Review

Immunization as Protection Against Long COVID in the Americas: A Scoping Review

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Review

Immunization as Protection Against Long COVID in the Americas: A Scoping Review

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Abstract: Introduction: Long COVID syndrome is defined as persistent or new symptoms that appear after an acute SARS-CoV-2 infection and last at least three months without explanation. It is estimated that between 10% and 20% of those infected develop long COVID; however, data is not precise in Latin America. Although high immunization rates have reduced acute symptoms and the pandemic's impact, there is a lack of evidence of its efficacy in preventing long COVID in the region. **Methods:** This scoping review followed PRISMA-ScR guidelines. Studies on vaccinated adults with long COVID from Central and South America and the Caribbean were included (Mexico was also considered). A comprehensive search across multiple databases was conducted. Data included study design, participant characteristics, vaccine type, and efficacy outcomes. Results were presented narratively and in tables. **Results:** Out of 3,466 initial records, eight studies met the inclusion criteria after rigorous selection processes. These studies encompassed populations from Brazil, Mexico, Latin America, and Bonaire, with 11,333 participants, 69.3% of whom were female. Vaccination, particularly with three or more doses, substantially reduces the risk and duration of long COVID. Variability was noted in the definitions and outcomes assessed across studies. **Conclusions:** This scoping review highlights that SARS-CoV-2 vaccination exhibits potential in reducing the burden of long COVID in the Americas. However, discrepancies in vaccine efficacy were observed depending on the study design, the population studied, and the vaccine regimen employed. Further robust, region-specific investigations are warranted to delineate the effects of vaccination on long COVID outcomes.

Keywords: post-acute COVID-19 syndrome; vaccines; efficacy; Latin America

1. Introduction

As the COVID-19 pandemic continued its course, it became increasingly clear that a significant percentage of those with the disease were experiencing unexplained symptoms after the resolution of the acute illness[1]. A greater consensus was established about these manifestations, and these symptoms were grouped into a syndrome called long COVID. Definitions of long COVID may still vary and continue to be updated[1].

Most experts agree it is a syndrome characterized by signs, symptoms, and conditions that continue or develop after acute COVID-19 infection[1]. According to the current and most widely adopted definition, these symptoms must be present for at least three months as a continuous, relapsing and remitting, or progressive disease state that affects one or more organ systems.[2]

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Studies have shown that around 40% of people infected with SARS-CoV-2 can develop symptoms that can be related to long COVID[3,4]. Although the exact number of people living with this condition is uncertain, it is believed that more than 17 million people across the European Region may have experienced it during the first two years of the pandemic[5].

The statistics become less apparent when evaluating the impact of this syndrome in the Americas. However, in several countries, efforts have been made to clarify the situation in the region[6,7]. Despite most symptoms described by those affected by long COVID are mild and self-limiting, there is a considerable proportion of patients who present with long-lasting and debilitating symptoms that lead to disability and withdrawal from the world of work in otherwise healthy people[8]. Mechanisms recently discovered as possible causes of these disorders have been proposed, such as the persistence of functional viral RNA in various tissues, which can last up to two years[9]. Furthermore, most studies indicate that women are disproportionately affected by this syndrome[8].

Regarding the direct consequences of the virus, the high general rate of immunization with the first vaccine platforms, along with a protective effect due to natural immunity, has significantly limited the acute post-viral effects, understood also as acute post-COVID conditions (PCC) or post-acute sequelae of COVID (PASC)[10]. The COVID-19 vaccines were designed to reduce hospitalization and mortality. Although the use of updated vaccine platforms is based on more updated lineages such as XBB1.5 (which has been prevalent in most of the northern hemisphere), its adoption is still new and in process in Latin America and has even begun to promote the use of mRNA platform for more recent lineages such as JN.1[11].

Information about the effects of vaccination on the long COVID condition is less clear. For instance, the risk of experiencing an adverse cardiovascular event such as stroke, acute myocardial infarction, venous thromboembolism, or type 2 diabetes increases dramatically after the first year of acute COVID infection[12].

Early vaccination has accelerated recovery from post-COVID conditions, demonstrating efficacy in reducing the risk of long COVID[13]. This protective effect was observed in people vaccinated with one or two doses, regardless of vaccination status before or after SARS-CoV-2 infection[13]. The emergence of hypertension and diabetes as post-COVID conditions underscores the importance of vaccination to mitigate the risk of long COVID, particularly among people without a history of vaccination[13].

Regarding the different symptoms presented in long COVID patients, European studies such as COVID Home identified three different phenotypes in convalescent patients: phenotype A, which affects middle-aged patients with few comorbidities and predominantly respiratory symptoms; phenotype B, observed in older women with multimorbidity and characterized by numerous neurological symptoms; and phenotype C, more prevalent in men, similar to phenotype A in the distribution of symptoms but with an average age similar to phenotype B[14].

Other forms of phenotyping, such as those proposed by Hao, further delineate sub-phenotypes based on cardiac-renal, respiratory, musculoskeletal, and digestive manifestations that can also be found in populations in the region and that could be prevented by vaccination[15].

Due to the exploratory nature of our research, we proposed a scoping review against other types of synthesis studies. This scoping review aims to comprehensively respond to the following research question: What was the role of SARS-CoV-2 immunization against the development or severity of long COVID in the Americas region?

2. Materials and Methods

2.1. Protocol and Registration

This study follows the PRISMA-ScR guidelines for reporting scoping reviews[16]. Before the search started, the protocol for this scoping review was uploaded to the Open Science Framework repository[17]. The protocol was elaborated following the Joanna Briggs Institute (JBI) guidelines for reporting Scoping reviews[18,19].

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2.2. Eligibility Criteria

This review included observational and experimental studies from Central America, South America, and the Caribbean (Mexico was also considered). The studies involved adults previously vaccinated against SARS-CoV-2 and later developed long COVID, diagnosed clinically by the authors' criteria. Case reports, case series, opinions, commentaries, systematic reviews, and letters to the editor that did not include original results were excluded. No restrictions on language or year of publication were imposed.

2.3. Information Sources

A comprehensive search was performed in the following bibliographic databases: MEDLINE through PubMed, Scopus, Embase, Web of Science, BIREME-BVS, and SciELO. The most recent search was executed on September 7th, 2024.

2.4. Search

The concepts evaluated were Long COVID and the Effectiveness of vaccination in the prevention of Long COVID. MEsH, DeCS, Emtree, and free terms were used and linked using Boolean operators. We adapted the search strategy for each source of information, which is provided in Supplementary Material Table S1. In addition, the search was supplemented by manual exploration of the bibliographies of all included studies and a search of grey literature through preprint repositories.

2.5. Selection of Sources of Evidence

The authors used the Rayyan Intelligent Systematic Review software[20] to select evidence. In a two-step process, at least two authors (Z-SG, RJ, and F-GL) independently screened and selected all potentially relevant sources of information.

After eliminating the duplicates, the title and abstract were screened to determine whether the study could respond to the review questions. Afterward, a full-text analysis determined whether they met the selection criteria before inclusion. Disagreements on the inclusion were resolved by consensus.

2.6. Data Charting Process

Data extraction was done using the tools suggested by the JBI guidelines for reporting Scoping reviews[18]. Two reviewers (Z-SG, RJ, and F-GL) did the extraction independently and managed disagreements through consensus. Each reviewer validated the data extraction tool before collecting the data.

2.7. Data Items

The variables extracted and assessed were the year and country of publication, study design, participants' characteristics, number of doses and the type of vaccine used in the analysis, the long-COVID definition, and the efficacy measures reported.

2.8. Critical Appraisal of Individual Sources of Evidence

Methodological quality or risk of bias was not assessed as it did not meet the aim of this scoping review.

2.9. Synthesis of Results

A qualitative synthesis was performed, and the results are presented narratively and through figures and tables.

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3. Results

3.1. Selection of Evidence Sources

3,466 items were extracted from the sources of information (Figure 1). 1,656 items were eliminated due to duplicates, and 1,810 articles were evaluated by title and abstract. 12 articles were analyzed by full text, discarding seven manuscripts. 5 studies were included from the sources of information, and 3 came from the manual search, with 8 articles included.

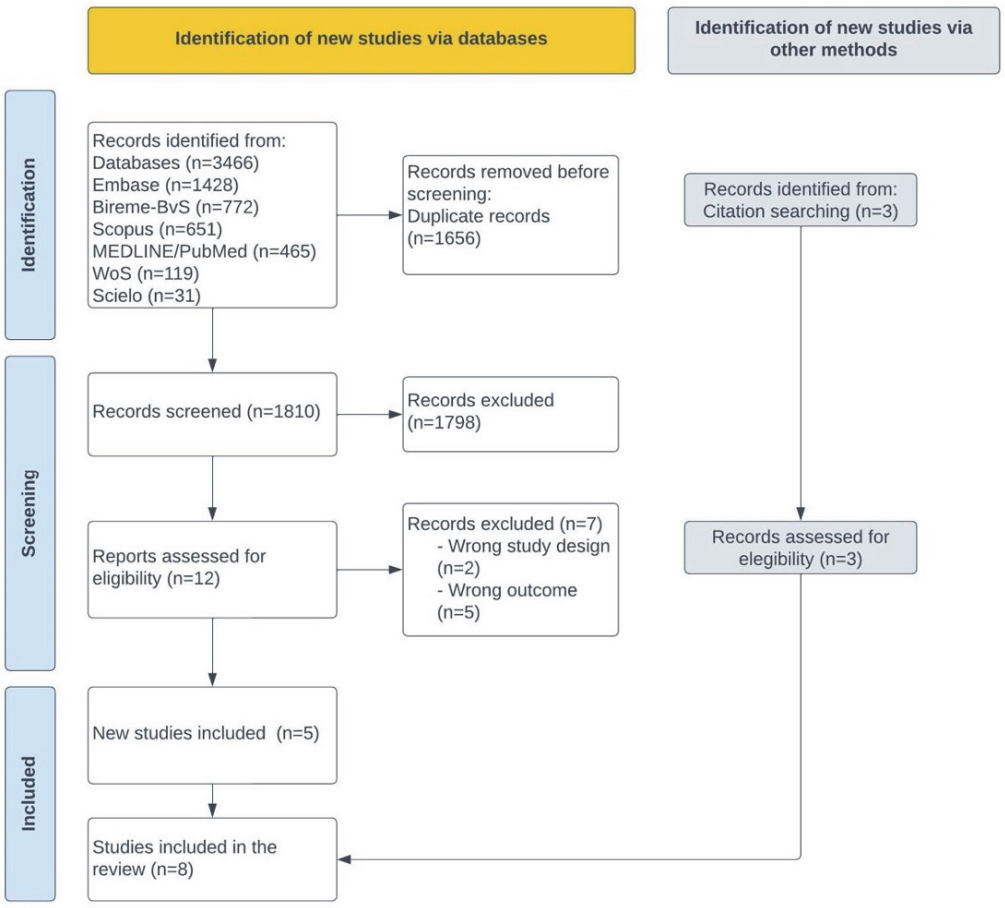

Figure 1. PRISMA flow diagram for studies selection

3.2. Characteristics and Results of the Sources of Evidence

62.5% (5) of the studies were published in 2023 [6,7,21–23] and 37.5% (3) in 2024 [24–26]. One article included a population from all of Latin America[6]; four were developed in Brazil [21,22,25,26], two in Mexico [7,24], and one in Bonaire [23]. The most commonly used research design was cohort studies with 50% (4) (3 prospective and one retrospective), 37.5% (3) were cross-sectional studies, and 12.5% (1) were case-control studies (Table 1).

Table 1. Characteristics of the included studies.

Author, year	Country	Design	Number of participants	
			Sex n, (%)	Age, years
Angarita-Fonseca, 2023[6]	Latin-America	Cross-sectional study	Men: 840 (34.1); Women:1,626 (65.9)	Mean (SD): 39.5 (53.3)

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Berry, 2023[23]	Bonaire	Retrospective cohort study	Men: 10 (21.2); Women:37 (78.8)	Median (range): 47 (14 - 89)
Marra, 2023[21]	Brazil	Case-control study	Men: 1,950 (27.6); Women: 5,101 (72.4)	Mean (SD): General: 37.5 (NR) - Cases: 38.1 (8.7); - Controls: 37.2 (9.0)
Neves, 2023[22]	Brazil	Prospective cohort study	Men: 338 (56.1); Women: 264 (43.9)	Mean (SD): 51 (12)
Nuñez, 2023[7]	Mexico	Prospective cohort study	Men: 126 (65.6); Women: 66 (34.4)	Median (range): 53 (45 - 64)
Batista, 2024[25]	Brazil	Cross-sectional study	Men: 59 (11.9); Women: 437 (88.1)	NR
Del Carpio-Orantes, 2024[24]	Mexico	Cross-sectional study	Men: 65 (32,0); Women: 138 (68,0%)	Mean (SD): 41.8 (11.3)
Fuller, 2024[26]	Brazil	Prospective cohort study	Men: 88 (31.8); Women: 188 (68.2)	Median (range): 45 (18 - 88)

3.3. Population Study

The eight articles analyzed included 11,333 participants, 69.3% (7,857) female. Four articles reported the mean and standard deviation of the participants' age in years; three studies described the median and range, with a minimum of 14 years and a maximum of 89 years; and one manuscript did not describe the age of the research subjects (Table 1).

The majority of the sample consisted of participants from Brazil (8,425), followed by Mexico (894), Ecuador (513), and Argentina (480). Panama, Nicaragua, and Costa Rica contributed to the fewest participants (Supplementary Material Figure S1).

3.4. Definitions of Long COVID

The eight articles included define Long COVID, using different characteristics related to the diagnosis of acute COVID-19 infection, the presence of symptoms, and the duration of symptomatology compared with the current definition proposed by Ely et al. (Figure 2, Table 2).

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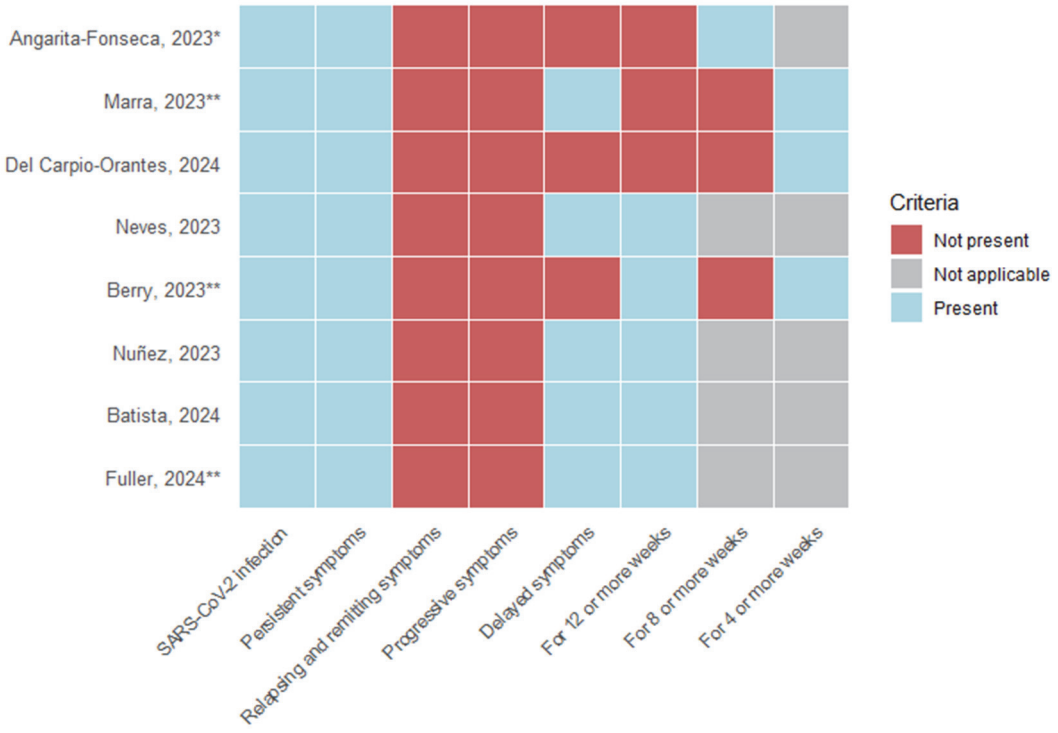

Figure 2. Variability in Long COVID definitions: Comparison of diagnostic criteria, symptomatology, and duration across primary articles.

Table 2. Efficacy of the immunization against Long COVID.

Author, year	"Fully vaccinated" status	Vaccine type	Long-COVID definition	Efficacy measures	Conclusions	Limitations
Angarita-Fonseca, 2023[6]	Two doses	NR	Individuals with a history of probable or confirmed SARS-CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms that last for at least 2 months and cannot be explained by an	Outcome: Risk of development of LCC. Multivariable logistic regression. - 1 dose: OR: 0.82; 95% CI 0.6-1.1; - 2 doses: OR: 0.75; 95% CI 0.6-0.9; - 3 or more doses: OR: 0.81; 95% CI 0.6-1.0.	Fully vaccinated patients were less likely to have LCC compared with unvaccinated or partially vaccinated subjects.	The design of the study allows the occurrence of the different bias. Data collection (electronic survey) and the non-probabilistic sampling, decrease the methodological quality of the study, the effect size, and the potential generalization of results.

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			alternative diagnosis.			
Berry, 2023[23]	At least one dose of the Pfizer vaccine at least 8 weeks after SARS-CoV-2 infection	mRNA: 36, Unvaccinated: 11	Individuals with a laboratory-confirmed SARS-CoV-2 positive test result, for whom at least one symptom self-attributed to the experienced SARS-CoV-2 infection lasted longer than four weeks.	Outcome: Self-reported change in symptom severity. Multiple covariate adjusted linear regression model. Regression coefficients and 95% CI: - Chest pain:0.17; -0.31 – 0.65; - Concentration problems: 0.01; -0.57 - 0.59; - Cough: -0.36; -1.11 - 0.39; - Fatigue: 0.0; -0.73 – 0.73; - Headache: 0.60; -0.04 – 1.24; - Heart palpitations: 0.60; 0.18 – 1.02; - Loss of appetite: 0.15; -0.36 - 0.66; - Reduced muscle strength: 0.45; -0.24 – 1.14; - Loss of sense of smell: 0.18; -0.33 - 0.69; - Loss of sense of taste: 0.05; -0.49 - 0.58; - Muscle ache: 0.22; -0.6 – 1.05; - Reduced physical endurance: -0.15; -0.98 – 0.68; - Shortness of breath: 0.63; -0.25 - 1.52; - Sleeping problems: 0.08; -0.61 - 0.77.	Vaccination was significantly associated with reduced severity of heart palpitations.	Small sample size; residual confounding may exist due to unmeasured confounding variables; the collection of data outcome data at one point in time, at different intervals since infection (and vaccination, for those applicable limited the comparison of severity scores of Long-COVID symptoms at multiple moments after initial infection at an individual level; Authors reported a linear regression using cathegorical variables to report the effect measures.

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Marra, 2023[21]	Analysis were performed whether 1,2,3, or 4 doses were administered.	Inactivated virus= 3,259; Viral vector= 3,255; mRNA=148	Signs and symptoms that developed during or following a SARS-CoV-2 RT-PCR confirmed infection, continued for >4 weeks, and could not explained by an alternative diagnosis.	Outcome: Risk of development of long COVID. Logistic Regression multivariable analysis. - 0 vs 1 doses: OR:0.91; 95%CI: 0.60 - 1.39; - 0 vs 2 doses: OR: 1.17; 95%CI: 0.79 - 1.76; - 0 vs 3 doses: OR: 0.63; 95%CI: 0.39 - 1.02; - 0 vs 4 doses: OR: 0.05; 95%CI: 0.01 - 0.19.	Four doses of COVID-19 vaccines is associated with a lower probability of develop Long-COVID.	As the study was performed only in Healthcare personnel with positive COVID-19 laboratory results, some infected individuals with no laboratory confirmed results may be lost. Also, information bias could be present.
Neves, 2023[22]	Two doses	Homologous inactivated whole-virion vaccine: 189 (36%); Homologous mRNA vaccine: 24 (5%); Homologous viral-vector vaccine:96 (19%); Heterologous inactivated + mRNA: 86 (17%); Heterologous inactivated + viral vector: 44 (9%); Heterologous mRNA + viral vector: 68 (13%); Other heterologous regimens: 5 (1%)	Physical complaints newly developed during or after the acute phase, persisting for >12 weeks, and not explained by an alternative diagnosis.	Complete vaccination schedule and the risk of Long COVID. HR: 0.89; 95% CI: 0.57–1.41	Complete vaccination schedule was not statistically significant with the risk of develop Long-COVID	A relatively modest participation rate, Also, notable qualitative disparities emerged between survey responders and nonresponders, especially regarding the vaccination rates and the acute-phase symptoms
Nuñez, 2023[7]	At least one dose of any SARS-CoV-2 vaccine at	NR	Patients experiencing any symptoms	Outcome: probability to experience a shorter time to PCC resolution.	Prior SARS-CoV-2 vaccination and acute	Study power/sample size calculations

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	least 14 days before the date on which symptoms of acute infection began		not present before acute COVID-19 onset, and that persisted for longer than 90 days after acute COVID-19 onset.	HR: 3.16; 95%CI 1.21-8.26	COVID-19 symptom were associated with a shorter time to Long-COVID resolution.	were not performed given the explorative nature of this study and the lack of reliable data on PCC prevalence when it was designed.
Batista, 2024[25]	NR	NR	Symptoms that remain or appear for the first time within three months of SARS-CoV-2 infection.	NR±	The occurrence of prolonged COVID was higher among those who were unvaccinated compared with those who received COVID-19 vaccine.	The sampling method used. The survey was published on social networks, which may have limited its representation of the Brazilian population. Self-selection bias.
Del Carpio-Orantes, 2024[24]	One dose or more	NR	Persistence of COVID-19 symptoms four weeks after the acute episode.	- Neurological symptoms: OR: 3.768 (CI 0.684-20.766); - Cardiac symptoms: OR: 0.213 (CI 0.028-1.640); - Pulmonary symptoms: OR: 1.649 (CI 0.645-1.640); - Gastrointestinal symptoms: OR: 0.391 (CI 0.087-1.753); - Musculoskeletal symptoms: OR: 0.422 (CI 0.138-1.286)	In the present analysis, no risk association was found with the history of vaccination.	The design of the study does not permit to establish proper associations, and the low number of participants.
Fuller, 2024[26]	Two or more doses	NR	Symptoms that began within three months of the positive SARS-CoV-2 test.	Outcome: Persistence of Long COVID in not fully vaccinated people. HR: 1·96, 95 % CI: 1·03–3·7	There was a significant association between the persistence of Long-COVID over time with	The fact that was a single center study with a small sample size. The frequency of comorbidities

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	not being fully vaccinated.	was high among participants, which may restrict the generalizability of our findings to healthier populations. Furthermore, since the analysis was conducted during the Omicron period, there were no participants who remained uninfected with COVID-19.

- SARS-CoV-2 infection: All eight articles, as a requirement, include a history of acute COVID-19 infection; 37.5% (3) of the studies describe the need for a positive laboratory test for SARS-CoV-2, and 12.5% (1) include suspicion and confirmation of acute infection.
- Symptoms: The persistence of symptoms from the acute stage was considered by 100% (8) of the studies; remitting and recurrent symptoms and symptom progression were not included in any definition. 62.5% (5) described developing new symptoms after the acute stage of infection.
- Time of presentation: 100% (8) of the studies describe a specific time of permanence of symptomatology following acute infection. 50% (4) consider 12 weeks or more, 12.5% (1) describe 8 weeks or more, and 37.5% (3) use 4 weeks or more as a defining criterion.

3.5. Vaccination Status

Six articles reported the number of doses required to be considered complete vaccination status; 50% (3) used one dose or more of COVID-19 vaccine as a criterion, and the remaining 50% (3) used two doses as a definition.

Two studies included temporality in their definitions of the onset of symptoms of acute SARS-CoV-2 infection. Nuñez et al. [7] required administering a dose of any vaccine at least 14 days before the onset of symptoms, and Berry et al. [23] considered administering a dose 8 weeks after infection.

3.6. Reducing the Incidence of Long COVID

Four studies evaluated the risk of developing Long COVID, using different comparisons concerning the number of doses administered and vaccination status (Figure 3).

- Administration of one dose: Two studies report a neutral effect on the risk of Long COVID [6,21].
- Administration of 2 doses: One study described a decrease in the risk of Long COVID [6], and 2 articles reported a neutral effect [21,22].
- Administration of 3 or more doses: One article reports that the administration of 3 doses has no effect, while four doses decrease the risk of Long COVID [21]. One study describes that after administering three or more doses, the risk decreases [6].

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Batista et al. evaluated the complete vaccination status, demonstrating that it decreases the risk of Long COVID [25].

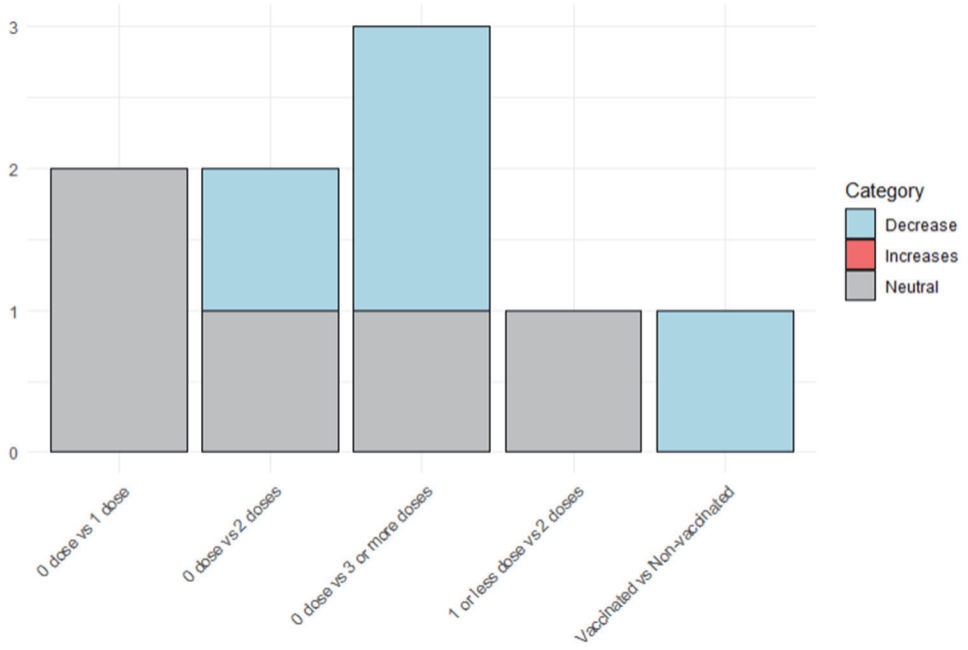

Figure 3. Impact of vaccination on Long COVID incidence: Dose-dependent risk reduction of primary.

3.7. The severity of Symptoms Related to Long COVID

One article studied the change in symptom severity and evaluated 14 symptoms, 13 with neutral results. Describes that vaccination increases the severity of heart palpitations [23].

3.8. Duration of Long COVID Symptoms

Two studies considered symptom persistence as an outcome. Fuller et al. [26] found that vaccination with two or more doses decreases Long COVID symptoms. Del Carpio-Orantes et al. [24] did not identify a significant decrease in vaccinated participants' neurologic, cardiac, pulmonary, gastrointestinal, and musculoskeletal symptoms. One study demonstrated that administering one or more doses before acute COVID-19 infection decreases the time to resolution of long COVID [7].

4. Discussion

This scoping review underscores the complex relationship between SARS-CoV-2 vaccination and long COVID in the Americas. Despite considerable advances in understanding long COVID, including its clinical definitions and phenotypes, the role of immunization in mitigating the syndrome remains unclear.

4.1. What is Already Known About This Topic

The evidence suggests that SARS-CoV-2 immunization, especially with multiple doses, could provide protection against long COVID. For instance, in a systematic review and meta-analysis, Watanabe et al. reported that two vaccine doses were related to a lower risk of developing long COVID compared to no vaccination (OR= 0.64; 95% CI 0.45-0.92) and a significant effect compared to one-dose vaccination (OR= 0.60; 95% CI, 0.43-0.83)[27].

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4.2. Main Findings

In Latin America, some studies found no effect with one or two doses of vaccination [21,22], while others found a risk reduction with three or more doses[6,21]. These results contrast with large population-based European studies where COVID-19 vaccination was strongly associated with decreased probability of developing long COVID (HR=0.48; 95% CI 0.34–0.68)[28]. The findings emphasize the necessity for consistency in defining the "complete vaccination" status and its temporal association with SARS-CoV-2 infection.

The protective effect reported with greater vaccine doses is consistent with previously proposed mechanisms, such as reduced virus persistence and immune response regulation [9,11]. However, the neutral effects found in certain studies require additional research into individual and geographical characteristics that may affect vaccine efficacy, such as sex[29], age[13,28], comorbidities[30], time of vaccination (before or after SARS-CoV-2 infection[13,27] or during delta or omicron phases[31]) and type of vaccines[28].

The effect of vaccination on the severity and duration of long COVID is less clear because of the lack of appropriate definitions. Large studies demonstrated that vaccination reduced the incidence of severe thromboembolic and cardiovascular complications of long COVID[32]. Locally, Fuller et al. [26] found that immunization with two or more doses reduced the persistence of symptoms, confirming its possible effect in speeding recovery reported by Peluso et al.[9] On the other hand, Carpio-Orantes et al. [20] reported no significant reduction in specific symptoms among vaccinated individuals. These contradictory results can be related to different long COVID phenotypes and their response to immunization, as previously shown in other cohorts[31].

Additionally, assessing adverse effects was another relevant issue in the selected studies. Berry et al.[23] reported an increase in the severity of heart palpitations following immunization in select populations, emphasizing the need to weigh the benefits of vaccination against the potential hazards described in numerous studies[33–35].

4.3. Implications for Public Health in the Americas. A call to action

The vast majority of studies evaluating the impact of immunization in long COVID have been developed in regions different than Latin America. Moreover, differences in regional vaccine access and adoption underline critical public health challenges in these countries. With most included studies originating from Brazil and Mexico, the findings may not fully represent the diverse contexts of the region. Expanding research efforts to include underrepresented countries, such as those in Central America, the Caribbean, and the Andean region, is essential for a comprehensive understanding of the impact of vaccination on long COVID.

The emergence of new vaccine platforms designed to cover new lineages offers promising alternatives for reducing long COVID risks. However, their implementation in the Americas has been slow, highlighting the need for robust vaccination campaigns and policies to ensure equitable access.

4.4. Limitations

This review is subject to limitations related to small sample sizes, varied methodologies, and inconsistent definitions of long COVID. Furthermore, the absence of data on specific populations and the restricted scope of observational designs limit the generalizability of findings. Future regional research should prioritize longitudinal and interventional studies to determine the causal association between vaccination and long-term COVID outcomes.

5. Conclusions

In Latin America, vaccination against SARS-CoV-2 appears to reduce the incidence and duration of long COVID, but its effectiveness varies depending on the population and vaccine regimen. These findings highlight the necessity of ongoing research and public health initiatives to improve immunization strategies, especially in areas with varying socioeconomic and healthcare landscapes.

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Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/doi/s1, Figure S1: Geographic distribution of the participants; Table S1: Main concepts and related keywords.

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