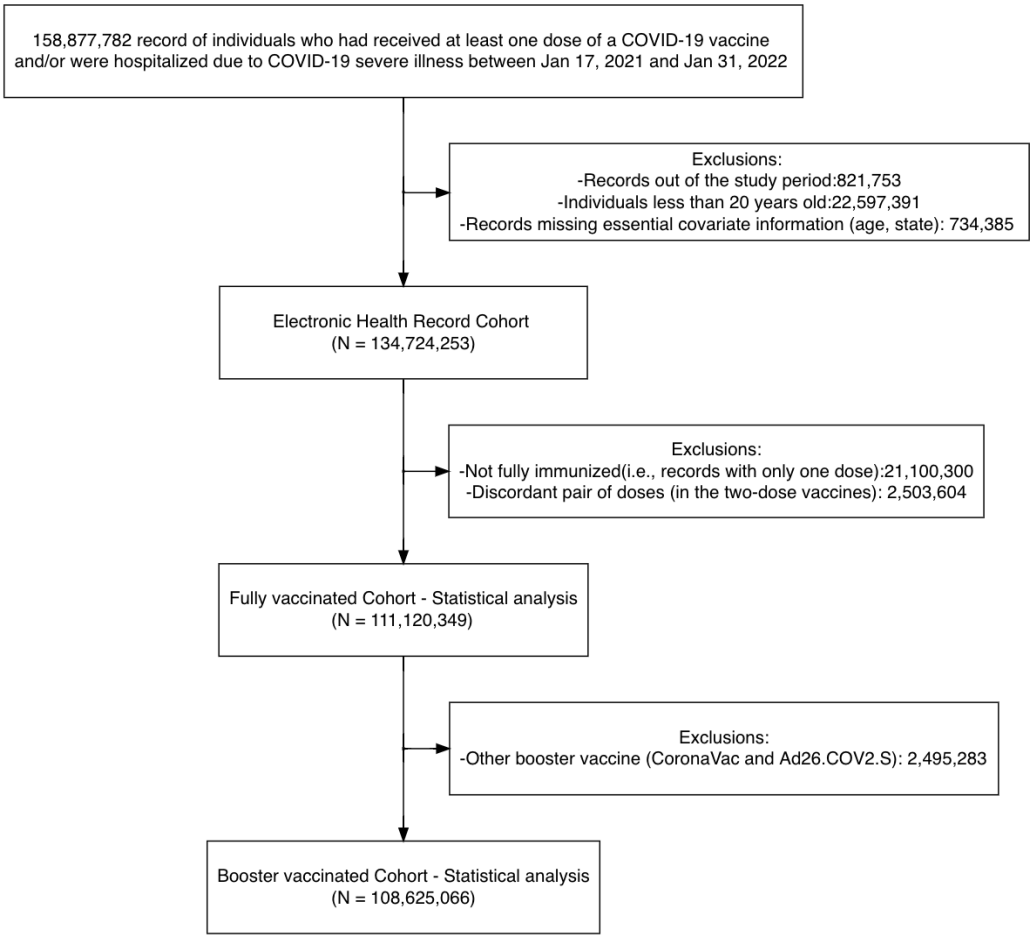
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	Tables 1 and 2 and STROBE flowchart (and Supplementary material Figure SX)
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	Results, Tables 1 and 2 and STROBE flowchart (and Supplementary material Figure SX)
Outcome data	15*	Report numbers of outcome events or summary measures over time	Results, Tables 1 and 2 and STROBE flowchart (and Supplementary material Figure SX) and Supplementary material
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Results, Absolute and relative vaccine effectiveness for severe disease, Vaccine effectiveness against death, Vaccine effectiveness in the periods of dominance of the omicron variant sections andSupplementary material
Discussion			

Key results	18	Summarise key results with reference to study objectives	Discussion, 1st and 2nd paragraphs
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Discussion, 3rd and 4th paragraphs
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Discussion, 3rd and 4th paragraphs
Generalisability	21	Discuss the generalisability (external validity) of the study results	Discussion, 3rd and 4th paragraphs
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Acknowledgements

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Figure S1. STROBE Flow diagram of the study population from surveillance databases



Methodological details about the data linkage of the Brazilian surveillance databases

Records were linked sequentially by the Individual Taxpayer Registration (*Cadastro de Pessoa Física - CPF*) and the combination of full name and mother's name. The remaining records were then probabilistically linked by a concatenated variable including the full name and mother's name using a blocking strategy, which used a variable given by the concatenated string including the code of the municipality of residence, age, gender, the two first letters of the individual's name, and the mother's name. This variable allowed efficiency and validation of the probabilistic linking algorithm. Records with a Levenshtein distance of 4 or less were considered a match. This threshold was chosen after a validation step. The linkage was performed by the Brazilian Ministry of Health, which provided the resulting dataset linked and anonymised to the researchers involved in this study. Authors not affiliated with the Ministry of Health did not have access to nominal data from the immunisation program at any time.

Figure S2: Weekly vaccination rollout by age and vaccine. (A) First dose rollout. (B) Second dose rollout. (C) Booster dose rollout. Each line corresponds to an age group.

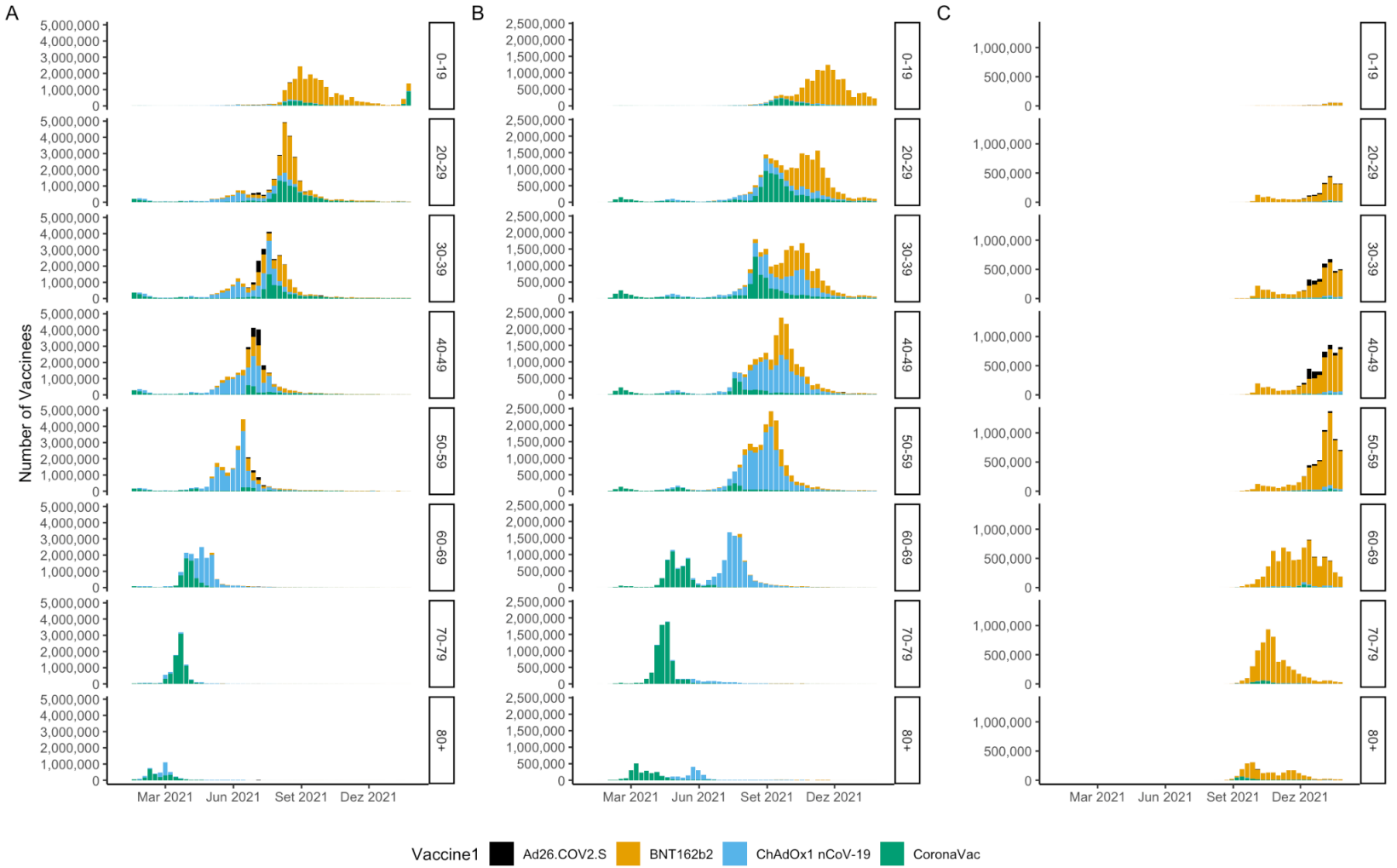


Figure S3. Weekly incidence of severe COVID-19 cases and deaths by age group. (A) All confirmed severe COVID-19 cases. (B) Deaths due to COVID-19.

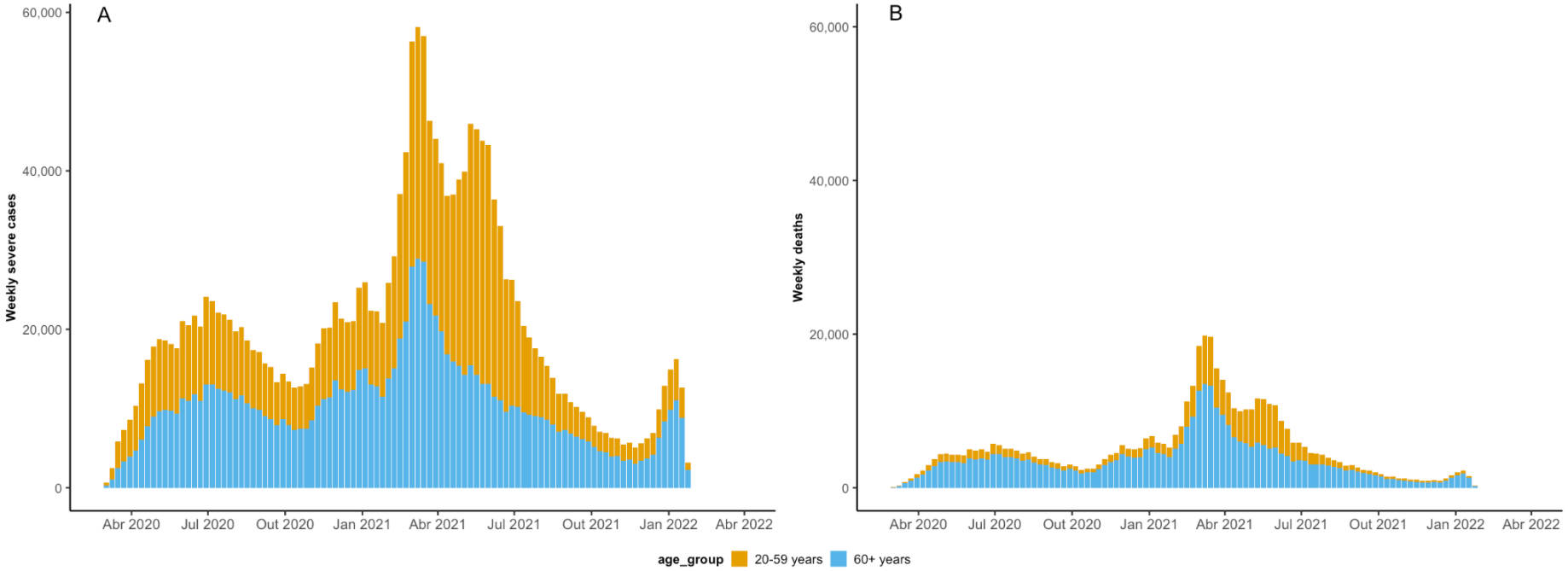


Figure S4: Weekly dominance of variants over time in Brazil, stratified by state

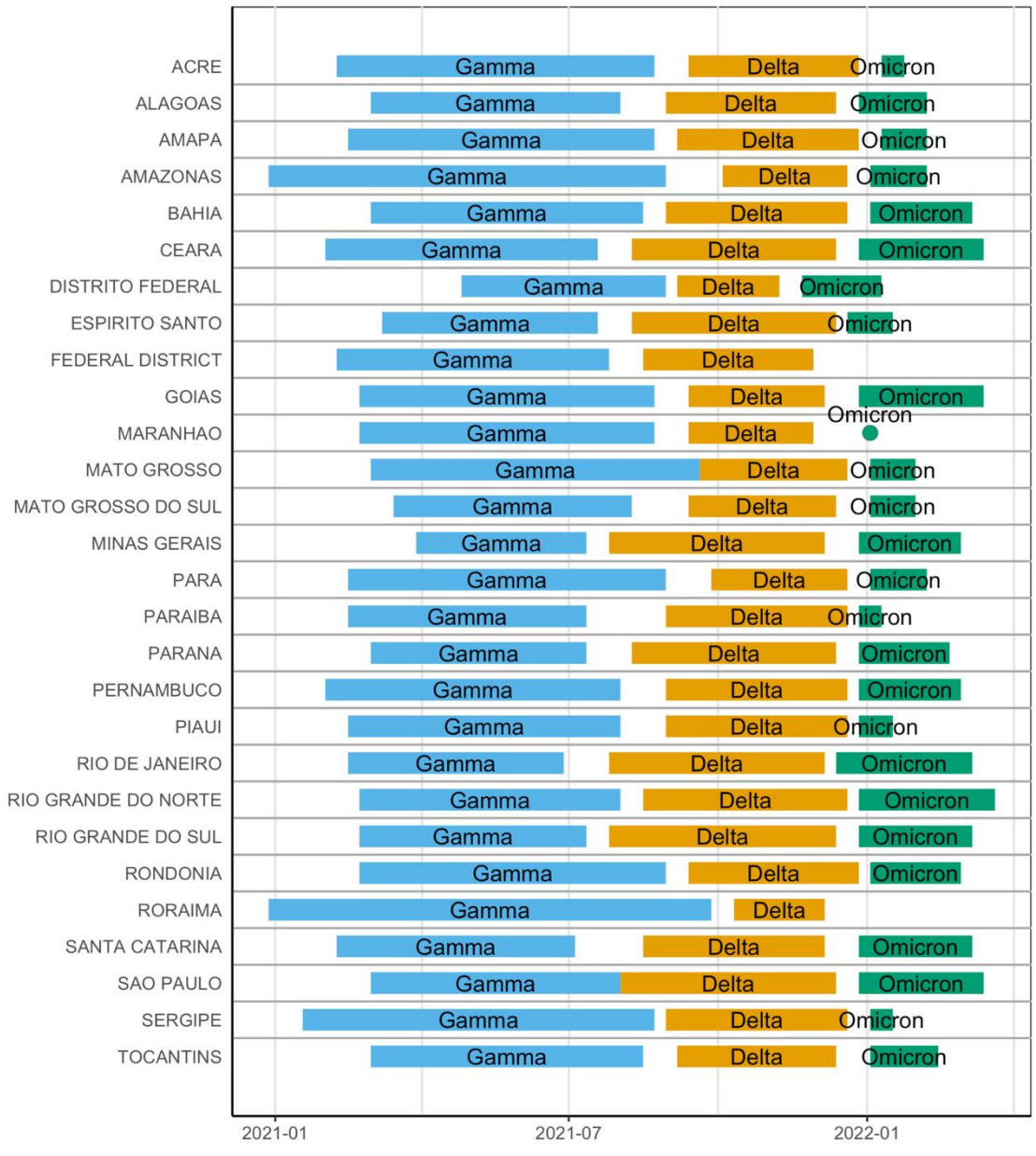


Figure S5. Absolute effectiveness of the booster dose of vaccines against COVID-19 severe cases and deaths for age groups by length of the time since the booster dose. (A) Effectiveness for the vaccines against COVID-19 severe cases compared to unvaccinated. (B) Effectiveness for the vaccines against deaths due to COVID-19. Each line correspond to a age group and each column correspond to the primary scheme of the vaccine.

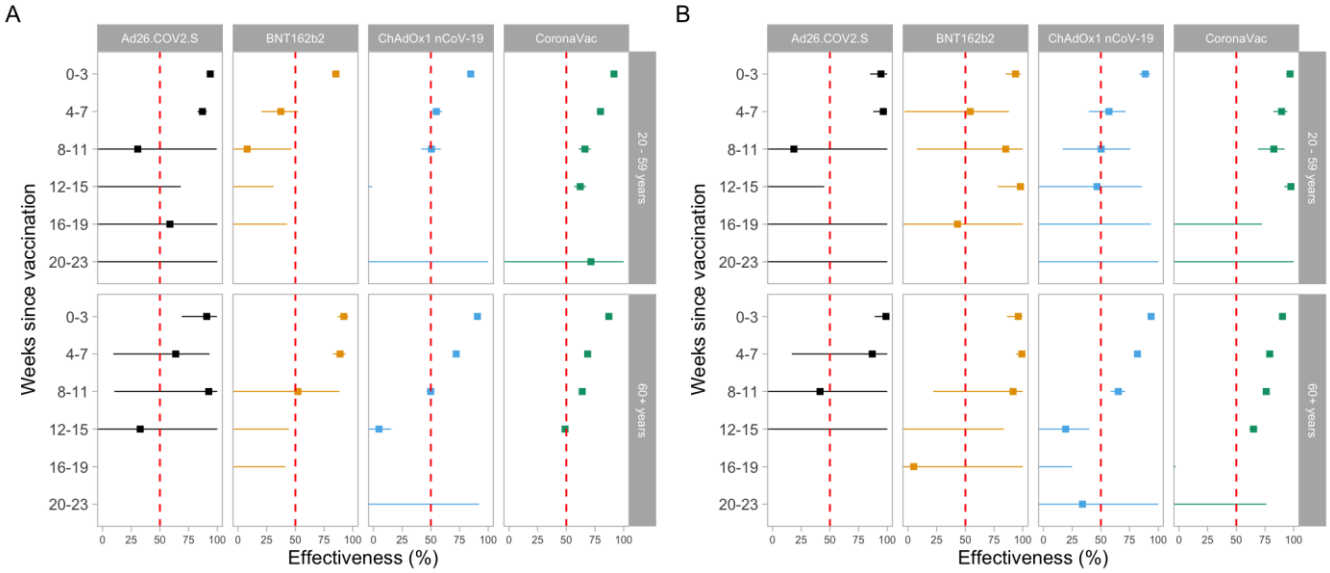


Figure S6. Estimates of vaccine effectiveness against severe disease after completing the vaccine schedule and booster according to the primary vaccine schedule for age groups by length of the time since vaccination in periods of dominance of the Delta variant. (A) Effectiveness of the ChAdOx1 nCoV-19 vaccine against severe COVID-19. (B) Effectiveness of the CoronaVac vaccine against severe COVID-19. (C) Effectiveness of the BNT162b2 vaccine against severe COVID-19. (D) Effectiveness of the Ad26.COV2.S vaccine against severe COVID-19. Panel lines corresponds to age groups and columns correspond to the vaccine dose.

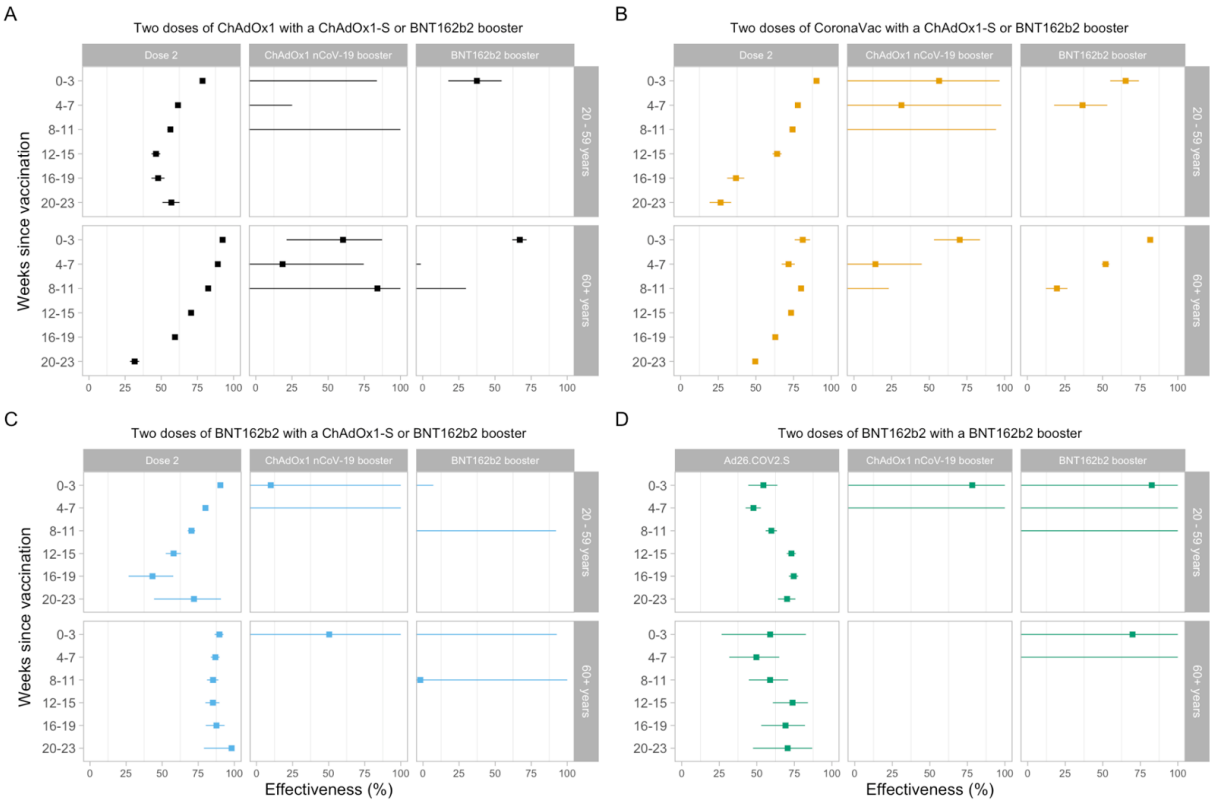
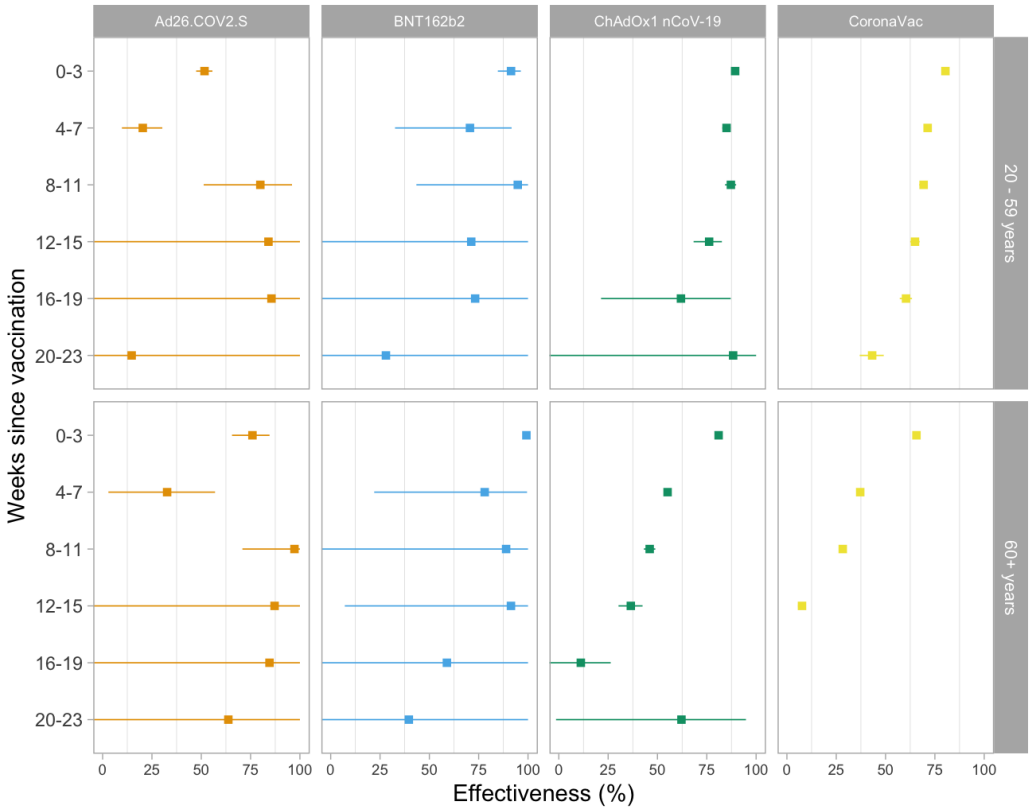


Figure S7. Estimates of vaccine effectiveness of the primary course of vaccination against severe disease after completing the vaccine schedule for age groups by length of the time since vaccination in periods of dominance of the gamma variant. Panel lines correspond to age groups and columns correspond to the primary course of vaccination.



APÊNDICE C – Material suplementar do manuscrito Estimated COVID-19 severe cases and deaths averted in the first year of the vaccination campaign in Brazil: A retrospective observational study.

Supplementary Material for

Estimated COVID-19 severe cases and deaths averted in the first year of the vaccination campaign in Brazil: A retrospective observational study

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BRAZILIAN MINISTRY OF HEALTH DEFINITIONS

DEFINITION 1: SEVERE ACUTE RESPIRATORY INFECTION (SARI)

Individual with flu-like illness: dyspnea/respiratory distress OR chest pain OR O2 saturation less than 95% OR cyanosis of the lips or face.

DEFINITION 2: CONFIRMED CASE OF COVID-19

By clinical criteria

Case of flu-like illness or SARI associated with acute anosmia (olfactory dysfunction) OR ageusia with no other previous cause.

By clinical-epidemiological criteria

Case of flu-like illness or SARI with a history of close contact or home contact, in the 14 days prior to the appearance of signs and symptoms with a confirmed case for COVID-19.

By clinical criteria-image

Case of flu-like illness or SARI or death by SARI that could not be confirmed by laboratory criteria AND that presents at least one of the following tomographic changes:

- Peripheral GROUND GLASS OPACITY, bilateral, with or without consolidation or visible intralobular lines (“paving”); OR
- Multifocal GROUND GLASS OPACITY of rounded morphology with or without consolidation or visible intralobular lines (“paving”); OR
- REVERSE HALO SIGN or other organizing pneumonia findings.

By laboratory criteria in individuals not vaccinated against covid-19

Case of flu-like illness or SARI with test of:

MOLECULAR BIOLOGY: DETECTABLE result for SARS-CoV-2 performed by the following methods:

- Real-time RT-PCR.
- RT-LAMP.

Immunological: REAGENT result for IgM, IgA and/or IgG performed by the following methods:

- Enzyme immunoassay (ELISA).
- Immunochromatography (rapid test) for antibody detection.
- Electrochemiluminescence Immunoassay (ECLIA).
- Chemiluminescence Immunoassay (CLIA).

Antigen screening: REAGENT result for SARS-CoV-2 by Immunochromatography method for antigen detection.

References

Ministério da Saúde. Guia de vigilância epidemiológica: emergência de saúde pública de importância nacional pela doença pelo coronavírus 2019. Brasília : Ministério da Saúde, 2022. Available at https://www.gov.br/saude/pt-br/coronavirus/publicacoes-tecnicas/guias-e-planos/guia-de-vigilancia-epidemiologica-covid-19.

METHODOLOGICAL DETAILS ON THE DATA LINKAGE PERFORMED BY THE BRAZILIAN MINISTRY OF HEALTH

The records were linked sequentially by the Individual Taxpayer Registration (*Certidão de Pessoa Física* - CPF) and the combination of the individual's full name and their full mother's name. The remaining records were then linked probabilistically by a concatenated variable including the full name and full mother's name using a blocking strategy, which used a variable given by the concatenated string including the code of the municipality of residence, the individual age, gender, the first two letters of the individual's name, and the mother's name. This variable allowed efficiency and validation of the probabilistic linking algorithm. Records with a Levenshtein distance of 4 or less were considered a match. This threshold was chosen after a validation step. The linkage was performed by the Ministry of Health itself, which provided the resulting dataset already linked and anonymized to the researchers involved in this study in accordance with the Brazilian Personal Data Protection General Law (LGPD). Authors not affiliated with the Brazilian Ministry of Health did not have access to nominal data from the immunization program at any time.

FLOW DIAGRAM DEPICTING THE STEPS TO REACH THE ELIGIBLE STUDY POPULATION.