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POLIANA DO CARMO PIMENTA

EVENTOS SUPOSTAMENTE ATRIBUÍVEIS À VACINAÇÃO OU IMUNIZAÇÃO CONTRA A COVID-19

Alfenas/MG

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POLIANA DO CARMO PIMENTA

EVENTOS SUPOSTAMENTE ATRIBUÍVEIS À VACINAÇÃO OU IMUNIZAÇÃO CONTRA A COVID-19

Dissertação apresentada como parte dos requisitos para obtenção do título de Mestre em Ciências Biológicas pela Universidade Federal de Alfenas. Área de concentração: Biologia Celular, Molecular e Estrutural das doenças agudas e crônicas.

Orientadora: Profª. Drª. Livia Máris Ribeiro Paranaiba Dias.
Coorientador: Prof. Dr. Murilo César do Nascimento.

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POLIANA DO CARMO PIMENTA

EVENTOS SUPOSTAMENTE ATRIBUÍVEIS À VACINAÇÃO OU IMUNIZAÇÃO CONTRA A COVID-19

O Presidente da banca examinadora abaixo assina a aprovação da Dissertação apresentada como parte dos requisitos para a obtenção do título de Mestre em Ciências Biológicas pela Universidade Federal de Alfenas. Área de concentração: Biologia Celular, Molecular e Estrutural das doenças agudas e crônicas.

Aprovada em: 18 de agosto de 2023.

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Dedico este trabalho à população geral, para que nunca se esqueçam da indispensabilidade das vacinas.

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A gratidão é a virtude mais bela, que nos torna humildes e iguais a todos seres humanos. Com toda felicidade deixo meus agradecimentos finais.

Aos meus queridos ICs e amigos, cada um de vocês por mérito próprio, garra e brilhantismo se juntaram a mim nessa busca pelo conhecimento. Obrigada. Vocês me sustentaram a determinação nos momentos de desafio, foram meus pilares e força motriz. À medida que nos dedicávamos a este estudo, testemunhei a evolução de futuros médicos que trilharão seus caminhos deixando um impacto positivo no mundo.

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“Os flagelos, na verdade, são uma coisa comum, mas é difícil acreditar neles quando se abatem sobre nós. Houve no mundo igual número de pestes e de guerras. E contudo, as pestes, assim como as guerras, encontram sempre as pessoas igualmente desprevenidas”.

(A PESTE, Albert Camus, 1947, p. 24)

RESUMO

Introdução: Diante da crise sanitária desencadeada pelo coronavirus SARS-CoV-2, vacinas contra a COVID-19 foram desenvolvidas e se mostraram eficazes na prevenção da morbimortalidade pela doença, porém, ainda é necessário avançar na quantificação e caracterização dos Eventos Supostamente Atribuíveis à Vacinação ou Imunização (ESAVI) contra a COVID-19. **Objetivo:** Os objetivos deste estudo foram analisar a incidência de ESAVI contra a COVID-19 no Brasil e analisar o risco de Eventos Adversos Pós Vacinação (EAPV) contra a COVID-19 entre países desenvolvidos e países em desenvolvimento. **Métodos:** Esta dissertação contemplou dois delineamentos metodológicos, um estudo transversal analítico para o objetivo um e uma revisão sistemática com metanálise para o segundo objetivo. Para a abordagem observacional foram utilizados dados secundários obtidos do Sistema e-SUS Notifica e do Sistema Vacivida. A investigação abrangeu variáveis demográficas, clínicas e epidemiológicas presentes nos registros de ESAVI notificados na população brasileira no ano de 2021. A incidência acumulada de eventos e a proporção de sinais e sintomas (dentre as notificações encerradas) por 100.000 doses administradas foi calculada como medida de interesse. Quanto à revisão sistemática da literatura com metanálise, após definição criteriosa dos critérios de elegibilidade, elaboração e registro do protocolo de revisão na base PROSPERO, houve busca de artigos nas bases EMBASE, PubMed/MEDLINE e SCOPUS. A fase um e a fase dois contaram com dois revisores independentes e um terceiro revisor para dirimir as divergências. Durante a etapa de verificação do risco de viés, um quarto revisor foi incluído para auxiliar no consenso. Os dados extraídos foram agrupados, tendo a heterogeneidade e a sensibilidade entre os estudos avaliadas. As estimativas de efeito foram expressas como riscos relativos, com intervalos de confiança de 95%, com auxílio do software RevMan versão 5.4. **Resultados:** Com o estudo transversal foi possível identificar baixa incidência acumulada de ESAVI/COVID-19 no Brasil (0,038%), com predomínio de eventos não graves, gênero feminino, pessoas brancas, idade de 30 a 39 anos, evolução para cura sem sequela, regiões Sul e Sudeste do Brasil com maior incidência de casos. Os sintomas mais comuns foram dor de cabeça e febre, e o Sistema Órgão Classe mais comum foi o geral. Na revisão sistemática, mundialmente, os sintomas mais comuns foram dor, dor de cabeça e mialgia. Foi possível identificar que as pessoas de países desenvolvidos apresentaram maior risco relativo de desenvolver um EAPV/COVID-19, em comparação com os indivíduos de países em desenvolvimento, sem justificativa encontrada na literatura. **Conclusão:** Verifica-se que, em 2021, houve distribuição heterogênea dos ESAVI/COVID-19 no Brasil, caracterizada por baixa incidência e não gravidade dos casos. A subnotificação no Brasil e em outros países do mundo é um problema a ser enfrentado no contexto da imunização segura. Mundialmente, o padrão de baixa gravidade dos EAPV/COVID-19 permanece, contudo, os países desenvolvidos apresentaram maior risco relativo destes eventos, evidência não explicada até o momento na literatura. Apesar do rápido desenvolvimento, uso emergencial e posterior aplicação de imunizações em massa das vacinas contra a COVID-19, os resultados do estudo corroboram a viabilidade e relevância das vacinas, assim como a baixa gravidade da maioria dos eventos adversos pós-vacinação contra a COVID-19, tantos nos países desenvolvidos quanto nos países em desenvolvimento.

Palavras-chave: Eventos adversos; COVID-19, imunização.

ABSTRACT

Introduction: With the health crisis triggered by the new coronavirus SARS-CoV-2, vaccines against COVID-19 were developed and proved to be effective in terms of morbidity and mortality due to the disease, however, it is still necessary to advance in the quantification and characterization of Events Supposedly Attributable to Vaccination or Immunization (ESAVI) against COVID-19. **Objective**: The objectives of this study were to analyze the incidence of ESAVI against COVID-19 in Brazil and to analyze the risk of Adverse Events Following Immunization (AEFI) against COVID-19 between developed and developing countries. **Methods**: This dissertation included two methodological designs, an analytical cross-sectional study for objective one and a systematic review with meta-analysis for the second objective. For the observational approach, secondary data obtained from the e-SUS Notifica System and the Vacivida System were used. The investigation covered demographic, clinical and epidemiological variables present in the records of ESAVI reported in the Brazilian population in the year 2021. The cumulative incidence of events and the proportion of signs and symptoms (among closed reports) per 100,000 administered doses was calculated as the measure of interest. As for the systematic review of the literature with meta-analysis, after careful definition of the eligibility criteria, elaboration and registration of the review protocol in the Próspero database, there was a search for articles in the EMBASE, PubMed/MEDLINE and SCOPUS databases. Phases one and two had two independent reviewers and a third reviewer to resolve disagreements. During the risk of bias check step, a fourth reviewer was included to assist in consensus. The extracted data were pooled, with heterogeneity and sensitivity among studies assessed. Effect estimates were expressed as relative risks, with 95% confidence intervals, using RevMan software version 5.4. **Results:** With a cross-sectional study, it was possible to identify a low accumulated incidence of AEFI/COVID-19 in Brazil (0.038%), with a predominance of non-severe, female gender, white people, age 30 to 39 years, evolution to cure without sequelae and the South and Southeast regions of the Brazil. The most common symptoms were headache and fever, and the most common System Organ Class was general**.** In the systematic review, the most common symptoms worldwide were pain, headache and myalgia. it was possible to identify that developed countries have a higher relative risk of developing an AEFI/COVID-19 compared to developing countries, with no justification found in the literature. **Conclusion**: It appears that in 2021 there was a heterogeneous distribution of AEFI/COVID-19 in Brazil, characterized by low incidence and non-seriousness of cases**.** Underreporting in Brazil and in other countries around the world is a problem to be faced in the context of safe immunization. Worldwide, the low gravity standard of AEFI/COVID-19 persists; However, developed countries have exhibited a higher relative risk of these events, which remains unexplained in the literature to date. Despite the rapid development, emergency use and subsequent application of mass immunizations of vaccines against COVID-19, the results of the study corroborate the viability and relevance of vaccines, as well as the low severity of most adverse events post-vaccination against COVID-19, so many in the developed countries as well as in developing countries.

Keywords: Adverse events; COVID-19, immunization.

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LISTA DE ABREVIATURAS E SIGLAS

AE	Adverse Events
ESAVI	Eventos Supostamente Atribuíveis à Vacinação ou Imunização
EA	Eventos Adversos
WHO	World Health Organization
AEFI	Adverse Event Following Immunization
IE	Immunization Error
IR	Incidence Rate
mRNA	Messenger RNA
CDC	Centers for Disease Control and Prevention
COVID-19	Coronavirus disease 2019
CAPES	Coordenação de Aperfeiçoamento de Pessoal de Nível Superior
US	United States
SDG	Sustainable Development Goals
UN	United Nations
RNA	Ácido ribonucleico
DNA	Ácido desoxirribonucleico
FAPEMIG	Fundação de Amparo à Pesquisa do Estado de Minas Gerais
CAPES	Coordenação de Aperfeiçoamento de Pessoal de Nível Superior
IBGE	Instituto Brasileiro de Geografia e Estatística
UNIFAL-MG	Universidade Federal de Alfenas-MG
OMS	Organização Mundial da Saúde
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
SOC	System, Organ, Class
PT	Preferential Term
MedDra	Medical Dictionary for Regulatory Activities
RR	Risk ratio

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1 INTRODUÇÃO GERAL

No final de 2019, em Wuhan (China) foi detectado o *severe acute respiratory syndrome coronavirus 2* (SARS-CoV-2) (CORONAVIRIDAE STUDY GROUP OF THE INTERNATIONAL COMMITTEE ON TAXONOMY OF VIRUSES, 2020; INTERNATIONAL COMMITTEE ON TAXONOMY OF VIRUSES, 2023) causador da *Coronavirus Disease 2019* (COVID-19) (YUAN *et al.*, 2020). Rapidamente, o vírus da família *Coronaviridae* espalhou-se em todo o mundo e deu início a um estado de emergência global (YUAN *et al*., 2020). Em 11 de março de 2020 foi declarada pandemia pela Organização Mundial de Saúde (OMS).

Apesar das medidas de prevenção e ineficácia dos recursos terapêuticos existentes, a imunização da população geral mundial foi considerada a melhor intervenção em custo-benefício e eficácia (HARDT *et al.*, 2013). De acordo com dados da OMS (2022), até 08 de fevereiro de 2022, já havia 33 vacinas contra COVID-19 aprovadas, algumas em uso emergencial já aprovado (CHEN *et al.*, 2021a; MEO *et al*., 2021a; PETOUSIS-HARRIS, 2020; TOBAIQY; ELKOUT; MACLURE, 2021).

As tecnologias vacinais das vacinas utilizadas no Brasil são vetor viral, vírus atenuados, ácido nucleico e proteínas (TAVILANI *et al*., 2021), mas no mundo todo, haviam tecnologias aprovadas como, peptídeo de antígeno, proteína spike conjugada com meningococo tipo B, Partícula semelhante a vírus baseada em plantas [VLP (*Virus-like particles*)] recombinante, Proteína spike derivada de células CHO (*Chinese Hamster Ovary),* entre outras (WORLD HEALTH ORGANIZATION, 2022).

No mundo, a primeira vacina contra COVID-19 aplicada foi em 13 de dezembro, no Reino Unido (MATHIEU *et al.*, 2021). Depois disso, vários países como Estados Unidos da América, Eslovênia, Estônia, Suécia, Finlândia, entre outros iniciaram a aplicação ainda em 2020 (CNN BRASIL, 2020; GARGANO *et al.*, 2021). A vacinação no Brasil se iniciou em janeiro de 2021, com o uso emergencial, autorizado pela Agência Nacional de Vigilância Sanitária (ANVISA) da Coronavac/Sinovac, Oxford/Astrazeneca e da Pfizer/BioNTech (FUNDAÇÃO OSWALDO CRUZ - FIOCRUZ).

O processo de desenvolvimento acelerado das vacinas contra COVID-19 pode levantar importantes preocupações em relação aos seus potenciais problemas de efetividade, segurança e confiabilidade e, portanto, aumentar a hesitação vacinal entre as pessoas, o que ocasiona relevantes preocupações dos gestores e pesquisadores

mundiais (CHEN *et al*., 2021a). Desde o sequenciamento do genoma do Sars-CoV-2 até o desenvolvimento de algumas vacinas passou tempo inferior a um ano, tornando fundamental a realização de estudos sobre a farmacovigilância dos imunobiológicos.

Entende-se a farmacovigilância como a análise dos eventos adversos e reações, da segurança, além da melhor compreensão do respectivo fármaco por um conjunto de procedimentos. Até o momento, as vacinas atuais têm demonstrado boa eficácia com redução da morbidade e da mortalidade e, em geral, têm sido bem toleradas. Embora relata-se baixo risco de eventos adversos, alguns deles são motivo de preocupação como a miocardite, a anafilaxia (reações alérgicas) e eventos trombóticos com desfechos fatais (BANERJI *et al.*, 2021; RUTKOWSKI *et al*., 2021).

Considerando que a incidência e os fatores associados aos Eventos Adversos relacionados aos imunizantes contra COVID-19 ainda são incertos na população brasileira e mundial, e que há pouco conteúdo publicado na literatura atual, torna-se necessário e fundamental os presentes estudos. Portanto, este trabalho teve como objetivos analisar a incidência acumulada de Eventos Supostamente Atribuíveis à Vacinação ou Imunização (ESAVI)[1] contra a COVID-19 no Brasil e analisar o risco de ESAVI/COVID-19 entre países desenvolvidos e países em desenvolvimento.

[1] Após a conclusão do primeiro artigo (estudo transversal) e durante a elaboração do protocolo para a revisão sistemática (segundo artigo), o termo "Evento adverso pós-vacinação" (EAPV) foi atualizado para "Evento supostamente atribuível à vacinação ou imunização" (ESAVI). Por esse motivo, ambas as expressões foram utilizadas nesta dissertação.

2 DESENVOLVIMENTO

2.1 ARTIGO 1 - EVENTS SUPPOSEDLY ATTRIBUTABLE TO VACCINATION OR IMMUNIZATION OF COVID-19 VACCINES IN BRAZIL: A CROSS-SECTIONAL STUDY

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Events Supposedly Attributable to Vaccination or Immunization of COVID-19 vaccines in Brazil: a cross-sectional study

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Running title: Incidence of adverse reactions after COVID-19 vaccination in Brazil.

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Abstract

Vaccines against COVID-19 reduce morbimortality from this disease and may cause Events Supposedly Attributable to Vaccination or Immunization (ESAVI). The objective was to analyze the incidence of ESAVI against COVID-19 in Brazil. This is a cross-sectional study with data from ESAVI notifications contained in the *e-SUS Notifica* and *Vacivida* System, referring to the year 2021. The ESAVI incidences (concluded notifications) considered the number of people with at least 1 reported Adverse Event and the number of signs and symptoms (concluded notifications) for 100,000 applied doses. Descriptive statistics (simple and relative frequency measures) were used. There were 136,013 notifications of ESAVI with closed investigation. ESAVI were more frequent in white people, female, 30 to 39 years old, from the south of the country. The rates were 38.31 AEFI and 92.31 signs and symptoms per 100,000 administered doses. The most frequent findings were headache, fever, myalgia, general disorders and administration site changes, nervous system disorders, musculoskeletal and connective tissue disorders. AstraZeneca vaccine was the most registered. The causality of ESAVI “related to the product, according to the literature” predominated. Most events were non-severe, with unknown evolution, followed by cure without sequelae. It is therefore concluded that the ESAVI COVID-19 were heterogeneously distributed throughout the national territory, with low incidence and a predominant profile of non-severe cases. The evident underreporting in Brazil and in other countries is a problem to be faced in favor of strengthening surveillance systems in the context of safe immunization.

Keywords: Side effects; Events Supposedly Attributable to Vaccination or Immunization; COVID-19; immunization; viral disease; Brazil.

Highlights

- There were 109,424 cases of ESAVI COVID-19 with investigation closed in Brazil in 2021.
- People of female gender, white, 30-39 years old, from South were the most affected.
- The incidences were 38.31 cases and 92.31 signs and symptoms per 100,000 doses.
- Headache, fever, general disorder and at the site of injection were predominant.
- Non-severe AEFI prevailed, with unknown evolution, followed by cure without sequelae.

Introduction

When infections with the new Coronavirus (SARS-CoV-2) began in December 2019, the world experienced important changes caused by the COVID-19 disease[1,2]. On March 11, 2020, the World Health Organization declared a pandemic. By January 2023, according to them, there are already more than 753 million confirmed cases and 6.8 million deaths worldwide, a lethality rate of 0.9%[3–5]. According to the Brazilian Ministry of Health, until January 2023, approximately 36 million cases of COVID-19 had already been confirmed, and deaths reached approximately 697 thousand, and 1.9% lethality rate[6].

Collective immunization is considered the most cost-effective and effective intervention to control and end the pandemic[7]. It is noteworthy that with the rapid transmissibility of the disease in the world, scientists were driven to quickly develop effective and safe vaccines to avoid a global health crisis [8]. According to World Health Organization in January 26, 2023 had 176 vaccines in clinical development and 199 vaccines in pre-clinical development [9]. These vaccines fall into four groups using many technologies: (1) viral vector vaccines, (2) whole virus vaccines, (3) nucleic acid vaccines, and (4) protein-based vaccines [10,11]. The vaccination in Brazil started in January 2021, with emergency use, authorized by the National Health Surveillance Agency. The immunizers administered were Coronavac/Sinovac, Oxford/Astrazeneca, Pfizer/BioNTech e Johnson & Johnson/Janssen. Along with collective vaccination, adverse events related to vaccination also occurred, defined

as any unfavorable medical occurrence after vaccination, and need not be causally related to the use of immunization[12]. The accelerated development process of COVID-19 vaccines may raise important concerns regarding their potential effectiveness, safety and reliability issues and, therefore, increase vaccine hesitancy among people, which causes relevant concerns for managers and researchers worldwide [10]. From the sequencing of the virus to the development of some vaccines, less than a year has passed, thus, it is necessary to carry out immunological studies, analysis of adverse events and reactions, safety, in addition to a better knowledge of the medicine through a set of procedures [11,13]. Current vaccines have shown good efficacy with reduced morbidity and mortality and, in general, have been well tolerated[3,14,15].

Previous studies have already noted local effects, such as pain at the site of administration, redness, swelling, and also systemic effects, fever, myalgia, malaise, headache and fatigue[3,7,16]. Although a low risk of adverse events is reported, some of them are of concern such as myocarditis, anaphylaxis (allergic reactions) and thrombotic events with fatal outcomes[3,7,14,17,18].

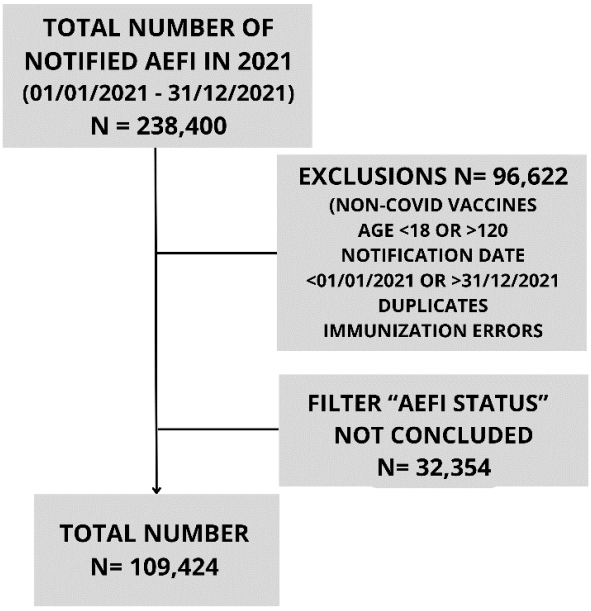
Considering that the incidence and characteristics of adverse events in Brazil and in the world are still little explored in the literature, it is necessary to advance in the analysis of these reactions to better understand them, in the face of public health. Efforts in this direction are relevant both from an academic point of view and in the context of assertive epidemiological surveillance actions, which are so necessary to guarantee the safety and reliability of vaccines in their post-marketing phase [19]. Therefore, the objective of this study was to analyze the incidence of Post-Vaccination Adverse Events against COVID-19 in Brazil.

Methodology

This is a cross-sectional study of reported cases of the COVID-19 Events Supposedly Attributable to Vaccination or Immunization extracted from the *e-SUS Notifica* database (a Brazilian surveillance system for health professionals to report ESAVI occurring up to 30 days after vaccination) and the *Vacivida* database (a surveillance system in the state of São Paulo for health professionals to notify) covering the entire national territory during the period from January 1 to December 31, 2021.

The database initially used contained 238,400 notifications of ESAVI due to COVID-19 and other diseases. For the analyses, the records of cases closed in the established period (109,424 notifications) were analyzed, according to the flowchart (Figure 1).

Figure 1. Flowchart for selection of ESAVI COVID-19 records in Brazil in 2021 from the "*e-SUS Notifica*" and "*Vacivida"* System.



The definition of Events Supposedly Attributable to Vaccination or Immunization (ESAVI) was adopted as any unfavorable manifestation after immunization, not necessarily having a causal relationship with the use of the vaccine. Every patient who registers an ESAVI must be followed up until the case is completely resolved, which is case it is called concluded[12,20]. Exclusion criteria were: 1. notifications in which the immunobiological was not against Covid-19; 2. notification date before January 1, 2021; 3. Patient age greater than 120 years or number less than 18, 4. Immunization Errors, and 5. notification date later than December 31, 2021.

The variables analyzed were sex; age; patient's region of residence; type of notification (Adverse Event - AE or immunization error - IE), the applied immunobiological (AstraZeneca, Coronavac, Janssen e Pfizer); the ESAVI type (not serious, serious or ignored); the evolution of the case (cure without sequelae, cure with sequelae, in follow-up, death, loss of follow-up and ignored) and the classification of the causality of the Adverse Event (A1. related to the product

according to literature, A2. related to product quality, A3. immunization errors, A4. immunization-related anxiety or stress, B1. consistent temporal reaction, but without evidence in the literature, B2. conflicting data, C. inconsistent, D. Unclassifiable and ignored).

The incidence rate (IR) was calculated for 100,000 administered doses, for the AEFI, using the following formulas:

$$\textbf{IR ESAVI} = \frac{\underline{\textit{Number of notifications (people with at least 1 reported Adverse Event) concluded}}}{\textit{Total of applied doses}} \times 100{,}000$$

And for the post-vaccination signs and symptoms, using the following formula:

$$\textbf{IR post-vaccination signs and symptoms} = \frac{\underline{\textit{Number of signs and symptoms (concluded)}}}{\textit{Total of applied doses}} \times 100{,}000$$

The numerator of the first measure used the total number of ESAVI cases based on notifications of at least 1 AE related to the COVID-19 vaccine (109,424 notifications with concluded investigation/assessment) and, in the denominator, the total doses of the same set of vaccines administered in the period (355,067,041). For the second measure, the total number of post-vaccination signs and symptoms of notifications with investigation/assessment completed was used in the numerator (294,974 signs and symptoms) and, in the denominator, the total doses administered in the year of the search. As a constant, 100,000 administered/applied doses were considered [8,21,22].

The numeric codes of the adverse event classes were obtained according to the Medical Dictionary for Regulatory Activities – MedDRA. In this tool there are two concepts used: the Preferential Term (PT) - specific descriptor and the Class of Systems and System Organ Class (SOC) - general descriptor. For the data referring to the geographic base of municipalities, federative units and regions, the digital grids provided by the Brazilian Institute of Geography and Statistics were used [23]. The signs and symptoms more frequently were calculated from concluded reports

with at least one AE classified as A1 (related to the product according to literature), totaling 231,780 events.

This study may contain information bias, since it included secondary data. The authors had no control over this bias, other than assuming this characteristic as a weakness in the discussion and being cautious in the conclusions.

Descriptive statistics were used in the analysis, using simple and relative frequency measures such as percentage and incidence rates. As tools, the software R version 4.2.2 (interface RStudio version 2022.12.0+353) was used and Excel version 2013.

The study was approved by the Research Ethics Committee of the Federal University of Alfenas, under the protocol CAAE 57035922.1.0000.5142 and legal opinion 5.812.620 of 2022.

Results

Between January 1, 2021 and December 31, 2021, 355,067,041 doses of vaccine against COVID-19 were applied (Oxford-AstraZeneca, Coronavac, Johnson & Johnson/Janssen and Pfizer/BioNTech) in Brazilian territory (173,391,371 first dose, 148,254,895 second dose and 33,420,774 boosters). Based on these vaccinations, there were 109,424 ESAVI COVID-19 notifications with completed investigations across the territory (Figure 2).

Figure 2. Spatial distribution of AE notifications of COVID-19 by the five major Brazilian regions, 2021.

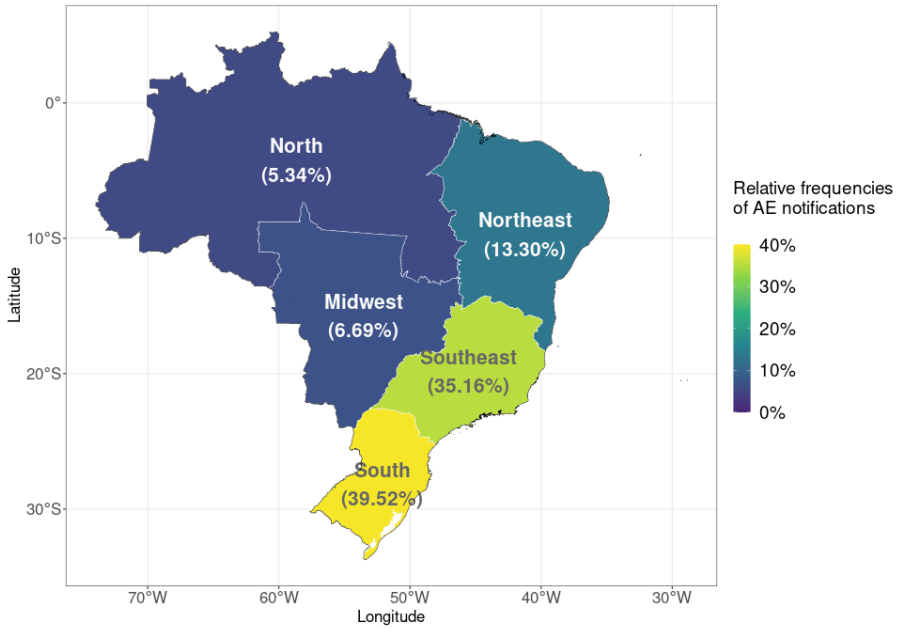


Table 1 presents the incidence rate of ESAVI and signs and symptoms.

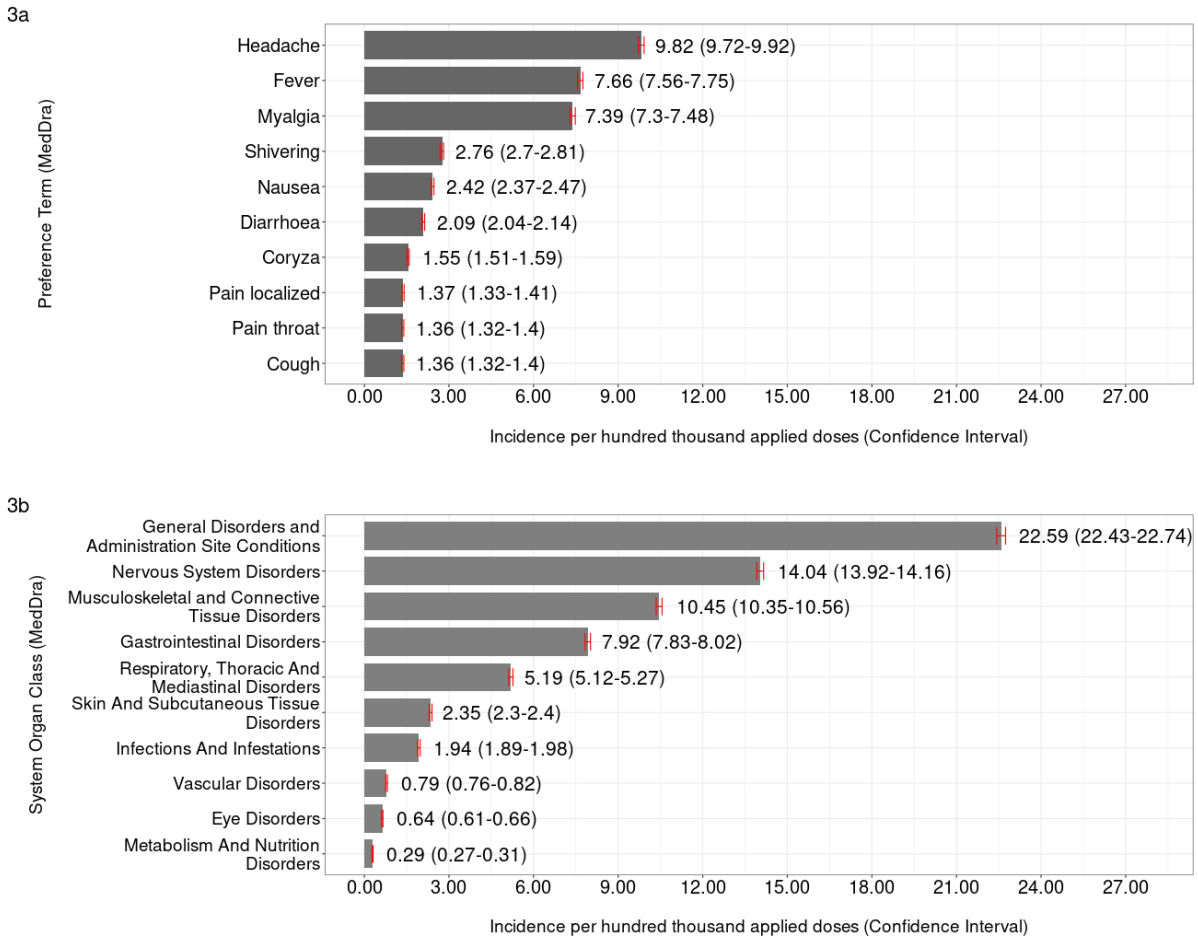
Table 1. Distribution and incidence of ESAVI by the five regions of Brazil.

Region of residence	Notifications	Total of signs and symptoms	Total number of administered doses	Incidence of notifications (CI 95%)	Incidence of signs and symptoms (CI 95%)
North	5,841	16,976	24,089,037	24.25 (23.63-24.88)	70.47 (69.42-71.54)
South	43,245	132,425	51,451,111	84.05 (83.26-84.85)	257.38 (256-258.77)
Southeast	38,469	87,090	164,839,318	23.34 (23.1-23.57)	52.83 (52.48-53.19)
Midwest	7,318	21,203	25,479,242	28.72 (28.07-29.39)	83.22 (82.1-84.35)
Northeast	14,551	37,280	89,208,333	16.31 (16.05-16.58)	41.79 (41.37-42.22)
Total	109,424	294,974	355,067,041	30.82 (30.64-31)	83.08 (82.78-83.38)

*Per hundred thousand applied doses. **Fisher's 95% C.I.
The notifications analyzed for this calculation were those with the evaluation status “concluded”.

In Figure 3, the AE are indicated by term of preference (MedDRA code) as well as the signs and symptoms related to the immunization of COVID-19, and to the SOC (MedDRA code). The three signs and symptoms most common were headache (9.82), fever (7.66) e myalgia (7.39). The SOCs most common were General disorders and administration site conditions (22.59), Nervous system disorders (14.04) and Musculoskeletal and connective tissue disorders (10.45), as shown in Figure 3.

Figure 3. Signs and symptoms incidence per 100,000 doses of COVID-19 by term of preference and SOC, MedDRA.



The vast majority of cases of AEFI reported were related with the immunizing AstraZeneca (56.79%), consecutive of Coronavac (26.35%), Pfizer (15.08%) e Janssen (1.48%). The minority of the registers, 0.30% of the AEFI did not mention the vaccine in the registry.

According to the distribution of AE incidence across the five regions of Brazil, the South region had a relatively higher incidence, and lower incidence was at Northeast, in Table 1.

Regarding the severity of the notifications, most of them were classified as not serious (95.03%) and the severe ESAVI were only 4.97%. There were a large number of notifications without information about the evaluation status of the cases, 66,22% of the notifications did not inform the outcome condition (Table 2). The concluded cases with healing outcome without sequelae were 26.28%, the cases with healing outcome with sequelae were 0.20% and the deaths, 0.80%. About the causality classification at the conclusion of the notified case, the majority, 78.70% was classified in A1. (related to the product according to literature), followed by 11.17% of C. (inconsistent).

Table 2. ESAVI notifications according to type, classification, evolution, concluding and causality by region (to be continued)

Characteristics	Total number of AE		Region of residence									
			North		South		Southeast		Midwest		Northeast	
	n	%	n	%	n	%	n	%	n	%	n	%
Classification of severity in the notification												
Serious	14630	4.97%	345	2.04%	4275	3.23%	5960	6.85%	1542	7.32%	2508	6.75%
Not serious	279870	95.03%	16577	97.96%	128092	96.77%	81035	93.15%	19520	92.68%	34646	93.25%
Total	294500	-	16922	-	132367	-	86995	-	21062	-	37154	-
Evolution												
Healing with sequelae	577	0,20%	32	0,19%	232	0,18%	194	0,22%	42	0,20%	77	0,21%
Healing without sequelae	77391	26,28%	4111	24,29%	41029	31,00%	20414	23,47%	4364	20,72%	7473	20,11%
In follow-up	16388	5,56%	1412	8,34%	5043	3,81%	6666	7,66%	2040	9,69%	1227	3,30%
Death	2364	0,80%	37	0,22%	762	0,58%	941	1,08%	170	0,81%	454	1,22%
Follow-up loss	2748	0,93%	345	2,04%	2049	1,55%	203	0,23%	92	0,44%	59	0,16%
Ignored	195032	66,22%	10985	64,92%	83252	62,89%	58577	67,33%	14354	68,15%	27864	75,00%
Total	294500	100,00 %	16922	100,00 %	132367	100,00 %	86995	100,00 %	21062	100,00 %	37154	100,00 %
Classification of causality at concluding												
A1. Related to the product according to literature	231780	78,70%	13658	80,71%	111288	84,08%	64075	73,65%	16192	76,88%	26567	71,51%
A2. Related to product quality	114	0,04%	0	0,00%	41	0,03%	46	0,05%	3	0,01%	24	0,06%
A3. Immunization error	243	0,08%	41	0,24%	29	0,02%	49	0,06%	93	0,44%	31	0,08%
A4. Immunization-related anxiety or stress	1920	0,65%	82	0,48%	282	0,21%	1261	1,45%	92	0,44%	203	0,55%
B1. Consistent temporal reaction, but without evidence in the literature	11043	3,75%	1030	6,09%	2788	2,11%	3942	4,53%	696	3,30%	2587	6,96%
B2. Conflicting data	4926	1,67%	207	1,22%	757	0,57%	2894	3,33%	559	2,65%	509	1,37%
C. Inconsistent	32895	11,17%	1037	6,13%	12766	9,64%	11808	13,57%	2231	10,59%	5053	13,60%

Table 2. ESAVI notifications according to type, classification, evolution, concluding and causality by region (continuation)

Characteristics	Total number of AE		Region of residence									
			North		South		Southeast		Midwest		Northeast	
	n	%	n	%	n	%	n	%	n	%	n	%
D. Unclassifiable	2529	0,86%	334	1,97%	815	0,62%	498	0,57%	228	1,08%	654	1,76%
Ignored	9050	3,07%	533	3,15%	3601	2,72%	2422	2,78%	968	4,60%	1526	4,11%
Total	294500	100,00%	16922	100,00%	132367	100,00%	86995	100,00%	21062	100,00%	37154	100,00%

Considering the distribution between genders, women received a little more than half of the doses applied in the period evaluated in Brazil (53.36% of the total during the year 2021). Even so, in Table 3 it is possible to identify that women were the majority of ESAVI notifications (70.83%). About the age group that presented the major frequency of AE was between 20 and 49 years, with a mean of 20.73% among the three age groups (20-29, 30-39 e 40-49).

Table 3. ESAVI notifications according to sociodemographic characteristics.

Characteristics	Number of people with at least 1 AE notified N=109424		Total number of signs and symptoms			
			Not serious N=279870		Serious N=14630	
	n	%	n	%	n	%
Gender						
Female	77506	70.83%	208608	74.54%	8192	55.99%
Male	31918	29.17%	71262	25.46%	6438	44.01%
Age range						
15 to 19	1862	1.70%	4708	1.68%	136	0.93%
20 to 29	20351	18.60%	54970	19.64%	922	6.30%
30 to 39	25925	23.69%	70211	25.09%	1502	10.27%
40 to 49	21782	19.91%	58810	21.01%	1815	12.41%
50 to 59	15150	13.85%	40142	14.34%	2103	14.37%
60 to 69	13913	12.71%	33850	12.09%	2638	18.03%
70 to 79	5265	4.81%	9723	3.47%	2342	16.01%
80+	5176	4.73%	7456	2.66%	3172	21.68%
Color categories						
Yellow	815	0.74%	2061	0.74%	115	0.79%
White	52648	48.11%	141267	50.48%	6205	42.41%
Indigenous	167	0.15%	288	0.10%	29	0.20%
Brown	32873	30.04%	76933	27.49%	4264	29.15%
Black	5523	5.05%	13483	4.82%	787	5.38%
Ignored	17398	15.90%	45838	16.38%	3230	22.08%

Discussion

With the COVID-19 pandemic, several vaccines were quickly developed to offer the population a cost-effective solution that controlled the transmissibility of SARS-Cov-2[19,24]. The vaccination is one of the most economical and effective to control diseases and prevents between 2 and 3 million deaths annually[25]. According to WHO,

the lack of confidence represents one of the reasons why people is not vaccinated. Several studies analyzing Adverse Events related to vaccines against COVID-19 have already been carried out around the world [10,14], but no study has evaluated, until the current date, the entire Brazil. Our study is important, necessary and urgent, as it assessed adverse events related to vaccination against COVID-19 in Brazil, during the period from January 1, 2021 to December 31, 2021.

The incidence of cases notified after vaccination against COVID-19 in Brazil was calculated at 30.82, totaling 0.03% of notifications against the total number of doses applied in the analyzed period. A carried study evaluating Baja-Califórnia, state of Mexico, present incidence of 64.98[26]. Other study evaluated more than 4 million doses in Korea, finding an overall incidence for all symptoms of 452.96 [27], high value compared to that found in this study, however, the reporting methodology is different in countries to relate the data.

It is difficult to compare the incidence of Adverse Events with other countries. The sources present in the literature currently only evaluate a specific vaccine or a group of vaccines and not a set of all those applied in that period, evaluate a specific symptom or are clinical trials, which bring different data from the reality of mass vaccination, in which the incidence rates of AE are lower[10,28]. In addition, the found studies that evaluated the set of vaccines in the countries had scarce samples or extracted data from questionnaires on social networks, which could not reflect the reality of that location [29,30].

The calculated incidence to any sign and symptom related to the AE of immunobiologicals against COVID-19 was 83.08 (82.78-83.38). Wu et al., 2021 [28] conducted a systematic review with meta-analysis analyzing 87 articles and obtained a mean incidence of 47.6 for systemic reactions and 44.3 for local reactions. The rate may have been lower than that found in our study, as it evaluated mostly developed countries, in which the health conditions of residents are higher than those of Brazilians. In addition, the aforementioned study evaluated vaccines not applied in Brazil, such as Moderna, mRNA vaccine, Sputnik V, recombinant adenovirus vaccine and Sinopharm, inactivated virus vaccine, which may also express different reaction rates.

At the thematic map in Figure 2, was possible to observe that the vast majority of notifications were concentrated in the South and Southeast of the country, explained by the information in the field “type of event in the notification” (Table 2), in which the

notifications are presented quantitatively. At Table 1 it is possible to observe that the major incidence of ESAVI and signs and symptoms was presented too for the South region, respectively 84.05 and 257.38, relatively higher value than other regions. Hypotheses can be formulated, such as the effectiveness and sensitivity of the system and health professionals in the region, better oriented patients and population with comorbidities. A study carried out in 2011 already stated that in the previous 15 years, public medical services in the southern region of the country already reached vulnerable populations, which were previously not assisted, which reflects a sensitive health system [31].

Currently there is a national standardization for notifications, except in São Paulo state, through navigation manuals, regarding the completion of notifications in the system *e-SUS Notifica*, however, each State and Regional Health Secretariat can also produce materials in order to train its workers[32]. In addition, better oriented patients also result in higher incidence rates of ESAVI, since, in Brazil, the patients are the ones who report their symptoms to health professionals, that fills out the report by the system, so with more reports, there are more notifications[33].

The higher incidence in the states could also reflect a portion of the population with more comorbidities. In other studies, it was possible to verify that patients with preexisting diseases and allergies tend to present more ESAVI, such as allergy to some vaccine compound (such as polyethylene glycol, being from Pfizer)[34]. Another study identified 11.1 cases of anaphylaxis per million doses applied, concluding that most people who had the reaction already had an allergenic history[35]. Furthermore, TSAI et al., 2022[36] carried a study on the hesitation of people with comorbidities such as cancer, autoimmune diseases, among others, and concluded that for patients with severe comorbidities, hesitation was relatively high, mainly due to reports of ESAVI among those already vaccinated[36].

A study carried out only in the state of Minas Gerais showed a higher frequency of reactions (0.45%) after the vaccination against the COVID-19 than in this study (0.03%)[8]. However, this is in consonance with the thematic map, in which the southeast region has the highest frequency of reported adverse events. In addition, the short period of time that the aforementioned study evaluated, just over a month, also meant that the analysis was based only on two vaccines (AstraZeneca e Coronavac), in addition to evaluating suspected cases of ESAVI, and not just those concluded. Furthermore, it was possible to analyze that studies carried out in smaller samples in

Brazil, such as state from Brazil or in a hospital in a Brazilian city, brought higher frequencies of adverse reactions[8,37].

In Table 3, it is possible to verify that, even though 53.32% of the vaccines were administered to females, that is, almost half proportionally, in this study, women presented almost 71% of adverse events, a high percentage and similar in other studies. In a hospital in São Paulo, 85% of the occurrences were in women[37]. They were also responsible for 90% of the reactions in a study carried out by the CDC COVID-19 and Food and Drug at USA, in December 2020. A factor that may be related to this is the greater use of the health system and greater prevention by women[38,39]. In relation to the age, the AE frequency increased to the average of 30 to 39 years and after reduced similarly in percentage to the increase. The down at both extremities of age group can be explained by the lower amount of vaccine application in this population group[40].

Although the death it represent only 0.80% of notifications (Table 2), a low frequency, other studies present corresponding data, in which was concluded that the deaths are more related to older age, since the elderly are a risk group and are more likely to develop a serious illness[41]. The Immunization Errors were low, even according to the Ministry of Health (BR), in a published technical note, it was clarified that in mass vaccination campaigns, such as COVID-19 it is common for the frequency of EI to be higher than usual, result of the good efficacy of the vaccination campaign.[42].

The study that evaluated Minas Gerais, Brazil, presented an EI incidence rate of 8.62, a value considered low by the authors[8]. The “3. Evolution” field set had higher percentage of information loss, in which more than 66% of notifications were not completed. This may indicate a failure in the health system and in the professionals, who do not report back to the patient to fill in the evolution, as it can also be something common, such as the case mentioned above, of mass vaccination, with a large number of patients and notifications, and with that, the lack of continuity of notified cases. Still in the “evolution” field, it was possible to verify only 0.20% of cure with sequelae, which can be associated with serious cases, which were also a minority (4.97%), therefore, they confirm the immunization safety, corroborating the low severity profile.

About the classification of the event 's seriousness (Table 2), the serious events (4.97%) were less frequent compared to those found by Karayeva et al., 2021 [43], presenting about 11% of severe ESAVI. A factor that may be related to the higher number is that in the US the patient can himself enter the system and report what he

felt, therefore, only in cases of anaphylaxis, myocarditis, and immediate allergic reactions is a health professional called to evaluate and treat the patient. Sultana et al., 2021[30] identified that in Bangladesh 17% of the related AEFI were classificated such as serious.

About the classification of causality, 78.70% of the AE, the vast majority were classified as “A1. Related to the product, according to literature”, that is, the cause of that reaction was evaluated and related to some component of the immunobiological, be it the immunogen, adjuvants or other additives[44]. Which reflects that most of the Adverse Events notified in Brazil are, in fact, related to some product compound, which is already expected, because AE are common [45,46]. In fact, this demonstrates that the immunizer can cause reactions, even though these are infrequent overall.

About the main SOC, observed in Figure 3b, the most incidents were General disorders and administration site conditions (incidence rate 22.59), Nervous system disorders (14.04) and Musculoskeletal and connective tissue disorders (10.45). Corroborating our results, other studies share the same manifestations identified in our study [10,28]. The signs and symptoms most commonly related to the four applied immunobiologicals were headache, fever and myalgia, with incidence rate of 9.82, 7.66 e 7.39, respectively (Figure 3a). Studies that evaluated AE and security of the COVID-19 vaccines in other countries founded results similar to ours, such as Pakistan, who also presented fever and headache as two of the three most frequent symptoms[47]. At US, the majority of the patients also presented headache and fever[48], and a meta-analysis that evaluated 14 studies also identified such common fever and headache[10]. Another study, carried out in a hospital (São Paulo, Brazil), showed a higher frequency of symptoms such as headache, fatigue, myalgia and pain, with percentages between 50 and 80% of the analyzed population[37]. This demonstrates that, in general, common symptoms among studies that evaluated AE after vaccination against COVID-19 are mild and involve local pain, headache and fever. It is worth mentioning that although Janssen is responsible for the lowest percentage of overall AEFI, in the analysis of incidence by symptoms, it has the second highest incidence rate for the most common symptoms mentioned above, such as headache, myalgia and fever, which demonstrates that the low value of AE can be directly related to the low amount of applied doses, only 1.75% in the Brazilian population in the evaluated period[49].

In Brazil, local reactions such as pain at the injection site were less frequent than other local symptoms. The local symptom most common was headache, eight

times more common than pain. This may be related to the way in which notifications are made in the country or even with underreporting, since, in Brazil, the patient affected by the post-vaccination reaction has to go to the health unit and report it to the professional, who notifies via the national system. For mild and expected symptoms, such as pain at the injection site, fatigue, among other common ones, along with social inequality in the country, financial, organizational, information barriers and the geographic distribution and barriers of the health basic units can interfere with non-notification, due to the fact that the patient does not go to the health professional[50]. In Brazil, there are many municipalities with rural areas, and in 2018, almost 20% of the assistance coverage did not reach these residences, including, in some states such as Amapá, Acre, Tocantins and Roraima, the percentage was even lower [51]. As much as there is an active community surveillance by health professionals towards patients, this does not occur to investigate adverse events, as the routine is more related to primary care.

Secondary data are extremely relevant for the epidemiological study of ESAVI, however, they are related to the possibility of bias, such as information. Thus, in an attempt to approximate the proposed reality with this study, it is necessary to consider problems such as the incompleteness of certain fields and the existence of missing data, duly treated in our study in the form of filters and exclusion. Underreporting of ESAVI cases occurs both in Brazil and in other countries. It is hoped that studies such as ours will endorse the literature with current information on the benefit/risk of vaccines against COVID-19, enabling the National Immunization Program (PNI) to offer quick and clear responses to emerging ESAVI rumors. This contributes to the reliability of the system, which is important as a counterpoint to the anti-vaccination movement and the influence of social media on the social representations of the population[19]. We emphasize that mass vaccination based on something totally new for the population, the pandemic decree, isolation policies and new respiratory etiquette habits may have been barriers that directly affected vaccine coverage and reporting of adverse events. Although the frequency was low, 0.038% of all vaccines applied, it is necessary that these data be disseminated and analyzed, to alleviate vaccine hesitancy, cited by the WHO as one of the ten public health threats of 2019. Factor that is directly connected with some of the Sustainable Development Goals (SDGs) of the UN, such as the SDG 3: Good Health and Well-being and SDG 10: Reduced Inequalities, that improved, would bring easier access to health and care for the

population [52].

Conclusion

Vaccines are safe and effective products, however, like any other medicine, they can cause adverse events. It appears that in 2021 there was a heterogeneous distribution of ESAVI COVID-19 across the national territory, characterized by low incidence and a preponderant profile of non-severity of cases. The evident underreporting in Brazil and in other countries around the world is a problem to be faced in favor of strengthening surveillance systems in the context of safe immunization. Despite the rapid development, emergency use and subsequent application of mass immunizations in Brazil, the results of this work corroborate the feasibility and relevance of vaccines against the disease caused by the coronavirus in use in the country. It is suggested that further investigations be conducted in Brazil and worldwide addressing specific characteristics of immunizers and other factors possibly associated with the severity of ESAVI COVID-19.

Limitations

The data losses due to duplications and unresolved notifications in the state of São Paulo, as well as the incompatibility in the format of some variables between the databases of São Paulo and the Ministry of Health, are important factors to be taken into consideration when interpreting the results related to regions with higher incidence of ESAVI/COVID-19 in Brazil.

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2.2 ARTIGO 2 – COVID-19 ADVERSE EVENTS FOLLOWING IMMUNIZATION IN DEVELOPED AND DEVELOPING COUNTRIES: SYSTEMATIC REVIEW AND META-ANALYSIS

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COVID-19 Adverse Events Following Immunization in developed and developing countries: systematic review and meta-analysis

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Running title: Adverse events following vaccination against COVID-19

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ABSTRACT

Background: The aim of this study was to analyze the incidence of adverse events of COVID-19 vaccination or immunization in developed and developing countries. Methods: A systematic review with meta-analysis was conducted, searching the EMBASE, PubMed/MEDLINE, and SCOPUS databases. Methodological quality and risk of bias were assessed using the the Rob2 tool. Heterogeneity and sensitivity among the studies were evaluated. Relative risk was adopted as the measure of effect, with 95% confidence intervals. Results: Pain, headache, and myalgia were the most common adverse events among the 7,841 participants. It was found that the risk of events attributable to vaccination was higher in developed countries and with the second dose of the vaccine. There was a higher risk of local events compared to systemic events, regardless of the country's level of development. Conclusions: Adverse Events Following Immunization COVID-19 vaccination were predominantly mild in all countries, with a higher risk observed with the second dose and in developed countries. These results provide important information about the safety of vaccines and can assist in decision-making related to COVID- 19 vaccination.

Keywords: incidence, risk assessment; vaccination; immunization; COVID-19.

INTRODUCTION

COVID-19, caused by the SARS-CoV-2 virus, was declared a global pandemic in March 2020, triggering an urgent search for vaccines to control the spread of the disease and reduce its severe consequences [1,2].

Vaccination in different countries has been and is being implemented, however, concerns arise about Adverse Events Following Immunization of COVID-19 vaccines (AEFI). Although COVID-19 vaccines have demonstrated efficacy in preventing severe forms of the disease, cases of adverse events have also been reported, and it is important to emphasize that most of them are mild and temporary, with the benefits of vaccination outweighing the risks [3].

Economic, infrastructure, education, health and governance disparities between developed and developing countries have been accentuated during the pandemic [4–6]. Developing countries have faced challenges in vaccine procurement, distribution and uptake, as well as allocating more limited resources to combat COVID-19 [7–11].

However, it remains unclear whether there are differences in the incidence of adverse events related to COVID-19 vaccination between developed and developing countries. Considering the importance of vaccination in the COVID-19 pandemic context [12] and the influence of population characteristics on the response to immunization [13] we used a systematic review approach to compare the incidence of post-vaccination adverse events in individuals immunized with COVID-19 vaccines in developed and developing countries.

Therefore, the aim of this study was to analyze the incidence of COVID-19 Adverse Events Following Immunization Immunization in developed and developing countries.

MATERIALS AND METHODS

Guiding Question and Protocol Record

The guiding question was elaborated considering the PICO strategy (P= Problem, I= Intervention, C= Comparison and O= Outcome) [14] and was structured as follows: Do people who received the COVID-19 vaccine in developing countries

have different incidence rates of adverse events compared to people vaccinated in developed countries? The structured methodological protocol was registered in the PROSPERO (International Prospective Register of Systematic Reviews) database (registration CRD42022339632).

Guidance Definitions

Considering an unambiguous interpretation of the terms used in this review, the following definitions were adopted: (i) Vaccination (MeSH ID: D014611, National Library of Medicine); (ii) Adverse events (World Health Organization); (iii) Incidence (MeSH ID: D015994, National Library of Medicine); (iv) Developed Countries (United Nations, 2023); (v) Developing Countries (United Nations, 2023).

Electronic Databases and Search Strategy

The search for primary research records was conducted in three electronic databases: EMBASE, PubMed/MEDLINE and SCOPUS [15]. For all databases, search filters were developed based on specific descriptors stratified into three levels: (i) disease, (ii) intervention and (iii) outcome. The Boolean operator "OR" was used at the same level, and all levels were grouped using "AND". Search limits were applied to increase the specificity of the search for randomized controlled trials in Spanish, English or Portuguese. Chronological or population limits were not adopted in the search strategy. The full search strategies used across all databases are described in the supplementary files (Table S1).

PRISMA workflow, screening of records and secondary research

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 strategy and its checklist with 27 items, divided into sections and topics were considered in the development of this study [16].

Eligibility criteria and agreement between evaluators

Only studies that met all of the following inclusion criteria were screened and included: (i) primary studies reporting AEFI COVID-19 in developed or developing countries, (ii) randomized controlled trials, (iii) indexed studies, (iv) studies available in full text, (vi) studies reporting incidence, risk or cumulative incidence ratio based on the number of post-vaccination adverse events divided by the number of vaccine doses administered.

The following studies were excluded: (i) only title and abstract available, (ii) gray literature: studies that have not been formally published, (iii) studies with multiple interventions that prevent the attribution of adverse effects to vaccination, (iv) studies without a control group, (v) publications in languages other than Spanish, English and Portuguese, (vi) studies that do not specify the vaccine administered, (vii) studies that present methodological flaws in the calculation of incidence, (viii) studies that present only population over 65 years old, (ix) studies that present population only with comorbidities or physiological alteration, (x) studies that evaluate vaccines not authorized by WHO in the document "Status of COVID-19 Vaccines within WHO EUL/PQ assessment process", dated July 7, 2022, (xi) studies that evaluated more than one vaccine in the same work.

To minimize selection bias, eligibility criteria were reviewed by 2 independent reviewers (PCP and VGSG), they removed duplicate articles, screened titles and abstracts, and disagreements were reviewed by arbitration of a third expert researcher (LMRPD). At the end of the selection of studies, the results were used to calculate interobserver agreement based on the kappa coefficient (kappa = 0.684), substantial concordance [17]. The full list of articles included in the systematic reviews is described in the supplementary files (Table S2).

Categorization of studies and data extraction

To ensure consistency of the search results, the results of interest were extracted by 2 independent researchers. The objective data extraction was operationalized from collection masks contemplating the following characteristics of the selected studies: (i) general publication characteristics (author, year and country where the study was developed), (ii) vaccination protocol (type of vaccine, dose, site, route and frequency of administration), (iii) incidence of general adverse effects after vaccination and (iv) incidence of specific adverse effects after vaccination.

Adverse Events were classified by MedDRA code, by preferred term (PT), specific, or System, Organ, Class (SOC), general. The classification of studies conducted in developed and developing countries was established according to the criteria described by the United Nations Organization [18]. To calculate the incidence of AEFI/COVID-19, the number of people who presented the symptom and, in the numerator, the number of people who received the vaccine or placebo were extracted from the articles.

Research bias

Three independent reviewers (PCP, VGSG, and TCAL) applied the instruments to assess the risk of bias, and disagreements were analyzed by a third expert researcher (LMRPD) after conducting a meeting to reach a consensus.

The risk of bias in each reviewed study was analysed using the Revised Cochrane risk- of bias tool for randomized trials (RoB 2). This toll was applied from the Excel file provided by the RoB 2.0 development team [19]. The studies were categorized as "high risk," "low risk," or "some concerns" in the following domains: (i) randomization process, (ii) deviation from intended interventions, (iii) missing outcome data, (iv) measurement of the outcome, and (v) selection of the reported result. Overall risk of bias was defined as "some concerns" or "high risk of bias" when these categories were defined for at least one domain analyzed. The risk of bias was used to explore heterogeneity in meta-analyses, and a narrative discussion of the risk of bias was provided according to Cochrane Handbook [19].

The low risk of bias predominated. Traffic Light Plot and Summary Plot (robvis)[2] were used for graphical representation of the outcome of the risk of bias assessment, which can be seen in the supplementary materials.

Statistical Analysis

Meta-analyses investigating the effect of anti-SARS-CoV-2 immunization on

[2] McGuinness, LA, Higgins, JPT. VISualização de risco de viés (robvis): Um pacote R e um aplicativo Web Shiny para visualizar avaliações de risco de viés. Res Syn Metanfetamina. 2020; 1- 7. https://doi.org/10.1002/jrsm.1411

the incidence of local and systemic adverse effects have been conducted from Mantel-Haenszel random-effects modeling [21] with the aid of Cochrane Review Manager (RevMan) version 5.4 [20]. Continuous data were analyzed by calculating the risk ratio (RR) and the corresponding 95% confidence interval (CI), since the studies reported results using the same scales. A significance level of 5% was considered.

Statistical heterogeneity was analyzed and reported using the I2 statistic, and interpreted as follows: 0%-40%=may not be important, 30%-60% moderate heterogeneity, 50%-90%=substantial heterogeneity, and 75%-100%= considerable heterogeneity. The higher (more conservative) range was chosen when a study had an I2 spanning two ranges. Heterogeneity was explored from sensitivity and subgroup analyses [20]. We performed subgroup analysis to investigate heterogeneity and the possibility of effect modification for local and systemic adverse events [20].

The I2 statistic was used to examine differences between subgroups [21]. The studies were stratified into four subgroups based on (i) where the studies were developed (developing and developed countries) and (ii) risk of bias (low and some concern). The hypothesis is that the AE risk ratio may be influenced by the sociodemographic status to which each population is subjected, since sociodemographic determinants exert a direct impact on COVID-19 vaccine hesitancy, fear of infection and protection self-efficacy [22]. In addition, there is evidence that sources of bias potentially impact the effect of meta-analysis [23].

Certainty of the evidence

For the assessment and grading of the certainty of the evidence, MCN used the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach/system[3]. The results and conclusions for each outcome variable of interest can be seen in the supplementary material (GRADE evidence profile and Summary of findings).

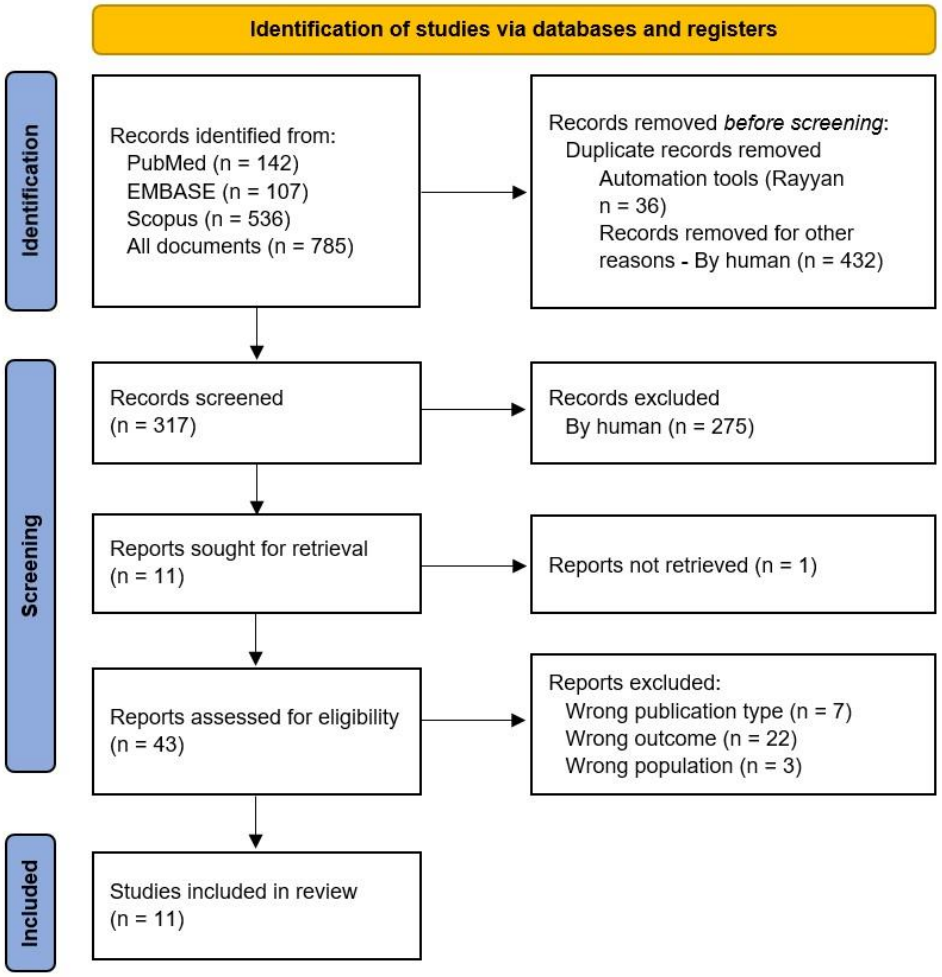
RESULTS

[3] The GRADE working group. [online] Disponível em: https://www.gradeworkinggroup.org/#pub. Acesso em: 31 de julho de 2023. BMJ Best Practice. What is GRADE? [online]. Disponível em: https://bestpractice.bmj.com/info/toolkit/learn-ebm/what-is-grade/. Acesso em: 31 de julho de 2023.

Systematic review: Incidence of AEFI/COVID-19

We initially identified 785 records in three databases during the preliminary search. Study selection was conducted according to well-defined eligibility criteria, resulting in the inclusion of 11 studies covering a number of 7,841 participants. Of the included studies, seven were conducted in developed countries and four in developing countries. The literature screening flowchart used in this study is presented in Figure 1.

Figure 1. PRISMA flowchart of study selection for systematic review [16].



Several vaccine technologies were identified: covering viral vector, mRNA, inactivated virus and recombinant nanoparticle. In total, seven types of vaccines were employed in the studies reviewed, including Ad5-vectored vaccines [24], Ad26-COV2.S [25], CoronaVac [26], mRNA-1273 [27,28], NVX-CoV2073 [29,30],

ChAdOx1 nCoV-19 [31,32] and BNT162b1/b2 [33,34].

The characteristics of the included studies, as well as the participants and vaccines used in the randomized controlled trials, are presented in Table 1. This table provides an overview of the different studies analyzed, providing information on the phases, participants and vaccination protocols used in the studies.

Table 1. Characteristics of the studies, subjects and vaccines used in the randomized controlled trials.

Study	Study phase	Individuals (Women/Men)	Age (mean ± SD)	Vaccine / Control	Vaccine / adjuvant technology
Zhu et al., 2020	II	V1: 127 W / 126 M	40 ± 12,8	Ad5-vetor	viral vector / NA ~
		V2: 65 W / 64 M	39,7 ± 12,5	Ad5-vetor	viral vector / NA ~
		C: 62 W / 64 M	39,2 ± 12,5	control	(-) / (-)
Sadoff et al., 2021	I/II #	V3: 84 W / 78 M	36,1 ± 10,1	Ad26.COV2.S	viral vector / NA
		V4: 85 W / 72 M	34,8 ± 10,3	Ad26.COV2.S	viral vector / NA
		C: 42 W / 40 M	35,4 ± 10,0	control	(-) / (-)
Masuda et al., 2022b	I/II	V5: 65 W / 85 M	53.3	mRNA-1273	mRNA/NA
		C: 23 W / 27 M	52.4	control	(-) / (-)
Madhi et al., 2022	II #	V6: 872 W / 1217 M	31,5 ± 12,9	NVX-CoV2073	recombinant nanoparticle / Matriz-M
		C: 1708 W / 2456 M	31,8 ± 13,2	Control	(-) / (-)
Asano et al., 2022	I/II	V7: 25 W / 71 M	45,6 ± 8,2	AZD1222	viral vector / Polysorbate 80 ~
		C: 8 W / 24 M	46,1 ± 6,7	control	(-) / (-)
Masuda et al., 2022b	I/II	V8: 65 W / 85 M	52,6**	NVX-CoV2073	recombinant nanoparticle / Matrix-MTM ~
		C: 21 W / 29 M	50,8**	control	(-) / (-)
Folegatti et. al, 2020	I/II	V9: 265 W / 278 M	34	ChAdOx1 nCoV-19	viral vector / Polysorbate 80 ~
		C: 271 W / 263 M	36	control	(-) / (-)
Walsh et al.,, 2020	I	V10: 5 W / 7 M	29,4 ± 6,4	BNT162b1	mRNA/LPN ~
		V11: 3 W / 9M	44,8 ± 8,3	BNT162b1	mRNA/LPN ~
		V12: 6 W / 6 M	35,8 ± 10,0	BNT162b1	mRNA/LPN ~
		V13: 7 W / 5 M	38,3 ± 9,3	BNT162b1	mRNA/LPN ~
		C: 5 W / 7 M	36,3 ± 11,3	control	(-) / (-)
		V14: 7W / 5M	36,8 ± 12,2	BNT162b2	mRNA/LPN ~
		V15: 6 W / 6 M	37,6 ± 10,1	BNT162b2	mRNA/LPN ~
		V16: 9 W / 3 M	37,3 ± 9,8	BNT162b2	mRNA/LPN ~
		C: 4 W / 5 M	34,4 ± 13,2	control	(-) / (-)
Zhang et al., 2021	I/II	V17: 77 W / 67 M	42,4 ± 10,2	CoronaVac	inactivated virion / aluminum hydroxide
		V18: 86 W / 58 M	42,8 ± 9,0	CoronaVac	inactivated virion / aluminum hydroxide
		C2: 44 W / 40 M	42,4 ± 8,8	control	(-) / (-)
		V19: 75 W / 69 M	41,8 ± 9,4	CoronaVac	inactivated virion / aluminum hydroxide
		V20: 70 W / 74 M	41,2 ± 10,2	CoronaVac	inactivated virion / aluminum hydroxide
		C2: 45 W / 38 M	44,1 ± 9,1	control	(-) / (-)
Li et al., 2021	II	V21: 12 W / 12 M	37,9 ± 9,6	BNT162b1	mRNA/LPN
		V22: 12 W / 12 M	39,7 ± 9,0	BNT162b1	mRNA/LPN
		C: 12 W / 12 M	42,0 ± 8,7	control	(-) / (-)
Chu et al., 2021	II	V23: 64 W / 36 M	36,6	mRNA-1273	mRNA/NA
		V24: 53 W / 47 M	38.3	mRNA-1273	mRNA/NA
		C: 60 W / 40 M	37.3	control	(-) / (-)

(-) Not reported in the study; ~ Taken from another source; # Phase IIa (efficacy of a drug or regimen) or IIb (identifying a promising treatment to be tested in phase III trials); ** Only age range was reported; *** Only the median was reported; LPN: mRNA technology formulated with lipid nanoparticles (LNP); NA: No Adjuvant; V1 – V24: Vaccine group administered; C: Control.

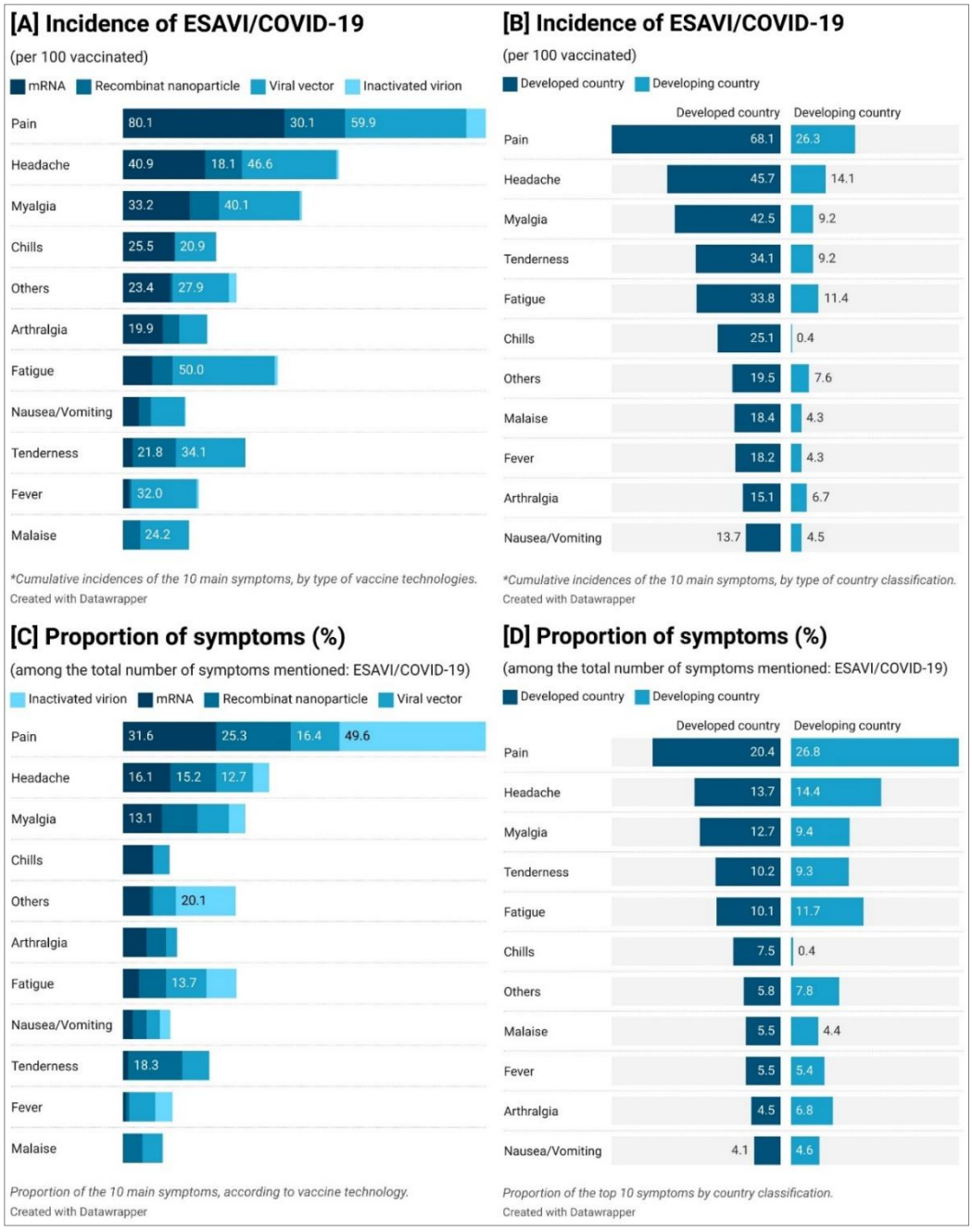
In Table S2 (supplementary material), the studies that used saline are presented [25,27–30,33,34] or the adjuvant itself as a control group [26]. One study used MenACWY vaccine as a control group instead of adjuvant or saline solution [31]. Of the 11 studies analyzed, three evaluated only a single dose, while the remaining eight studies investigated vaccines administered in two doses, with intervals ranging from 14, 21 to 28 days.

Figure 2a presents the ten most significant and highest incidence adverse events (per 100 vaccinated) related to COVID-19 vaccination/immunization. A higher frequency of these adverse events is observed in individuals who received vaccines developed with mRNA and viral vector technology.

Figure 2b shows that the most incident adverse events per 100 vaccinated individuals were reported in studies conducted in developed countries. The same pattern is observed when analyzing the ten most frequent adverse events related to COVID-19 vaccination.

Figure 2c illustrates the percentage of each symptom in relation to the total symptoms reported in the analyzed clinical trials. Pain remains the most common symptom across the different vaccine types. In addition, a higher percentage of pain and other symptoms is observed in individuals who received vaccines with inactivated viruses.

Figure 2: Incidence of Adverse Events Following Immunization (AEFI) and percentage of COVID-19-related post-vaccination symptoms[4], considering vaccine technologies and development status of countries.



[4] **Incidence of AEFI/COVID-19:** The numerator of the first measure encompassed the number of cases of AEPI/COVID-19, and the denominator, the total number of individuals who received vaccines/COVID-19 in the considered primary studies. It was then multiplied by 100 as a constant. **Percentage of signs and symptoms (%):** The sum of each post-vaccination sign and symptom, categorized by groups, was considered in the numerator (according to the Classification of Systems and System Organ Class (SOC) - general descriptor, from the Medical Dictionary for Regulatory Activities – MedDRA). In the denominator, the total number of post-vaccination signs and symptoms overall (considering all affected SOC). It was then multiplied by 100 (percentage).

When considering the percentage of symptoms according to the development status of the country, a reversal in some frequencies can be seen (Figure 2d). Symptoms such as pain, fatigue, arthralgia and others were more frequent in developing countries compared to the percentage of these same symptoms in developed countries.

Meta-analysis: AEFI/COVID-19 risk

This meta-analysis showed that the risk of COVID-19 AEFI was higher in developed countries when compared to the risk of events in developing countries. In Figure 3, which represents the result of the meta-analysis according to country classification, it is possible to note the reduced heterogeneity between articles, as also observed in the overall meta-analysis (Figures S1 and S2, from the supplementary material).

Figure 3: Meta-analysis with subgroups according to developed and developing countries - Dose 1 (a: any; b: local; and c: systemic).

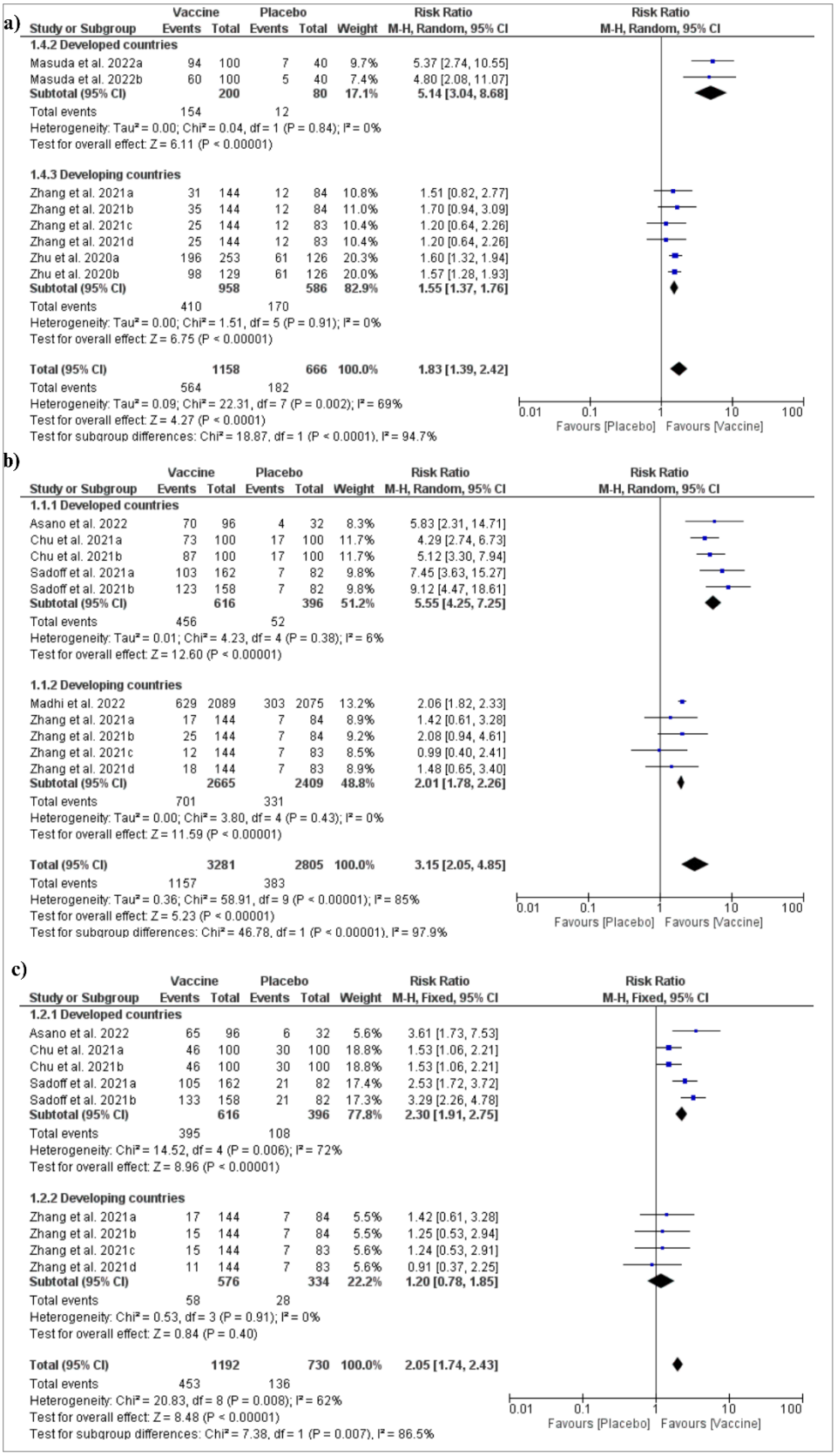
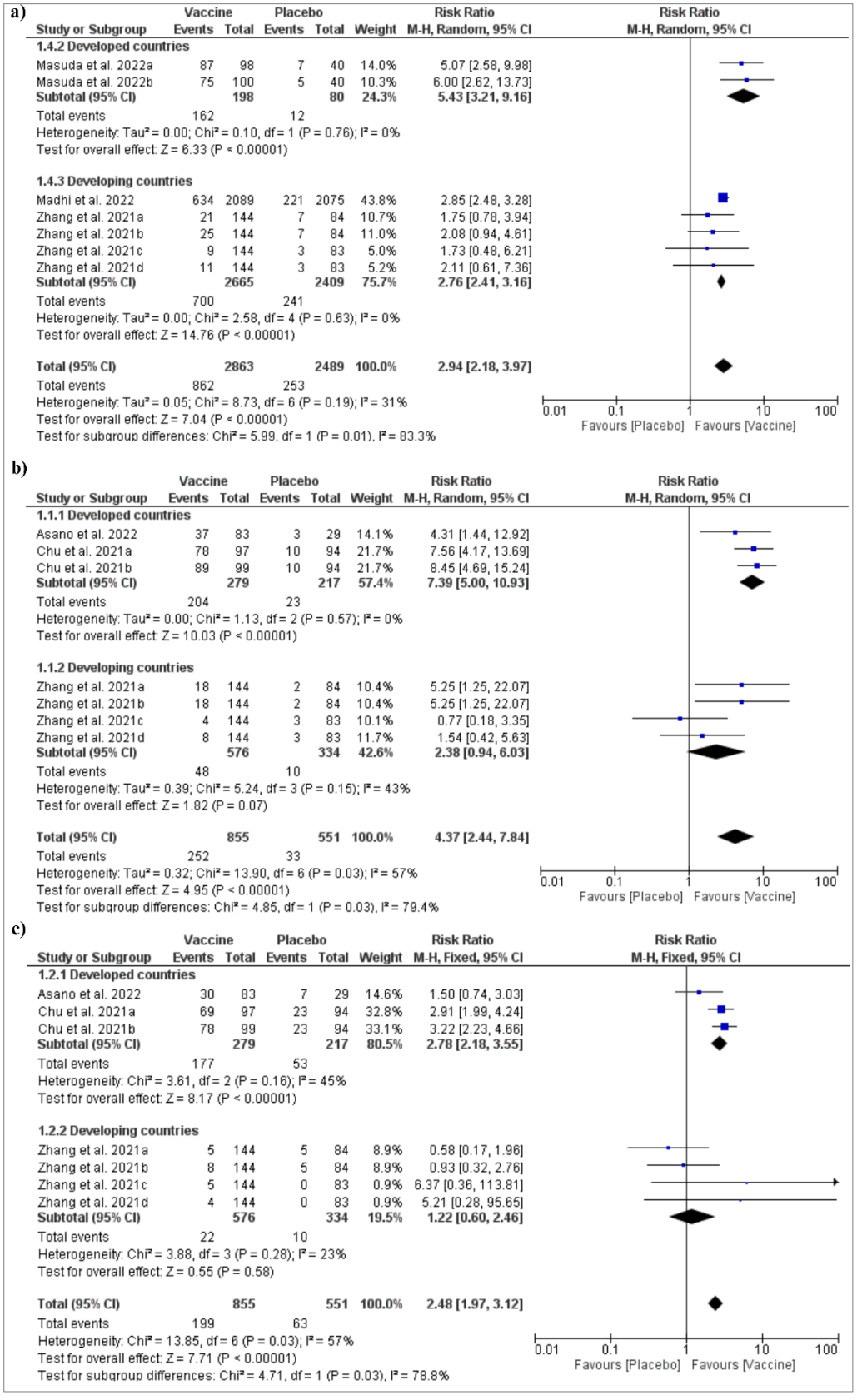


Figure 4: Meta-analysis with subgroups according to developed and developing countries - Dose 2 (a: any; b: local; and c: systemic).



The risk of COVID-19 AEFI during the first dose was higher in individuals who received the vaccine compared to those who received placebos. The combined analysis of Figures S1 and S2 (Supplementary material) revealed a higher relative risk (RR) pattern at the second dose.

Moreover, the pattern of higher relative risk (RR) at the second dose holds regardless of whether the events analyzed were systemic, local or any. Local symptoms (Figure S1b and S2b) showed a higher RR regardless of the country's level of development.

With regard to systemic symptoms, no significant differences in risk were found in four studies. The study conducted by Zhang et al,. 2021 [26] signaled the same null pattern of relative risk of AEFI between exposed and unexposed individuals, as shown in the forest plots. Another relevant factor to be considered is the higher RR for local symptoms (Figures 3b and 4b).

DISCUSSION

In this study, the incidence of adverse events was compared between developed and developing countries. In addition, post-vaccine adverse events against COVID-19 were analyzed among different vaccines, number of doses, considering the presence of adjuvants, the use of different phases of studies (Phase I and II), and comparing the incidence of adverse events between viral vector, mRNA, inactivated virus and recombinant nanoparticle vaccines, in line with the technological diversity of available vaccines against COVID-19.

Table 1 identifies phases I and II, which are studies authorized for human application. Phase I refers to the first study carried out in humans, with the objective of evaluating the safety of the immunizer. Phase II verifies the efficacy and immunogenicity of the vaccine [35]. The results presented in Tables 1 and 2 highlight the diversity of the studies included in this meta-analysis, considering geographical, technological and population aspects.

In a group of studies, vaccines with adjuvants, compounds that stimulate and enhance the host immune response, have been used to provide greater duration and magnitude of the protective effect. They are described in Table 2, aluminum hydroxide and Matrix-M [36,37]. However, some studies indicate that, according to the vaccine

technology used, the presence of adjuvants does not bring significant advantages, which may explain their absence in the composition of some vaccines [38,39].

Figure 2a shows the AEFI pain, headache, myalgia, fatigue and tenderness as the most incident. Pain was found to be the most frequent event, reaching percentages of 80% and 60% for certain vaccine technologies, in agreement with other randomized clinical trials [40–43]. It is important to emphasize that the occurrence of pain is an expected generic symptom due to the characteristics of the vaccine administration (intramuscular route) and the properties of the immunobiological agent [44].

Regarding vaccine technologies, mRNA and viral vector vaccines were found to contribute to a higher incidence of AEFI (Figure 2a). This is an expected result, as previous studies have shown that mRNA vaccines are associated with a higher risk of developing post- vaccine reactions compared to inactivated and viral vector vaccines [45,46] and have even been associated with Pfizer's Polyethylene glycol (PEG) adjuvant [47,48].

Furthermore, Figure 4a reveals a lower incidence of adverse events for inactivated virus vaccines, which converges with the statements of the Director of Innovation of the Butantan Institute (Brazil), Ana Marisa Chudzinski-Tavassi, that inactivated virus vaccines generally cause fewer adverse events of interest (AEFI) [49].

Although pain remains the most frequent symptom (Figure 2c), the percentage of individuals who received the inactivated virus vaccine (CoronaVac) stands out, with almost 50% presenting reactions. Other studies have reported percentages between 4% and 20.8%, lower than those found in this study [50–53]. However, a possible difference from other vaccine technologies is the presence of the aluminum hydroxide adjuvant, found only in the inactivated virus vaccines of this study. A previous study evaluating the DTP vaccine, which also contains the same adjuvant, found a direct association between pain and aluminum exposure, demonstrating a significant difference in the hazard ratio in the random effect model [54].

Figures 2b and 2d present the incidence of AEFI and the percentage of symptoms according to the level of development of the included countries. In contrast to the incidences of AEFI, the results showed that the percentage of symptoms such as pain, fatigue, arthralgia, headache and other manifestations was higher in developing countries compared to developed countries. As socioeconomic and

demographic factors, which may influence the perception and reporting of adverse events, are controlled for in a protocol manner in randomized controlled trials [55,56] no results contributing to causal explanations for the identified differences were identified in the literature.

When comparing the groups that received the vaccine or placebo and considering the dose number, a higher risk of adverse events was observed in cases, to the detriment of the lower risk among controls. These findings reinforce the need for special attention to symptoms during and after COVID-19 vaccination.

In addition, there was a reduction in overall heterogeneity when the analyses were done by subgroups of the country's level of development [18].

Regarding the pattern of vaccination against COVID-19 in the countries in question, heterogeneity was observed in relation to the date of initiation of vaccination and the percentage of the population that received at least one dose of the vaccine. There is a discrepancy, as China started vaccines earlier and achieved higher vaccination coverage, while South Africa had lower vaccination coverage [57]. Studies conducted in different developed countries showed more consistency regarding the date of vaccination initiation and the total number of doses administered [57].

The combined analysis of Figures 3 and 4 reveals a higher relative risk (RR) of developing a reaction after receiving the vaccine compared to the control group, as demonstrated in all studies. However, it is important to point out that part of the subjects who received the placebo also experienced AEFI. This can be attributed to the nocebo effect, which is especially common with COVID-19 vaccination, due to the pandemic/social isolation context and psychological harm. [59,60].

Regarding the higher incidence of AEFI observed in second doses, this trend was consistent in all meta-analyses, whether local or systemic manifestations, in agreement with studies conducted by [60-62]. This is in line with the findings of [63] who reported a higher incidence of adverse events after the first dose, although their study was conducted in people with Down syndrome.

One hypothesis for the increased occurrence of adverse events at the second dose is the effect of trained innate immunity, a recently discovered phenomenon, which suggests that prior exposure to antigen during vaccination may be further intensified and potentiated at the second encounter, a process already demonstrated in BCG vaccination [63,64]. These results highlight the importance of continued monitoring and follow-up of adverse events after administration of the second dose.

Regarding the meta-analysis stratified by level of development of the countries, as presented in Figures S1 and S2, a reduction in heterogeneity between studies is observed. It is interesting to note how studies become more similar when they are grouped according to this factor. A possible explanation for this is the methodological quality of the studies and the characteristics of the population, considering that the Human Development Index (HDI) also takes into account the health of the population [65].

In addition, when analyzing the groups separately according to the level of development of the countries, the second dose continues to show a higher relative risk compared to the first, regardless of the type of symptom. Moreover, higher-development countries showed a higher relative risk for adverse events of interest. However, as discussed in Figure 2d, there is currently no explanation in the literature for this higher occurrence of adverse events in more developed countries in randomized controlled trials, despite these countries producing more scientific research.

The increased risk of AEFI against COVID-19 in developed countries raises a question about the methodological quality of the phase I and II randomized controlled trials included in this systematic review and meta-analysis. However, the certainty of the evidence was rated as moderate and high, depending on the outcome of interest.

CONCLUSION

In conclusion, the studies conducted in developed countries showed a higher relative risk of COVID-19 AEFI when compared to published studies from developing countries. In addition, exposure to the second dose of COVID-19 vaccines was associated with a higher risk of adverse events, possibly related to the different immune response of vaccinated individuals. A higher risk of local reactions compared to systemic manifestations was also observed.

Therefore, we infer that the first doses of COVID-19 vaccines result in a slight increase in the risk of COVID-19 AEFI vaccines in developed countries when compared to the risk in developing countries. Additionally, the second doses of COVID-19 vaccines probably result in a significant increase in the risk of COVID-19 AEFI vaccines in developed countries when compared to the risk in developing countries.

FUTURE DIRECTIONS

Understanding the incidence and characteristics of adverse events following COVID-19 vaccination is crucial to maintaining public confidence in vaccination campaigns and ensuring the safety of individuals worldwide. By conducting a comprehensive analysis of AEFI incidence in developed and developing countries, this study has provided insights into potential variations in safety profiles and informed evidence-based decision-making for future immunization strategies.

However, it was not possible to identify, in this study or in the literature, justifications for the risk ratios according to the development status of the countries. This limitation calls for caution in extrapolating the results, which points to the need for further studies on the subject. Taken together, these results are important for helping monitor vaccine safety and may assist in decision-making regarding COVID-19 vaccination globally.

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3 CONSIDERAÇÕES FINAIS

Por meio do estudo transversal que avaliou a incidência acumulada de Eventos Supostamente Atribuíveis à Vacinação ou Imunização (ESAVI) contra a COVID-19 na população brasileira em 2021, e da revisão sistemática com metanálise, que investigou o risco relativo de ESAVI/COVID-19 em escala global, emergem as seguintes conclusões e considerações:

Primeiramente, os resultados obtidos reforçam a constatação de que as vacinas contra a COVID-19 são, de fato, capazes de causar eventos adversos pós-vacinais, o que corrobora com as expectativas iniciais. No entanto, destaca-se que a incidência acumulada desses eventos é baixa e, majoritariamente, caracterizada por sintomas leves, o que aponta para a relativa segurança das vacinas em relação aos ESAVI/COVID-19.

Adicionalmente, os achados desta dissertação revelam uma associação entre países desenvolvidos, a administração da segunda dose das vacinas e as manifestações locais, com um risco relativo maior de ESAVI/COVID-19. A despeito da constatação do menor risco de eventos pós-vacinais nos países em desenvolvimento, ressalta-se que, até o presente momento, não foi possível encontrar uma explicação definitiva para tal padrão. Assim, demanda-se a continuidade de investigações futuras que possam elucidar os fatores subjacentes a essa relação.

Os achados desta dissertação possuem significativo valor para o acúmulo de conhecimento sobre a segurança das vacinas contra a COVID-19 e ressaltam a importância da vigilância contínua em relação aos eventos adversos pós-vacinação. Nesse sentido, os resultados instigam a comunidade científica a persistir em estudos que enfoquem as especificidades dos imunizantes utilizados e outros potenciais fatores associados à gravidade dos ESAVI em diferentes contextos.

Assim, é imperativo que esforços contínuos sejam direcionados para garantir a eficácia e segurança dos programas de imunização, tanto no Brasil como em escala global. A compreensão aprofundada dos mecanismos subjacentes aos ESAVI permitirá o aproveitamento máximo dos benefícios das vacinas no controle da disseminação do SARS-CoV-2, fornecendo subsídios para o aprimoramento das estratégias de imunização e, por conseguinte, para o enfrentamento cada vez mais efetivo da COVID-19.

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APÊNDICE A – Materiais suplementares do artigo 2

(COVID-19 Adverse Events Following Immunization in developed and developing countries: systematic review and meta-analysis)

PROSPERO
International prospective register of systematic reviews

NHS National Institute for Health Research

UNIVERSITY of York
Centre for Reviews and Dissemination

Revisão sistemática

A list of fields that can be edited in an update can be found here

1. * Título da revisão.

Dê o título da resenha em inglês

Incidência de eventos adversos após a vacinação contra COVID-19 em países desenvolvidos e em desenvolvimento: uma revisão sistemática

2. Título na língua original.

Para comentários em outros idiomas que não o inglês, forneça o título no idioma original. Isso será exibido com o título em inglês.

3. * Data de início antecipada ou real.

Indique a data em que a revisão sistemática começou ou deve começar.

03/03/2022

4. * Data de conclusão antecipada.

Indique a data em que se espera que a revisão esteja concluída.

31/12/2022

5. * Etapa de revisão no momento desta submissão.

Este campo usa respostas para perguntas de triagem inicial. Ele não pode ser editado até depois do registro.

Marque as caixas para mostrar quais tarefas de revisão foram iniciadas e quais foram concluídas.

Atualize esse campo sempre que forem feitas alterações em um registro publicado.

The review has not yet started: No

PROSPERO
International prospective register of systematic reviews

NHS National Institute for Health Research

Etapa de revisão	Começou	Concluído
Pesquisas preliminares	No	No
Pilotagem do processo de seleção dos estudos	Yes	No
Triagem formal dos resultados da pesquisa em relação aos critérios de elegibilidade	No	No
Extração de dados	No	No
Avaliação do risco de viés (qualidade)	No	No
Análise de dados	No	No

Forneça qualquer outra informação relevante sobre o estágio da revisão aqui.

Temos o projeto e a metodologia escritos.

We have the project and methodology written.

6. * Contato nomeado.

O contato nomeado é o fiador da exatidão das informações no registro cadastral. Pode ser qualquer membro da equipe de revisão.

Poliana do Carmo Pimenta

Email salutation (e.g. "Dr Smith" or "Joanne") for correspondence:

Poliana

7. * Named contact email.

Give the electronic email address of the named contact.

polianacpimenta@outlook.com

8. Named contact address

Give the full institutional/organisational postal address for the named contact.

St Ana Clepf, 95, Zip Code 37.036-650, City: Varginha, State: Minas Gerais. Country: Brazil.

9. Named contact phone number.

Give the telephone number for the named contact, including international dialling code.

+5535997517537

10. * Organisational affiliation of the review.

Full title of the organisational affiliations for this review and website address if available. This field may be completed as 'None' if the review is not affiliated to any organisation.

UNIFAL - Universidade Federal de Alfenas

Organisation web address:

https://www.unifal-mg.edu.br/ppgcb/

livia.paranaiba@unifal-mg.edu.br

11. * Review team members and their organisational affiliations.

Give the personal details and the organisational affiliations of each member of the review team. Affiliation refers to groups or organisations to which review team members belong.
NOTE: email and country now MUST be entered for each person, unless you are amending a published record.

Miss Poliana do Carmo Pimenta. UNIFAL
Dr Livia Maris Ribeiro Paranaiba Dias. UNIFAL
Miss Vitoria Gabriele Souza Geraldine. UNIFAL
Miss Thais Cristina Aquino Lima. UNIFAL
Mrs Fillipe Silva Tourinho. UNIFAL
Dr Murilo César Nascimento. UNIFAL
Dr Rômulo Dias Novaes. UNIFAL

12. * Funding sources/sponsors.

Details of the individuals, organizations, groups, companies or other legal entities who have funded or sponsored the review.

None

Grant number(s)

State the funder, grant or award number and the date of award

13. * Conflicts of interest.

List actual or perceived conflicts of interest (financial or academic).

None

14. Collaborators.

Give the name and affiliation of any individuals or organisations who are working on the review but who are not listed as review team members. **NOTE: email and country must be completed for each person, unless you are amending a published record.**

15. * Review question.

State the review question(s) clearly and precisely. It may be appropriate to break very broad questions down into a series of related more specific questions. Questions may be framed or refined using PI(E)COS or similar where relevant.

Our guiding question was structured considering the PICO (P= Problem, I= Intervention, C= Comparison and O= outcome) strategy. Thus, the following guiding question was adopted in this review: Do people who received the COVID-19 vaccine in developing countries have different incidence rates of adverse events compared to people vaccinated in developed countries?

16. * Searches.

State the sources that will be searched (e.g. Medline). Give the search dates, and any restrictions (e.g. language or publication date). Do NOT enter the full search strategy (it may be provided as a link or attachment below.)

Sources: PubMed/MEDLINE, EMBASE, Scopus and Web of Science.

Inclusion:

(i) Primary studies reporting adverse events post-COVID-19 vaccination in developed or developing countries, (ii) randomized clinical trials, (iii) indexed studies, (iv) studies available in full-text, (vi) studies reporting incidence proportion, risk or cumulative incidence based on: (a) the number of post-vaccination adverse events (PVAE) divided by the number of vaccine doses administered; and/or (b) the number of post-vaccination adverse event reports (number of notifications) divided by the number of vaccine doses administered.

Additional search strategy information can be found in the attached PDF document (link provided below).

17. URL to search strategy.

Upload a file with your search strategy, or an example of a search strategy for a specific database, (including the keywords) in pdf or word format. In doing so you are consenting to the file being made publicly accessible. Or provide a URL or link to the strategy. Do NOT provide links to your search **results**.

https://www.crd.york.ac.uk/PROSPEROFILES/339632_STRATEGY_20220614.pdf

Alternatively, upload your search strategy to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

Do not make this file publicly available until the review is complete

18. * Condition or domain being studied.

Give a short description of the disease, condition or healthcare domain being studied in your systematic review.

The adverse effects of COVID-19 vaccines around the world.

19. * Participants/population.

Specify the participants or populations being studied in the review. The preferred format includes details of both inclusion and exclusion criteria.

Inclusion: People who have had adverse effects from vaccination against COVID-19 in developed countries and developing countries; Adolescents (under 18 years of age); People who had no adverse effects.

Exclusion: [illegible]

20. * Intervention(s), exposure(s).

Give full and clear descriptions or definitions of the interventions or the exposures to be reviewed. The preferred format includes details of both inclusion and exclusion criteria.

Considering the relevance of vaccination to limit the transmission, morbidity and mortality rates caused by COVID-19, as well as the influence of population characteristics on the response to immunization, but all vaccines have the risk of adverses effects, which is any unfavorable medical occurrence after the vaccination, and need not be causally related to the use of the immunizer. Can affect healthy people and need to be promptly identified.

21. * Comparator(s)/control.

Where relevant, give details of the alternatives against which the intervention/exposure will be compared (e.g. another intervention or a non-exposed control group). The preferred format includes details of both inclusion and exclusion criteria.

Adverse effects of COVID-19 immunizing in people from developed countries in comparison with developing countries.

22. * Types of study to be included.

Give details of the study designs (e.g. RCT) that are eligible for inclusion in the review. The preferred format includes both inclusion and exclusion criteria. If there are no restrictions on the types of study, this should be stated.

(i) Primary studies reporting adverse events post-COVID-19 vaccination in developed or developing countries, (ii) randomized clinical trials, (iii) indexed studies, (iv) studies available in full-text, (vi) studies reporting incidence proportion, risk or cumulative incidence based on: (a) the number of post-vaccination adverse events (PVAE) divided by the number of vaccine doses administered; and/or (b) the number of post-vaccination adverse event reports (number of notifications) divided by the number of vaccine doses administered.

23. Context.

Give summary details of the setting or other relevant characteristics, which help define the inclusion or

exclusion criteria.

24. * Main outcome(s).

Give the pre-specified main (most important) outcomes of the review, including details of how the outcome is defined and measured and when these measurement are made, if these are part of the review inclusion criteria.

Association of the Incidence of adverses effects due to vaccines against COVID-19 with sociodemographic, [illegible] and in developing countries.

Measures of effect

Please specify the effect measure(s) for you main outcome(s) e.g. relative risks, odds ratios, risk difference, and/or 'number needed to treat.

Relative risk (RR) and/or hazard ratio (HR) and/or odds ratio (OR) - for comparison of incidence.

25. * Additional outcome(s).

List the pre-specified additional outcomes of the review, with a similar level of detail to that required for main outcomes. Where there are no additional outcomes please state 'None' or 'Not applicable' as appropriate to the review

None.

Measures of effect

Please specify the effect measure(s) for you additional outcome(s) e.g. relative risks, odds ratios, risk difference, and/or 'number needed to treat.

Not applicable.

26. * Data extraction (selection and coding).

Describe how studies will be selected for inclusion. State what data will be extracted or obtained. State how this will be done and recorded.

To ensure consistency of research results, outcomes of interest were extracted by 2 independent researchers. The objective data extraction was operationalized from collection masks contemplating the following characteristics of the selected studies: (i) general characteristics of publication (author, year and country where the study was developed), (ii) vaccination protocol (vaccine type, dose, site, route and frequency of administration), (iii) incidence of adverse effects after vaccination. The classification of studies carried out in developed and developing countries was established according to the criteria described by the United Nations Organization.

27. * Risk of bias (quality) assessment.

State which characteristics of the studies will be assessed and/or any formal risk of bias/quality assessment tools that will be used.

The Downs & Black checklist was used to verify the reporting quality and potential risk of bias in all studies reviewed. This methodological tool is based on 27 questions stratified into five categories as follows: (i) the reporting quality, (ii) the external validity, (iii) the bias, (iv) the confounding, and (v) the statistical power. This scale presented high test-retest reliability (r= 0.88) and internal consistency (KR20 formula= 0.89). Due to previous recommendations and high ambiguity, question 27 (statistical power) was not applied. The overall result obtained from the Downs and Black checklist was graphically expressed, and the average score was calculated. Considering the qualitative nature of the D&B checklist, the Jadad Scale was used to complement the risk of bias assessment and estimates study quality. This scale evaluates, independently, the quality and risk of bias of each study. It was used and, through questions that assess the following aspects of the study: randomization, blinding and description of segment losses was given a score from 0 to 5 to each of them.

28. * Strategy for data synthesis.

Describe the methods you plan to use to synthesise data. This **must not be generic text** but should be **specific to your review** and describe how the proposed approach will be applied to your data. If meta-analysis is planned, describe the models to be used, methods to explore statistical heterogeneity, and software package to be used.

Relative risk for factors associated with the incidence of adverse events after COVID-19 vaccination (for longitudinal studies)

Odds ratio for factors associated with the incidence of adverse events after COVID-19 vaccination (for cross-sectional studies)

We will express the relative risks (RR) with 95% confidence intervals (CI) of the outcome measures for studies.

We will do meta-analyses using a random-effects model or fixed-effect model, according to the heterogeneity across the studies

We will use R Software.

29. * Analysis of subgroups or subsets.

State any planned investigation of 'subgroups'. Be clear and specific about which type of study or participant will be included in each group or covariate investigated. State the planned analytic approach.

If there is sufficient scientific production, we intend to analyze according to sociodemographic, economic, cultural and health (and/or development status) aspects of the countries.

30. * Type and method of review.

Select the type of review, review method and health area from the lists below.

Type of review

Cost effectiveness
No

Diagnostic
No

Epidemiologic
Yes

Individual patient data (IPD) meta-analysis
No

Intervention
No

Living systematic review
No

Meta-analysis
Yes

Methodology
No

Narrative synthesis
No

Network meta-analysis
No

Pre-clinical
No

Prevention
No

Prognostic
No

Prospective meta-analysis (PMA)
No

Review of reviews
No

Service delivery
No

Synthesis of qualitative studies
No

Systematic review

Yes

Other

No

Health area of the review

Alcohol/substance misuse/abuse

No

Blood and immune system

No

Cancer

No

Cardiovascular

No

Care of the elderly

No

Child health

No

Complementary therapies

No

COVID-19

Yes

For COVID-19 registrations please tick all categories that apply. Doing so will enable your record to appear in area-specific searches

Chinese medicine
Diagnosis
Epidemiological
Genetics
Health impacts
Immunity
Long COVID
Mental health
PPE
Prognosis
Public health intervention
Rehabilitation
Service delivery
Transmission
Treatments
Vaccines
Other

Crime and justice
No

Dental
No

Digestive system
No

Ear, nose and throat
No

Education
No

Endocrine and metabolic disorders
No

Eye disorders
No

General interest
No

Genetics
No

Health inequalities/health equity
No

Infections and infestations
Yes

International development
No

Mental health and behavioural conditions
No

Musculoskeletal
No

Neurological
No

Nursing
No

Obstetrics and gynaecology
No

Oral health
No

Palliative care
No

Perioperative care
No

Physiotherapy
No

Pregnancy and childbirth
No

Public health (including social determinants of health)
Yes

Rehabilitation
No

Respiratory disorders
No

Service delivery
No

Skin disorders
No

Social care
No

Surgery
No

Tropical Medicine
No

Urological
No

Wounds, injuries and accidents
No

Violence and abuse
No

31. Language.

Select each language individually to add it to the list below, use the bin icon to remove any added in error.
English

There is not an English language summary

32. * Country.

Select the country in which the review is being carried out. For multi-national collaborations select all the countries involved.

Brazil

33. Other registration details.

Name any other organisation where the systematic review title or protocol is registered (e.g. Campbell, or The Joanna Briggs Institute) together with any unique identification number assigned by them. If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here. If none, leave blank.

34. Reference and/or URL for published protocol.

If the protocol for this review is published provide details (authors, title and journal details, preferably in Vancouver format)

Add web link to the published protocol.

Or, upload your published protocol here in pdf format. Note that the upload will be publicly accessible.

No I do not make this file publicly available until the review is complete

Please note that the information required in the PROSPERO registration form must be completed in full even if access to a protocol is given.

35. Dissemination plans.

Do you intend to publish the review on completion?

Yes

Give brief details of plans for communicating review findings.?

This article intends to be published in some website/journal.

36. Keywords.

Give words or phrases that best describe the review. Separate keywords with a semicolon or new line. Keywords help PROSPERO users find your review (keywords do not appear in the public record but are included in searches). Be as specific and precise as possible. Avoid acronyms and abbreviations unless these are in wide use.

Side effects; Immunization; Histopathology; SARS-CoV-2; Viral disease

37. Details of any existing review of the same topic by the same authors.

If you are registering an update of an existing review give details of the earlier versions and include a full bibliographic reference, if available.

38. * Current review status.

Update review status when the review is completed and when it is published.New registrations must be ongoing so this field is not editable for initial submission.

Please provide anticipated publication date

Review_Ongoing

39. Any additional information.

Provide any other information relevant to the registration of this review.

40. Details of final report/publication(s) or preprints if available.

Leave empty until publication details are available OR you have a link to a preprint (NOTE: this field is not editable for initial submission). List authors, title and journal details preferably in Vancouver format.

Give the link to the published review or preprint.

Table S1. Complete search strategy with search filters and number of studies recovered in databases PubMed-Medline, Embase and Scopus.

PubMed-MEDLINE – Search filters	***Records***
#1 Disease: (“COVID-19”[MeSH Terms] OR “SARS-CoV-2”[MeSH Terms] OR “COVID-19”[TIAB] OR “SARS-CoV-2”[TIAB])	**269,318**
#2 Intervention: (“Vaccination”[MeSH Terms] OR “Vaccines”[MeSH Terms] OR “Vaccin*”[TIAB] OR “COVID-19 vaccines”[MeSH Terms] OR “COVID-19 vaccin*”[TIAB] OR “BNT162 vaccine”[MeSH Terms] OR “BNT162 vaccin*”[TIAB] OR “SARS-CoV-2 inactivated vaccin*”[TIAB] OR “2019-nCoV Vaccine mRNA-1273”[MeSH Terms] OR “2019-nCoV Vaccine mRNA-1273”[TIAB] OR “Vaccines, Inactivated”[MeSH Terms] OR “Inactivated Vaccin*”[TIAB] OR “SARS-CoV-2 inactivated vaccin*”[TIAB] OR “Viral Vaccines”[MeSH Terms] OR “Viral vaccin*”[TIAB] OR “Gam-COVID-Vac vaccin*”[TIAB] OR “Ad26COVS1”[MeSH Terms] OR “Ad26COVS1”[TIAB] OR “Ad5-nCoV vaccine”[TIAB] OR “ChAdOx1 nCoV-19”[MeSH Terms] OR “ChAdOx1 nCoV-19”[TIAB] OR “Immunogenicity, Vaccine”[MeSH Terms] OR “Vaccine Immunogenicity”[TIAB] OR “Non-replicating vaccin*”[TIAB] OR “mRNA vaccin*”[TIAB])	**448,924**
#3 Outcomes: (“Safety”[MeSH Terms] OR “Safety”[TIAB] OR “Side effect*”[TIAB] OR “Adverse event*”[TIAB] OR “Adverse effect*”[TIAB] OR “Adverse Reaction*”[TIAB] OR “Adverse Response*”[TIAB] OR “Toxicity”[TIAB])	**1,553,163**
#4 Combined search: (#1 AND #2 AND #3)	**6,327**
#5 Randomized Controlled Trial	**142**

**Database search was concluded in July 14, 2021 at 02:30 p.m.*

Table S1 (*continuation*). Complete search strategy with search filters and number of studies recovered in databases PubMed-Medline, Embase and Scopus.

Embase – Search filters	***Records***
#1 Disease: (COVID-19:de,ab,ti OR SARS-CoV-2:de,ab,ti)	**274,243**
#2 Intervention (exercise): (Vaccine:de,ab,ti OR COVID-19 vaccine:de,ab,ti OR BNT162 vaccine:de,ab,ti OR SARS-CoV-2 inactivated vaccine:de,ab,ti OR 2019-nCoV Vaccine mRNA-1273:de,ab,ti OR Inactivated Vaccine:de,ab,ti OR SARS-CoV-2 inactivated vaccine:de,ab,ti OR Viral vaccine:de,ab,ti OR Gam-COVID-Vac vaccine:de,ab,ti OR Ad26COVS1:de,ab,ti OR Ad5-nCoV vaccine:de,ab,ti OR ChAdOx1 nCoV-19:de,ab,ti OR Vaccine Immunogenicity:de,ab,ti OR Non-replicating vaccine:de,ab,ti OR mRNA vaccine:de,ab,ti)	**54,556**
#3 Outcomes: (Safety:de,ab,ti OR Side effects:de,ab,ti OR Adverse events:de,ab,ti OR Adverse effects:de,ab,ti OR Adverse Reactions:de,ab,ti OR Adverse Responses:de,ab,ti)	**85,744**
#4 Combined search: #1 AND #2 AND #3	**367**
#5 Search limit (Sources): Embase	**107**

**Database search was concluded in July 14, 2021 at 02:40 p.m.*

Table S1 (*continuation*). Complete search strategy with search filters and number of studies recovered in databases PubMed-Medline, Embase and Scopus.

SCOPUS – *Search filters*	***Records***
#1 Disease: (TITLE-ABS-KEY(“COVID-19”) OR TITLE-ABS-KEY(“SARS-CoV-2”))	**348,667**
#2 Intervention (exercise): (TITLE-ABS-KEY(“Vaccine”) OR TITLE-ABS-KEY(“COVID-19 vaccine”) OR TITLE-ABS-KEY(“BNT162 vaccine”) OR TITLE-ABS-KEY(“SARS-CoV-2 inactivated vaccine”) OR TITLE-ABS-KEY(“2019-nCoV Vaccine mRNA-1273”) OR TITLE-ABS-KEY(“Inactivated Vaccine”) OR TITLE-ABS-KEY(“SARS-CoV-2 inactivated vaccine”) OR TITLE-ABS-KEY(“Viral vaccine”) OR TITLE-ABS-KEY(“Gam-COVID-Vac vaccine”) OR TITLE-ABS-KEY(“Ad26COVS1”) OR TITLE-ABS-KEY(“Ad5-nCoV vaccine”) OR TITLE-ABS-KEY(“ChAdOx1 nCoV-19”) OR TITLE-ABS-KEY(“Vaccine Immunogenicity”) OR TITLE-ABS-KEY(“Non-replicating vaccine”) OR TITLE-ABS-KEY(“mRNA vaccine”))	**486,685**
#3 Outcomes: (TITLE-ABS-KEY(“Safety”) OR TITLE-ABS-KEY(“Side effects”) OR TITLE-ABS-KEY(“Adverse events”) OR TITLE-ABS-KEY(“Adverse effects”) OR TITLE-ABS-KEY(“Adverse Reactions”) OR TITLE-ABS-KEY(“Adverse Responses”))	**2,789,917**
#4 Search limit: NOT INDEX (medline)	**2,253**
#5 Search limit (Keywords - limit to): Adverse events, Articles	**536**
#6 Combined search: #1 AND #2 AND #3 AND #4 AND #5	**536**

**Database search was concluded in July 14, 2021 at 03:00 p.m.*

(TITLE-ABS-KEY ("COVID-19") OR TITLE-ABS-KEY ("SARS-CoV-2")) AND (TITLE-ABS-KEY ("Vaccine") OR TITLE-ABS-KEY ("COVID-19 vaccine") OR TITLE-ABS-KEY ("BNT162 vaccine") OR TITLE-ABS-KEY ("SARS-CoV-2 inactivated vaccine") OR TITLE-ABS-KEY ("2019-nCoV Vaccine mRNA-1273") OR

TITLE-ABS-KEY ("Inactivated Vaccine") OR TITLE-ABS-KEY ("SARS-CoV-2 inactivated vaccine") OR TITLE-ABS-KEY ("Viral vaccine") OR TITLE-ABS-KEY ("Gam-COVID-Vac vaccine") OR TITLE-ABS-KEY ("Ad26COVS1") OR TITLE-ABS-KEY ("Ad5-nCoV vaccine") OR TITLE-ABS-KEY ("ChAdOx1 nCoV-19") OR TITLE-ABS-KEY ("Vaccine Immunogenicity") OR TITLE-ABS-KEY ("Non-replicating vaccine") OR TITLE-ABS-KEY ("mRNA vaccine")) AND (TITLE-ABS-KEY ("Safety") OR TITLE-ABS-KEY ("Side effects") OR TITLE-ABS-KEY ("Adverse events") OR TITLE-ABS-KEY ("Adverse effects") OR TITLE-ABS-KEY ("Adverse Reactions") OR TITLE-ABS-KEY ("Adverse Responses")) not INDEX (medline) AND (LIMIT-TO (DOCTYPE , "ar")) AND (LIMIT-TO (EXACTKEYWORD , "Adverse Event"))

Table S2. Results from the PRISMA-based study selection used to quantify Cohen's *kappa coefficient* (κ) to measure inter-rater reliability of the search strategy.

Kappa calculation		**Researcher 2**	
		Paper included	**Paper excluded**
Researcher 1	**Paper included**	**11**	**32**
	Paper excluded	**20**	**686**

Statistical calculator: https://www.graphpad.com/quickcalcs/kappa1/

Statistical results:

Number of observed agreements: 697 (93.06% of the observations).

Number of agreements expected by chance: 584.5 (78.04% of the observations)

Kappa= 0.684

SE of kappa = 0.041

95% confidence interval: From 0.604 to 0.764

One way to interpret kappa is with this scale (1):

Kappa < 0: No agreement

Kappa between 0.00 and 0.20: Slight agreement

Kappa between 0.21 and 0.40: Fair agreement

Kappa between 0.41 and 0.60: Moderate agreement

Kappa between 0.61 and 0.80: Substantial agreement

Kappa between 0.81 and 1.00: Almost perfect agreement.

Complete list of papers selected and included in the systematic review

1. Masuda T, Murakami K, Sugiura K, Sakui S, Philip Schuring R, Mori M. A phase 1/2 randomised placebo-controlled study of the COVID-19 vaccine mRNA-1273 in healthy Japanese adults: An interim report. Vaccine. 2022 Mar 18;40(13):2044-2052. doi: 10.1016/j.vaccine.2022.02.030. Epub 2022 Feb 8. PMID: 35177302; PMCID: PMC8824367.
2. Chu L, McPhee R, Huang W, Bennett H, Pajon R, Nestorova B, Leav B; mRNA-1273 Study Group. A preliminary report of a randomized controlled phase 2 trial of the safety and immunogenicity of mRNA-1273 SARS-CoV-2 vaccine. Vaccine. 2021 May 12;39(20):2791-2799. doi: 10.1016/j.vaccine.2021.02.007. Epub 2021 Feb 9. PMID: 33707061; PMCID: PMC7871769.
3. Sadoff J, Le Gars M, Shukarev G, Heerwegh D, Truyers C, de Groot AM, Stoop J, Tete S, Van Damme W, Leroux-Roels I, Berghmans PJ, Kimmel M, Van Damme P, de Hoon J, Smith W, Stephenson KE, De Rosa SC, Cohen KW, McElrath MJ, Cormier E, Scheper G, Barouch DH, Hendriks J, Struyf F, Douoguih M, Van Hoof J, Schuitemaker H. Interim Results of a Phase 1-2a Trial of Ad26.COV2.S Covid-19 Vaccine. N Engl J Med. 2021 May 13;384(19):1824-1835. doi: 10.1056/NEJMoa2034201. Epub 2021 Jan 13. PMID: 33440088; PMCID: PMC7821985.
4. Zhu FC, Guan XH, Li YH, Huang JY, Jiang T, Hou LH, Li JX, Yang BF, Wang L, Wang WJ, Wu SP, Wang Z, Wu XH, Xu JJ, Zhang Z, Jia SY, Wang BS, Hu Y, Liu JJ, Zhang J, Qian XA, Li Q, Pan HX, Jiang HD, Deng P, Gou JB, Wang XW, Wang XH, Chen W. Immunogenicity and safety of a recombinant adenovirus type-5-vectored COVID-19 vaccine in healthy adults aged 18 years or older: a randomised, double-blind, placebo-controlled, phase 2 trial. Lancet. 2020 Aug 15;396(10249):479-488. doi: 10.1016/S0140-6736(20)31605-6. Epub 2020 Jul 20. PMID: 32702299; PMCID: PMC7836858.
5. Madhi SA, Moodley D, Hanley S, Archary M, Hoosain Z, Lalloo U, Louw C, Fairlie L, Fouche LF, Masilela MSL, Singh N, Grobbelaar C, Ahmed K, Benadé G, Bhikha S, Bhorat AE, Bhorat Q, Joseph N, Dheda K, Esmail A, Foulkes S, Goga A, Oommen Jose A, Kruger G, Kalonji DJ, Lalloo N, Lombaard JJ, Lombard Koen A, Kany Luabeya A, Mngqibisa R, Petrick FG, Pitsi A, Tameris M, Thombrayil A,

Vollgraaff PL, Cloney-Clark S, Zhu M, Bennett C, Albert G, Faust E, Plested JS, Fries L, Robertson A, Neal S, Cho I, Glenn GM, Shinde V; 2019nCoV-501 Study Group. Immunogenicity and safety of a SARS-CoV-2 recombinant spike protein nanoparticle vaccine in people living with and without HIV-1 infection: a randomised, controlled, phase 2A/2B trial. Lancet HIV. 2022 May;9(5):e309-e322. doi: 10.1016/S2352-3018(22)00041-8. PMID: 35489376; PMCID: PMC9045746.

6. Asano M, Okada H, Itoh Y, Hirata H, Ishikawa K, Yoshida E, Matsui A, Kelly EJ, Shoemaker K, Olsson U, Vekemans J. Immunogenicity and safety of AZD1222 (ChAdOx1 nCoV-19) against SARS-CoV-2 in Japan: a double-blind, randomized controlled phase 1/2 trial. Int J Infect Dis. 2022 Jan;114:165-174. doi: 10.1016/j.ijid.2021.10.030. Epub 2021 Oct 22. PMID: 34688944; PMCID: PMC8531242.

7. Taisei Masuda, Kyoko Murakami, Kenkichi Sugiura, Sho Sakui, Ron P Schuring, Mitsuhiro Mori. Safety and immunogenicity of NVX-CoV2373 (TAK-019) vaccine in healthy Japanese adults: Interim report of a phase I/II randomized controlled trial. Vaccine 40 (2022) 3380–3388. doi: https://doi.org/10.1016/j.vaccine.2022.04.035.

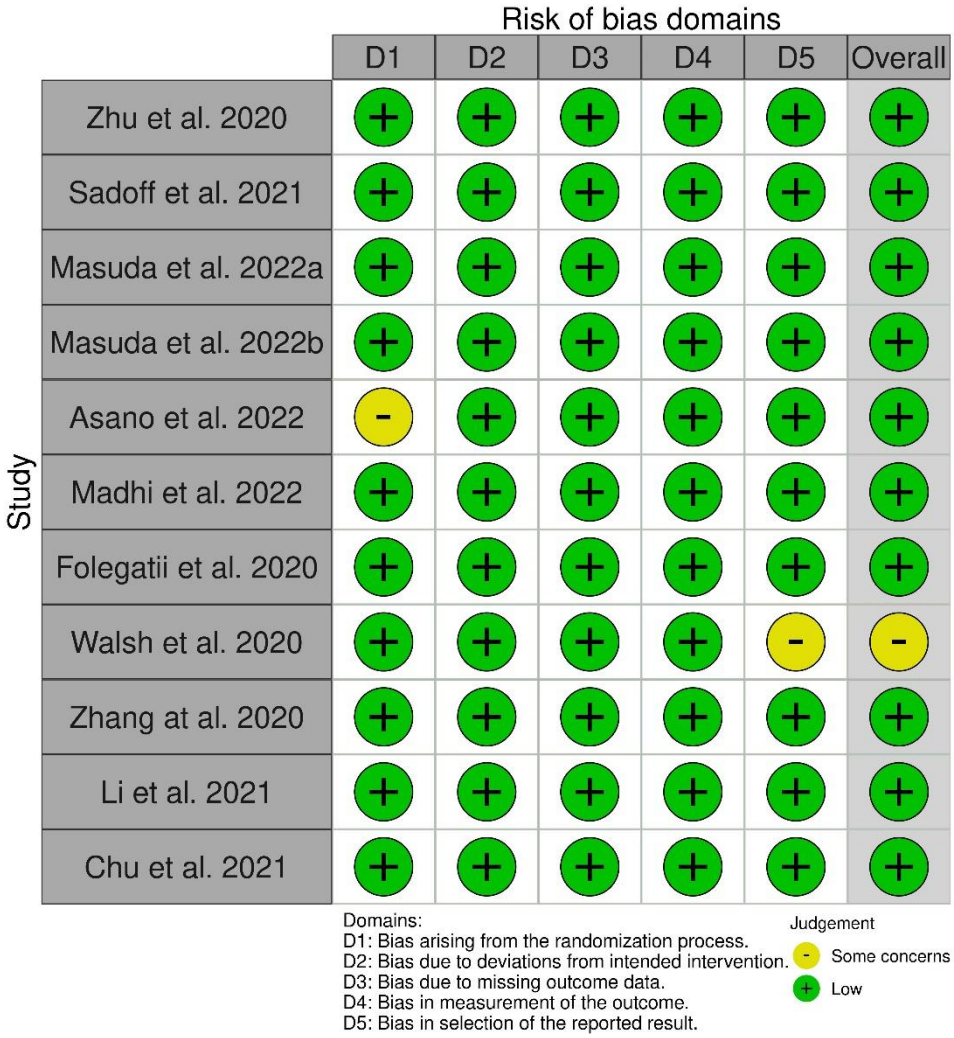
8. Folegatti PM, Ewer KJ, Aley PK, Angus B, Becker S, Belij-Rammerstorfer S, Bellamy D, Bibi S, Bittaye M, Clutterbuck EA, Dold C, Faust SN, Finn A, Flaxman AL, Hallis B, Heath P, Jenkin D, Lazarus R, Makinson R, Minassian AM, Pollock KM, Ramasamy M, Robinson H, Snape M, Tarrant R, Voysey M, Green C, Douglas AD, Hill AVS, Lambe T, Gilbert SC, Pollard AJ; Oxford COVID Vaccine Trial Group. Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial. Lancet. 2020 Aug 15;396(10249):467-478. doi: 10.1016/S0140-6736(20)31604-4. Epub 2020 Jul 20. Erratum in: Lancet. 2020 Aug 15;396(10249):466. Erratum in: Lancet. 2020 Dec 12;396(10266):1884. PMID: 32702298; PMCID: PMC7445431.

9. Li, J., Hui, A., Zhang, X. et al. Safety and immunogenicity of the SARS-CoV-2 BNT162b1 mRNA vaccine in younger and older Chinese adults: a randomized, placebo-controlled, double-blind phase 1 study. Nat Med 27, 1062–1070 (2021). https://doi.org/10.1038/s41591-021-01330-9.

10. Walsh EE, Frenck RW Jr, Falsey AR, Kitchin N, Absalon J, Gurtman A, Lockhart S, Neuzil K, Mulligan MJ, Bailey R, Swanson KA, Li P, Koury K, Kalina W, Cooper D, Fontes-Garfias C, Shi PY, Türeci Ö, Tompkins KR, Lyke KE, Raabe V, Dormitzer PR, Jansen KU, Şahin U, Gruber WC. Safety and Immunogenicity of Two RNA-Based Covid-19 Vaccine Candidates. N Engl J Med. 2020 Dec 17;383(25):2439-2450. doi: 10.1056/NEJMoa2027906. Epub 2020 Oct 14. PMID: 33053279; PMCID: PMC7583697.
11. Yanjun Zhang, Gang Zeng, Hongxing Pan, Changgui Li, Yaling Hu, Kai Chu, Weixiao Han, Zhen Chen, Rong Tang, Weidong Yin, Xin Chen, Yuansheng Hu, Xiaoyong Liu, Congbing Jiang, Jingxin Li, Minnan Yang, Yan Song, Xiangxi Wang, Qiang Gao, Fengcai Zhu. Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine in healthy adults aged 18–59 years: a randomised, double-blind, placebo-controlled, phase 1/2 clinical trial. Lancet. 2021 February; 21:181-192. doi: https://doi.org/10.1016/S1473-3099(20)30843-4.

Graphical representation of the result of the risk of bias assessment (robvis)[5]

Traffic Light Plot



Summary Plot

[5] McGuinness, LA, Higgins, JPT. VISualização de risco de viés (robvis): Um pacote R e um aplicativo Web Shiny para visualizar avaliações de risco de viés. Res Syn Metanfetamina. 2020; 1- 7. https://doi.org/10.1002/jrsm.1411

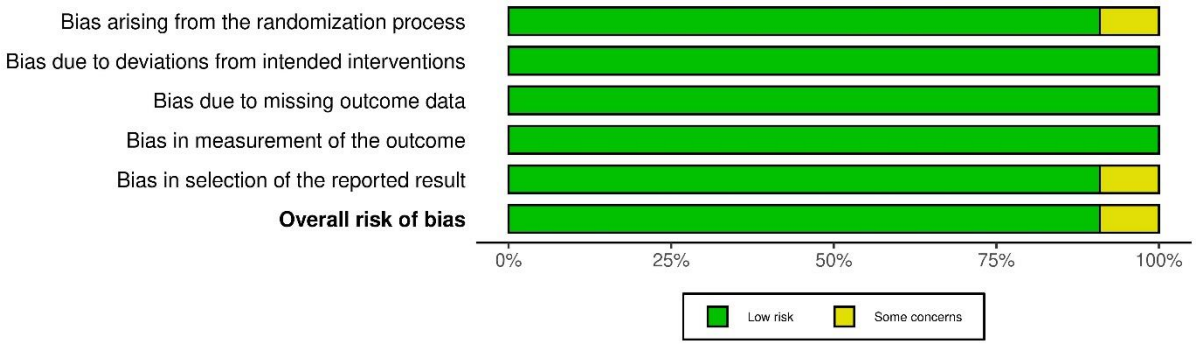
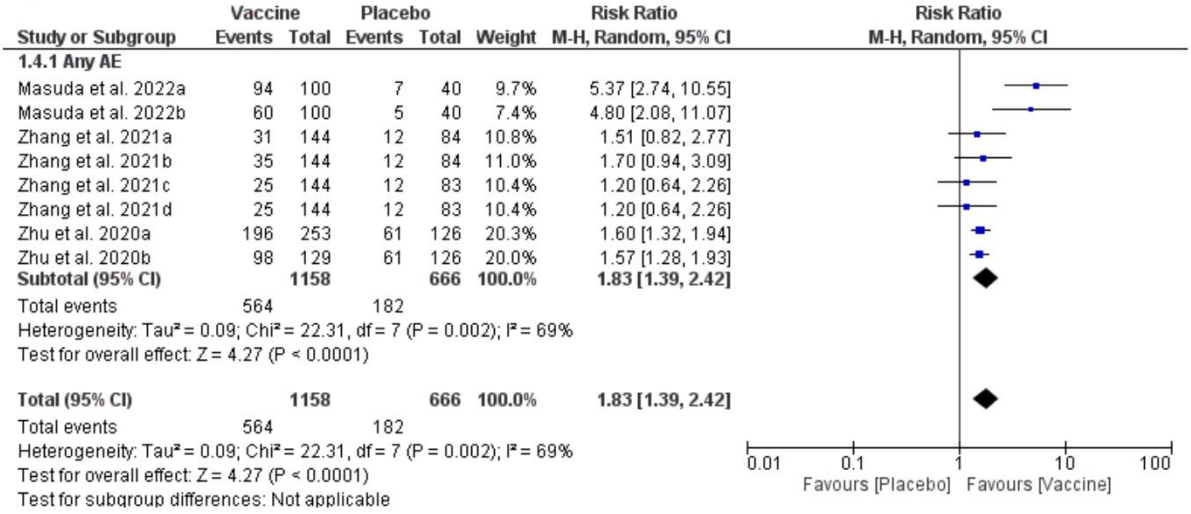
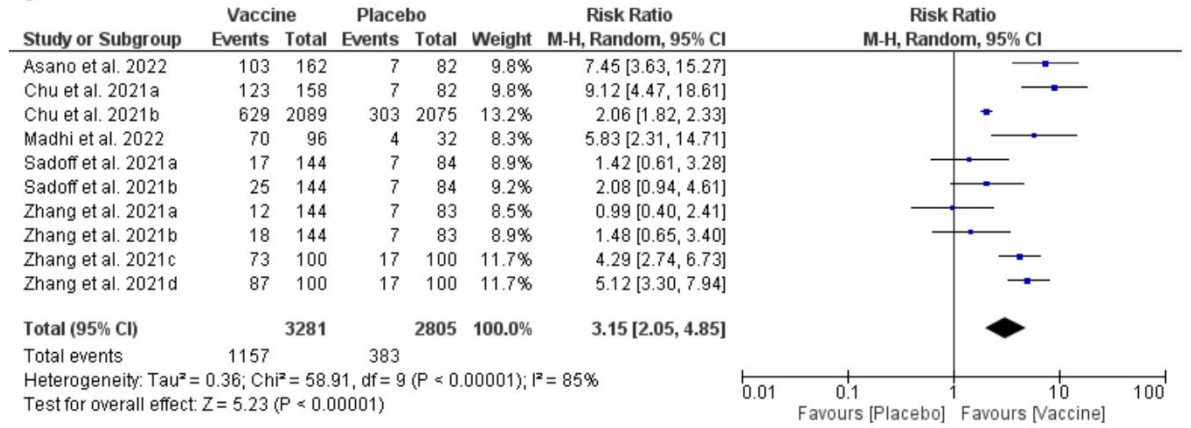

Bias arising from the randomization process
Bias due to deviations from intended interventions
Bias due to missing outcome data
Bias in measurement of the outcome
Bias in selection of the reported result
Overall risk of bias
0%
25%
50%
75%
100%
Low risk
Some concerns

Figure S1. Meta-analysis - dose 1 (a: any; b: local; and c: systemic).

a)



b)



c)

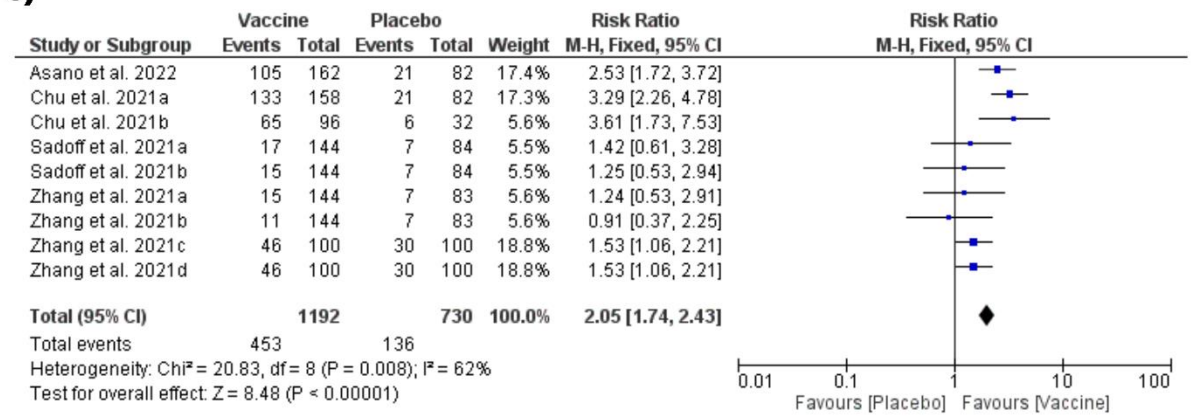
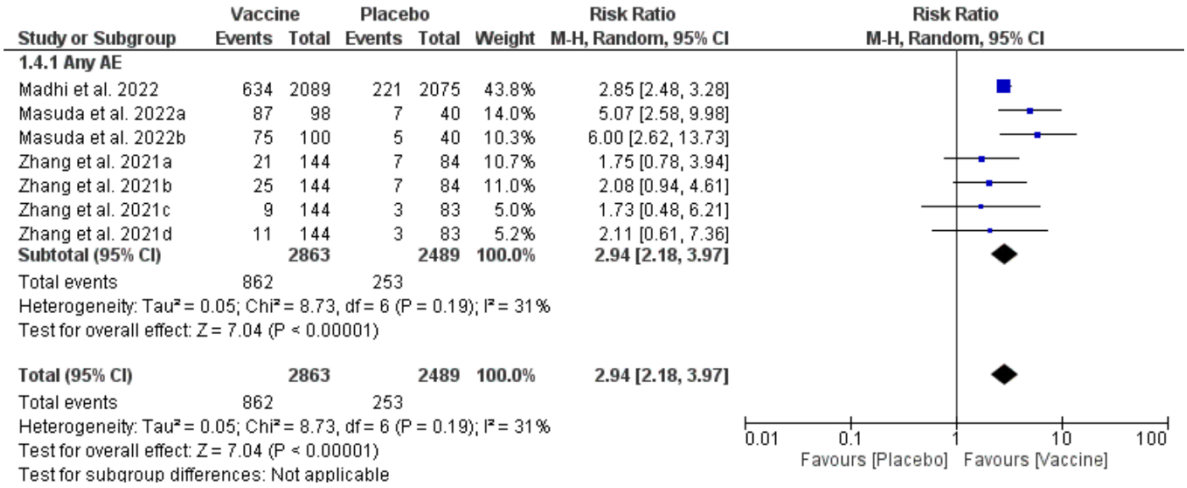
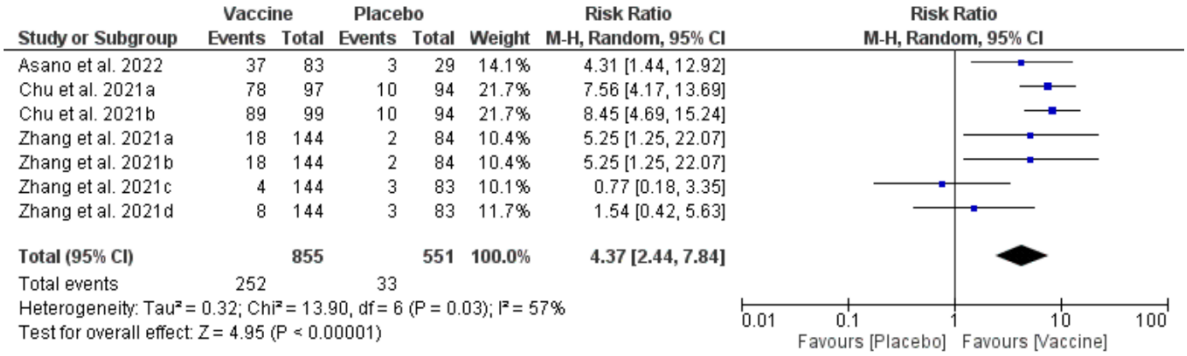


Figure S2. Meta-analysis - dose 2 (a: any; b: local; and c: systemic).

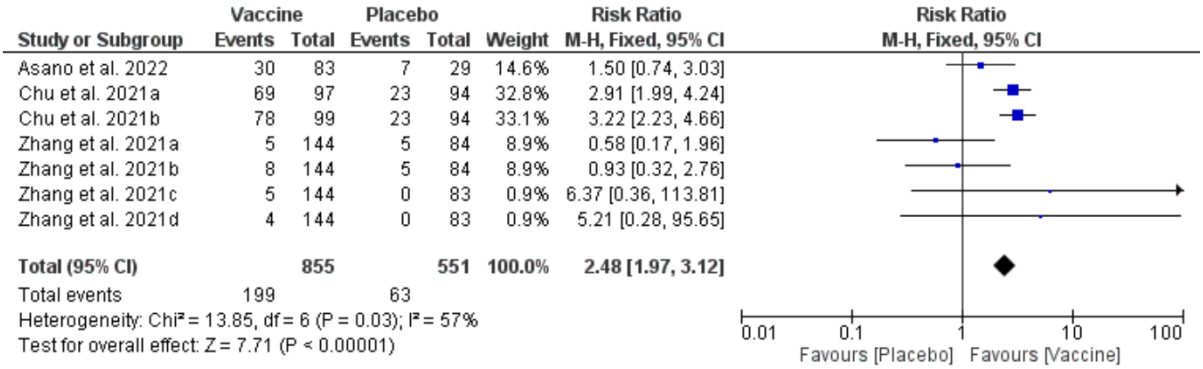
a)



b)



c)



GRADE evidence profile

Author(s): Pimenta PDC, Geraldine VGS, Lima TCA, Tourinho FS, Nascimento MC, Novaes RD, Dias LMRP (Asano et al., 2022, Chu et al., 2021, Folegatti et al., 2020, Li et al., 2021, Madhi et al., 2022, Masuda et al., 2022, Sadoff et al., 2021, Walsh et al., 2020, Zhang et al., 2021, Zhu et al., 2020).

Question: Vaccines compared to Placebo for against COVID-19 in the General Population (1st and 2st doses: developed and developing countries)

Setting: (i) Vaccination (MeSH ID: D014611, National Library of Medicine); (ii) Adverse events (World Health Organization); (iii) Incidence (MeSH ID: D015994, National Library of Medicine); (iv) Developed Countries (United Nations, 2023); (v) Developing Countries (United Nations, 2023).

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Certainty assessment							№ of participants		Risk of ESAVI/COVID-19		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vaccines/COVID-19	Placebos	Relative (95% CI)	Absolute (95% CI)		
Risk of ESAVI/COVID-19 vaccines in developed and developing countries: referring to the 1st doses. (assessed with: RR)												
8	randomised trials	not serious	not serious[a]	not serious	not serious	publication bias strongly suspected[b]	564/1158 (48.7%)	182/666 (27.3%)	**RR 1.83** (1.39 to 2.42)	**22.682 more per 100.000** (from 10.658 more to 38.805 more)	⨁⨁⨁◯ Moderate	NÃO IMPORTANTE

Risk of ESAVI/COVID-19 vaccines in developed and developing countries: referring to the 1st doses) (assessed with: RR)

Certainty assessment							№ of participants		Risk of ESAVI/COVID-19		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vaccines/COVID-19	Placebos	Relative (95% CI)	Absolute (95% CI)		
10	randomised trials	not serious	not serious	not serious	not serious	publication bias strongly suspected strong association[c]	1157/3281 (35.3%)	383/2805 (13.7%)	**RR 3.15** (2.05 to 4.85)	**29.357 more per 100.000** (from 14.337 more to 52.569 more)	⨁⨁⨁⨁ High	NÃO IMPORTANTE

Risk of ESAVI/COVID-19 vaccines in developed and developing countries: referring to the 1st doses (assessed with: RR)

9	randomised trials	not serious	not serious	not serious	not serious	publication bias strongly suspected strong association[d]	453/1192 (38.0%)	136/730 (18.6%)	**RR 2.05** (1.74 to 2.43)	**196 more per 1.000** (from 138 more to 266 more)	⨁⨁⨁⨁ High	NÃO IMPORTANTE

Risk of ESAVI/COVID-19 vaccines in developed and developing countries: referring to the 2st doses. (assessed with: RR)

7	randomised trials	not serious	not serious	not serious	not serious	publication bias strongly suspected strong association[e]	862/2863 (30.1%)	253/2489 (10.2%)	**RR 2.94** (2.18 to 3.97)	**197 more per 1.000** (from 120 more to 302 more)	⨁⨁⨁⨁ High	NÃO IMPORTANTE

Risk of ESAVI/COVID-19 vaccines in developed and developing countries: referring to the 2st doses (assessed with: RR)

7	randomised trials	not serious	not serious	not serious	serious[f]	publication bias strongly suspected strong association[g]	252/855 (29.5%)	33/551 (6.0%)	**RR 4.37** (2.44 to 7.84)	**202 more per 1.000** (from 86 more to 410 more)	⨁⨁⨁◯ Moderate	NÃO IMPORTANTE

Risk of ESAVI/COVID-19 vaccines in developed and developing countries: referring to the 2st doses) (assessed with: RR)

Certainty assessment							№ of participants		Risk of ESAVI/COVID-19		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vaccines/COVID-19	Placebos	Relative (95% CI)	Absolute (95% CI)		
7	randomised trials	not serious	not serious	not serious	serious[h]	publication bias strongly suspected strong association[i]	199/855 (23.3%)	63/551 (11.4%)	**RR 2.48** (1.97 to 3.12)	**169 more per 1.000** (from 111 more to 242 more)	⨁⨁⨁◯ Moderate	NÃO IMPORTANTE

CI: confidence interval; **RR:** risk ratio

Explanations

a. The hypothesis was that the risk of ESAVI/COVID-19 would be higher in developing countries, justified by the demographic, economic, health, epidemiological and care differences they present compared to developed countries.

b, c, d, e, g and i. 1) Statistically significant studies are more likely to be published. 2) Early systematic reviews, which are performed only when few and early studies are available, may overestimate the effect estimate since "negative" studies usually take longer to be published (lag-tme bias). Early studies with positive results should be considered suspect; 3) The empirical assessment of pattern of results (funnel plot).

f and h. Low number of cases among the control group, and more expressive confidence intervals in studies from developing countries.

Summary of findings

Summary of findings:

Vaccines compared to Placebo for against COVID-19 in the General Population (1st and 2st doses: developed and developing countries)

Population: General population of developed and developing countries.

Setting: (i) Vaccination (MeSH ID: D014611, National Library of Medicine); (ii) Adverse events (World Health Organization); (iii) Incidence (MeSH ID: D015994, National Library of Medicine); (iv) Developed Countries (United Nations, 2023); (v) Developing Countries (United Nations, 2023).

Intervention: Administration of the first and second doses of COVID-19 vaccines.

Comparison: Placebo administration instead of first and second doses of COVID-19 vaccines.

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Placebos	**Risk with Vaccines/COVID-19]**				
Risk of ESAVI/COVID-19 vaccines in developed and developing countries: referring to the 1st doses. (Figure 3a: considering all ESAVI, any = local and systemic) assessed with: RR	27.327 per 100.000	**50009 per 100.000** (37.985 to 66.132)	**RR 1.83** (1.39 to 2.42)	1824 (8 RCTs)	⨁⨁⨁◯ Moderate[a,b]	Conclusion: COVID-19 vaccines (1st dose) probably increase the risk of ESAVI/COVID-19 vaccines in developed countries when compared to the risk in developing countries.
Risk of ESAVI/COVID-19 vaccines in developed and developing countries: referring to the 1st doses) (Figure 3b: considering the local ESAVI) assessed with: RR	13.654 per 100.000	**43011 per 100.000** (27.991 to 66.223)	**RR 3.15** (2.05 to 4.85)	6086 (10 RCTs)	⨁⨁⨁⨁ High[c]	Conclusion: COVID-19 vaccines (1st dose) results in a slight increase in risk of ESAVI/COVID-19 vaccines in developed when compared to the risk in developing countries.
Risk of ESAVI/COVID-19 vaccines in developed and developing countries: referring to the 1st doses (Figure 3c: considering the systemic ESAVI) assessed with: RR	186 per 1.000	**382 per 1.000** (324 to 453)	**RR 2.05** (1.74 to 2.43)	1922 (9 RCTs)	⨁⨁⨁⨁ High[d]	Conclusion: COVID-19 vaccines (1st dose) increases risk of ESAVI/COVID-19 vaccines in developed when compared to the risk in developing countries.

Summary of findings:

Vaccines compared to Placebo for against COVID-19 in the General Population (1st and 2st doses: developed and developing countries)

Population: General population of developed and developing countries.

Setting: (i) Vaccination (MeSH ID: D014611, National Library of Medicine); (ii) Adverse events (World Health Organization); (iii) Incidence (MeSH ID: D015994, National Library of Medicine); (iv) Developed Countries (United Nations, 2023); (v) Developing Countries (United Nations, 2023).

Intervention: Administration of the first and second doses of COVID-19 vaccines.

Comparison: Placebo administration instead of first and second doses of COVID-19 vaccines.

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Placebos	**Risk with Vaccines/COVID-19]**				
Risk of ESAVI/COVID-19 vaccines in developed and developing countries: referring to the 2st doses. (Figure 4.a: considering all ESAVI, any = local and systemic) assessed with: RR	102 per 1.000	**299 per 1.000** (222 to 404)	**RR 2.94** (2.18 to 3.97)	5352 (7 RCTs)	⨁⨁⨁⨁ High[e]	Conclusion: COVID-19 vaccines (2st dose) results in a slight increase in risk of ESAVI/COVID-19 vaccines in developed when compared to the risk in developing countries.
Risk of ESAVI/COVID-19 vaccines in developed and developing countries: referring to the 2st doses (Figure 4.b: considering the local ESAVI) assessed with: RR	60 per 1.000	**262 per 1.000** (146 to 470)	**RR 4.37** (2.44 to 7.84)	1406 (7 RCTs)	⨁⨁⨁◯ Moderate[f,g]	Conclusion: COVID-19 vaccines (2st dose) probably results in a large increase in risk of ESAVI/COVID-19 vaccines in developed when compared to the risk in developing countries.
Risk of ESAVI/COVID-19 vaccines in developed and developing countries: referring to the 2st doses) (Figure 4.c: considering the systemic ESAVI) assessed with: RR	114 per 1.000	**284 per 1.000** (225 to 357)	**RR 2.48** (1.97 to 3.12)	1406 (7 RCTs)	⨁⨁⨁◯ Moderate[h,i]	Conclusion: COVID-19 vaccines (2st dose) probably results in an increase in risk of ESAVI/COVID-19 vaccines in developed when compared to the risk in developing countries.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio

Summary of findings:

Vaccines compared to Placebo for against COVID-19 in the General Population (1st and 2st doses: developed and developing countries)

Population: General population of developed and developing countries.

Setting: (i) Vaccination (MeSH ID: D014611, National Library of Medicine); (ii) Adverse events (World Health Organization); (iii) Incidence (MeSH ID: D015994, National Library of Medicine); (iv) Developed Countries (United Nations, 2023); (v) Developing Countries (United Nations, 2023).

Intervention: Administration of the first and second doses of COVID-19 vaccines.

Comparison: Placebo administration instead of first and second doses of COVID-19 vaccines.

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Placebos	**Risk with Vaccines/COVID-19]**				

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

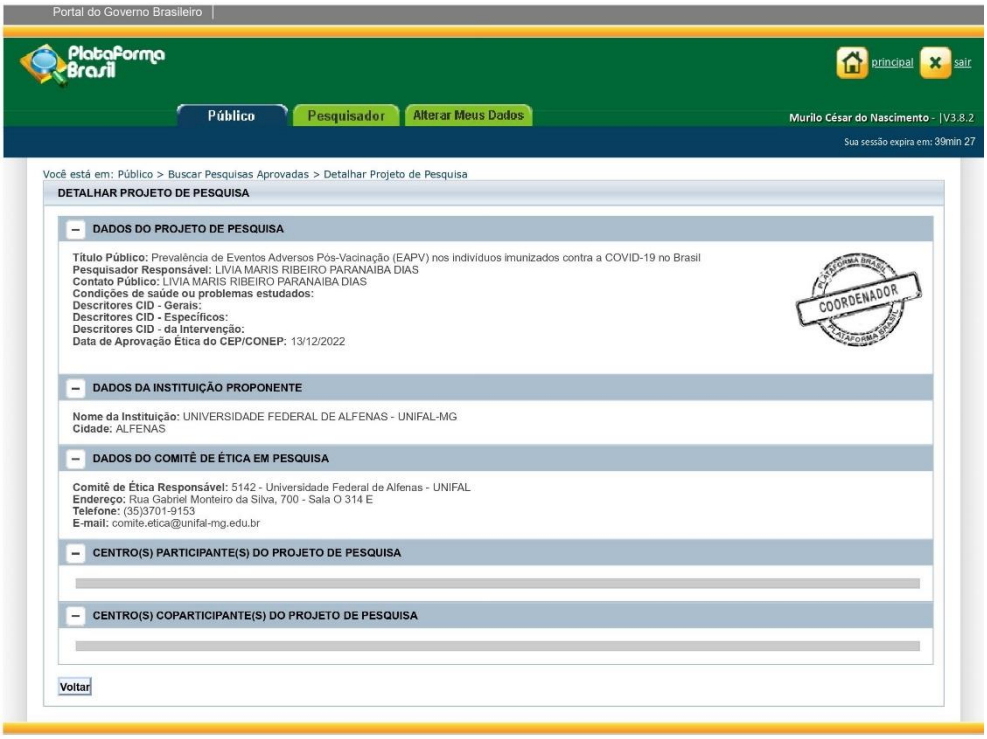
Explanations

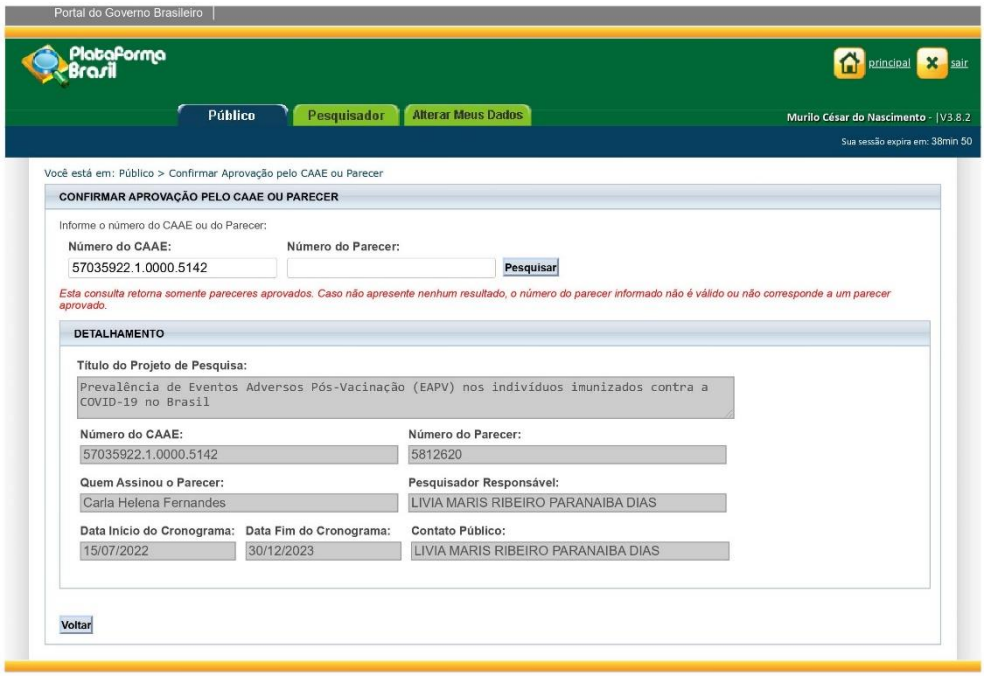
a. The hypothesis was that the risk of ESAVI/COVID-19 would be higher in developing countries, justified by the demographic, economic, health, epidemiological and care differences they present compared to developed countries.

b, c, d, e, g and i. 1) Statistically significant studies are more likely to be published. 2) Early systematic reviews, which are performed only when few and early studies are available, may overestimate the effect estimate since "negative" studies usually take longer to be published (lag-tme bias). Early studies with positive results should be considered suspect; 3) The empirical assessment of pattern of results (funnel plot).

f and h. Low number of cases among the control group, and more expressive confidence intervals in studies from developing countries.

APÊNDICE B - Aprovação do estudo no Comitê de Ética em Pesquisa (CEP) da UNIFAL-MG





UNIVERSIDADE FEDERAL DE ALFENAS

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Prevalência de Eventos Adversos Pós-Vacinação (EAPV) nos indivíduos imunizados contra a COVID-19 no Brasil

Pesquisador: LIVIA MARIS RIBEIRO PARANAIBA DIAS

Área Temática:

Versão: 3

CAAE: 57035922.1.0000.5142

Instituição Proponente: UNIVERSIDADE FEDERAL DE ALFENAS - UNIFAL-MG

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 5.484.975

Apresentação do Projeto:

"Prevalência de Eventos Adversos Pós-Vacinação (EAPV) nos indivíduos imunizados contra a COVID-19 no Brasil", é um projeto de Mestrado, com financiamento próprio, e sem conflitos de interesses declarados dos autores.

O projeto se propões a identificar "a prevalência dos Eventos Adversos Pós Vacinais (EAPV) causados pelos imunizantes Pfizer/BioNTech, Oxford-AstraZeneca,Johnson & Johnson/Janssen e Coronavac, disponíveis para o Ministério da Saúde Brasileiro através da análise das informações contidas em seu banco de dados, desde janeiro de 2021, quando iniciou o uso emergencial autorizado pela Agência Nacional de Vigilância Sanitária (ANVISA), até 25 de dezembro de 2022".

Objetivo da Pesquisa:

a. claros e bem definidos;

b. coerentes com a propositura geral do projeto;

c. exequíveis

Avaliação dos Riscos e Benefícios:

Os riscos de execução do projeto são bem avaliados; realmente inerentes ao projeto, ainda que evitáveis; e estão estão bem descritos no projeto.

Os benefícios oriundos da execução do projeto justificam os riscos corridos, e a propositura para

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minimização dos riscos é adequada.

Comentários e Considerações sobre a Pesquisa:

A Metodologia da pesquisa está adequada aos objetivos do projeto, é atualizada, e acredito ser a melhor disponível, com mínimos riscos aos participantes da pesquisa etc.

O Referencial teórico da pesquisa está atualizado e é suficiente para aquilo que se propõe - Projeto de Mestrado.

o Cronograma de execução da pesquisa é coerente com os objetivos propostos e está adequado ao tempo de tramitação do projeto.

Considerações sobre os Termos de apresentação obrigatória:

a. Termo de Dispensa do Consentimento Livre e Esclarecido (TCLE) – presente e adequado.
b. Termo de Assentimento (TA) – não se aplica
c. Termo de Assentimento Esclarecido (TAE) – não se aplica
d. Termo de Compromisso para Utilização de Dados e Prontuários (TCUD) – não se aplica
e. Termo de Anuência Institucional (TAI) – presente e adequado
f. Folha de rosto - presente e adequado
g. Projeto de pesquisa completo e detalhado - presente e adequado
h. DECLARAÇÃO DE COMPROMISSO – presente e adequado

Conclusões ou Pendências e Lista de Inadequações:

Conclusão:

PENDÊNCIA 1. Corrigir as datas finais de levantamento dos dados entre o Projeto Detalhado (objetivo) e o TERMO DE SOLICITAÇÃO DE DISPENSA DO TCLE que estão com data de dezembro de 2021 e o TAI e o projeto básico com data de 25 de dezembro de 2022.

RESPOSTA: As informações coletadas para este projeto abrangem o período de janeiro a dezembro de 2021. Portanto, a correção foi feita apenas no TAI. Esta correção implicou, secundariamente, na retificação de datas do cronograma geral do projeto (pag. 11 do Projeto detalhado) e do Cronograma de execução na Plataforma Brasil.

PENDÊNCIA ATENDIDA

Recomenda-se aprovação do Protocolo.

minimização dos riscos é adequada.

Comentários e Considerações sobre a Pesquisa:

A Metodologia da pesquisa está adequada aos objetivos do projeto, é atualizada, e acredito ser a melhor disponível, com mínimos riscos aos participantes da pesquisa etc.

O Referencial teórico da pesquisa está atualizado e é suficiente para aquilo que se propõe - Projeto de Mestrado.

o Cronograma de execução da pesquisa é coerente com os objetivos propostos e está adequado ao tempo de tramitação do projeto.

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f. Folha de rosto - presente e adequado
g. Projeto de pesquisa completo e detalhado - presente e adequado
h. DECLARAÇÃO DE COMPROMISSO – presente e adequado

Conclusões ou Pendências e Lista de Inadequações:

Conclusão:

PENDÊNCIA 1. Corrigir as datas finais de levantamento dos dados entre o Projeto Detalhado (objetivo) e o TERMO DE SOLICITAÇÃO DE DISPENSA DO TCLE que estão com data de dezembro de 2021 e o TAI e o projeto básico com data de 25 de dezembro de 2022.

RESPOSTA: As informações coletadas para este projeto abrangem o período de janeiro a dezembro de 2021. Portanto, a correção foi feita apenas no TAI. Esta correção implicou, secundariamente, na retificação de datas do cronograma geral do projeto (pag. 11 do Projeto detalhado) e do Cronograma de execução na Plataforma Brasil.

PENDÊNCIA ATENDIDA

Recomenda-se aprovação do Protocolo.