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Side effects of COVID-19 vaccines in paediatric patients: a review systematic and meta-analysis protocol

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ABSTRACT

Introduction The paediatric population represents a quarter of the world's population, and like adult patients, they have also suffered immeasurably from the SARS-CoV-2 pandemic. Immunisation is an effective strategy for reducing the number of COVID-19 cases. With the advancements in vaccination for younger age groups, parents or guardians have raised doubts and questions about adverse effects and the number of doses required. Therefore, systematic reviews focusing on this population are needed to consolidate evidence that can help in decision-making and clinical practice. This protocol aims to assess the safety of COVID-19 vaccines in paediatric patients and evaluate the correlation between the number of vaccine doses and side effects.

Methods and analysis We will search the PubMed, ClinicalTrials.gov, Web of Science, Embase, CINAHL, Latin American and Caribbean Health Sciences Literature, Scopus and Cochrane databases for randomised and quasi-randomised clinical trials that list the adverse effects of the COVID-19 vaccine and assess its correlation with the number of doses, without any language restrictions. Two reviewers will select the studies according to the inclusion and exclusion criteria, extract data and asses for risk of bias using the Cochrane risk-of-bias tool. The Review Software Manager (RevMan V.5.4.1) will be used to synthesise the data. We will use the Working Group's Grading of Recommendations Assessment, Development and Evaluations to grade the strength of the evidence of the results.

Ethics and dissemination Formal ethical approval is not required as no primary data are collected. This systematic review will be disseminated through a peer-reviewed publication.

PROSPERO registration number CRD42023390077.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ A comprehensive search strategy was developed by a librarian.
⇒ The possible heterogeneity among the included studies and comparisons between different types of vaccines can be challenging.
⇒ The risk of bias will be evaluated using a validated tool.
⇒ The protocol employed by pairs of independent researchers for the selection of studies increases the reliability of the results.
⇒ No language restrictions will be adopted.

INTRODUCTION

With more than 6 million deaths reported worldwide due to the COVID-19 pandemic, there is an urgency to expand immunisation.[1] According to the Centers for Disease Control and Prevention, unlike the adult population, paediatric patients, who represent a quarter of the world's population, have a higher number of critical or severe cases (>5 years).[2] WHO defines paediatric patients as persons aged >2 to <19 years at the time of their diagnosis or treatment.[3]

Vaccines against COVID-19 have been developed and used in a relatively short period compared with other vaccines. Therefore, their efficacy, safety and side effects require continuous and extensive surveillance and research. Since then, randomised controlled trials have been conducted to confirm the efficacy of the existing vaccines against new variants.[4 5]

The primary hurdle in accepting the COVID-19 vaccine has been the lack of confidence in the safety of newly discovered vaccines. The most common reactions observed in adult patients are local pain, erythema, swelling and lymphadenopathy at the injection site. The most common systemic side effects associated with the COVID-19 vaccines are headache, fatigue, myalgia and nausea.[6 7]

Currently, with the efforts of regulatory agencies, the scientific community and government, the vaccinations for younger age groups have advanced, in addition to the administration of existing vaccines and emergence of others with different mechanisms of action.[8–10]

The benefits and security of vaccines in the paediatric population are yet to be widely

publicised. Furthermore, this population has particular characteristics, and the behaviours adopted by parents or guardians directly affect childhood vaccination.[11 12]

Objective

This systematic review protocol aims to evaluate the safety of COVID-19 vaccines in paediatric patients and identify the correlation between the number of doses and side effects.

MATERIALS AND METHODS

This systematic review protocol was developed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRIDMA) Protocol.[13] This review was registered in PROSPERO (No: CRD42023390077).

Inclusion criteria

Randomised and quasi-randomised clinical trials that evaluated COVID-19 vaccine side effects in paediatric patients and were published from January 2020 in any language will be included in the study.

Exclusion criteria

Articles that are not peer-reviewed and that are observational studies, review articles, reports and case series will be excluded. Additionally, studies that did not have paediatric patients as a population will be excluded.

Patients, intervention, comparison, outcome strategy and types of studies

- Patients: children and adolescents (0–17 years) who were healthy and previously SARS-CoV-2 infection-free.
- Intervention: COVID-19 vaccine or a combination of vaccines against COVID-19.
- Comparator/control: placebo or no vaccination.
- Outcome: Side effects, safety and tolerability of the COVID-19 vaccine or the combination of vaccines against COVID-19.
- Types of studies: Clinical trials.

Primary outcome

Side effects, safety and tolerability of the COVID-19 vaccine or the combination of COVID-19 vaccines.

Secondary outcomes

Correlation between the number of vaccine doses and side effects, and death caused by adverse events of vaccination.

Patient and public involvement

None

Search strategy

The following databases will be searched: PubMed, ClinicalTrials.gov, Web of Science, Embase, CINAHL, Latin American and Caribbean Health Sciences Literature, Scopus, and the Cochrane Central Register of Controlled Trials (CENTRAL). In addition, the reference lists of the retrieved articles will be manually searched to identify eligible studies. No language restrictions will be imposed.

Our search keywords will be based on Medical Subject Headings (MeSH) in the following combinations: "Pediatrics", "Infant", "Child", "Adolescents" "vaccines", "vaccination", "vaccine COVID-19", "SARS-CoV-2 vaccine", "toxicity", "side effects", "adverse events", "clinical trial", "controlled clinical trial". The search strategy to be used in PubMed is presented in table 1. The search strategy for all databases is available in online supplemental file.

Table 1 Search strategy for PubMed

	Mesh terms and keywords
1	Pediatrics
2	Infant
3	Child
4	Children
5	Adolescents
6	Adolescence
7	Teens
8	Teenagers
9	OR / 1–8
10	Vaccines
11	Vaccination
12	vaccine COVID-19
13	SARS-CoV-2 vaccine
14	NT162 vaccine
15	mRNA-1273 vaccine
16	Covid-19 aAPC vaccine
17	INO-4800 vaccine
18	LV-SMENP-DC COVID-19 vaccine
19	Ad5-nCoV vaccine
20	ChAdOx1 COVID-19 vaccine
21	SARS-CoV-2 S1 MNA subunit vaccines
22	PittCoVacc
23	OR / 10–22
24	Toxicity
25	side effects
26	adverse events
27	OR / 24–26
28	clinical trial
29	Controlled Clinical Trial
30	OR / 28–29
31	9 AND 23 AND 27 AND 30

Data collection and analysis

Study selection

Three researchers (CLF, ACAS and KSM) will independently select the studies of interest. Initially, the Rayyan (Mourad Ouzzani, University of Oxford, UK) will

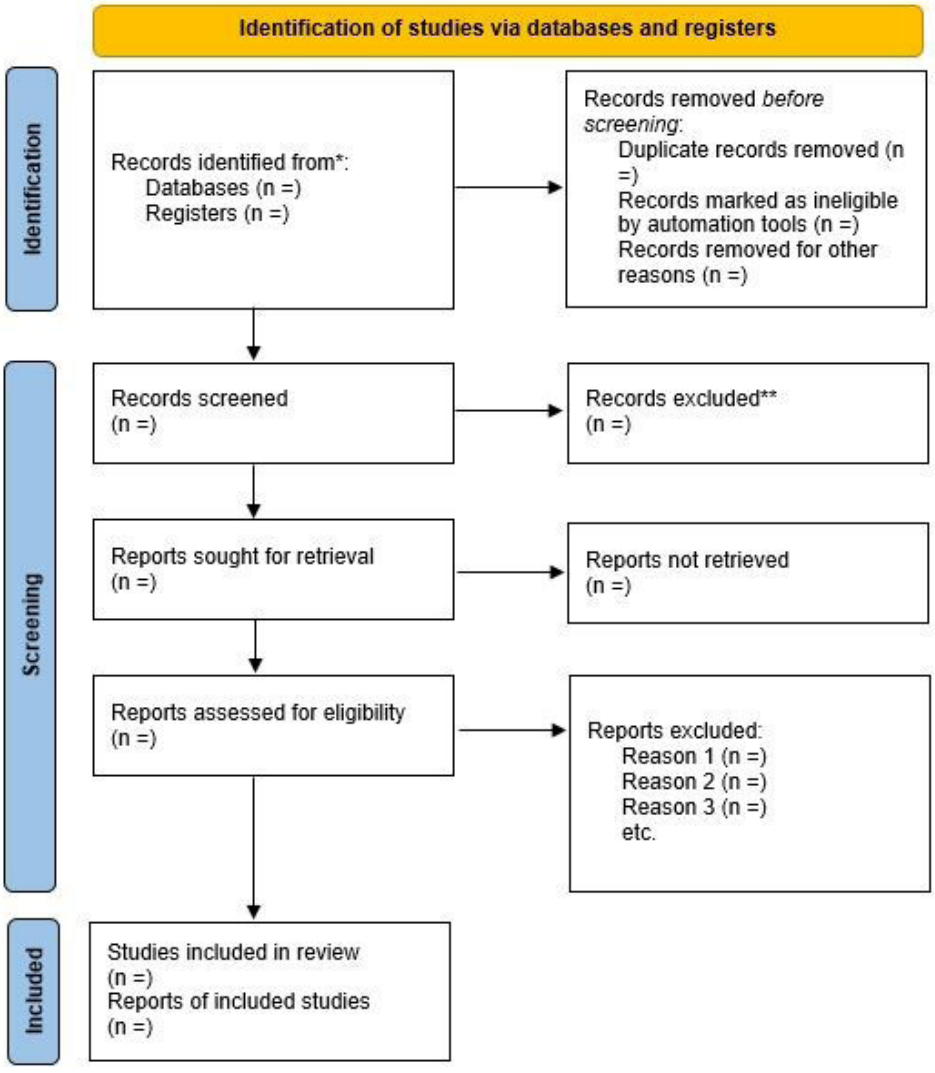

Figure 1 PRISMA flow diagram for systematic review and meta-analysis. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

***Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).**
****If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.**

be used to identify duplicates. Subsequently, the titles and abstracts of the selected articles will be analysed to identify relevant papers. The same authors will analyse the whole texts according to the inclusion criteria. Discrepancies will be resolved by a fourth author (AKG). The study selection process is summarised in the PRISMA flow chart (figure 1).

Data extraction

The authors developed and tested a data collection form. Data from each included study will be extracted independently by two authors (CLF and ACAS), and any subsequent discrepancies will be resolved through discussion with a third author (AKG). The extracted data will include authors, year of publication, study site, study type, main objectives, mean age of the population, vaccination schedule, follow-up of participants and side effects.

Missing data

For studies with incomplete or missing data, the authors will contact the article authors by telephone or email. In case of no response, the data will be excluded from the analysis and discussed in the discussion section.

Data synthesis

Data will be entered and analysed using Review Manager (RevMan, V.5.4, The Cochrane Collaboration, 2020). We will evaluate the heterogeneity between studies using the I^2 statistic (<25%, low heterogeneity; 25%–50%, moderate heterogeneity and >50%, high heterogeneity).

Fixed-effects models will be used, except when significant heterogeneity exists in the included studies (I^2>50%). ORs with 95% CI will be estimated to determine the corresponding risk. Dichotomous data from each eligible study will be combined for meta-analysis using the Mantel/Haenszel model.

A sensitivity analysis will be performed to verify the possible sources of heterogeneity, removing one study at a time and verifying whether there is a considerable change in the 95% CI. Studies with high risks of bias will be excluded.

Quality assessment

KSM, ACAS and CLF will independently assess the risk of bias in eligible studies using the Cochrane risk-of-bias tool.[14] Bias will be assessed as high, low or unclear for individual elements from five domains (selection, performance, attrition, reporting and others). Publication bias will be assessed by inspecting the funnel plot and asymmetry of the funnel plot will be tested using Egger's test.

Assessing certainty in the findings

The quality of the evidence will be assessed based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE). The GRADE tool classifies studies as low, moderate or high quality.[15]

Ethics and dissemination

The result of this systematic review will be disseminated through publication in an open-access peer-reviewed journal, scientific publications and reports. Ethical review is not required because we will only search and evaluate against publicly available literature.

DISCUSSION

The decision to vaccinate paediatric patients raises several questions even though the rigour of vaccine production and release is constantly being disclosed.[16] According to the WHO emergency list, 13 vaccines have been approved, and more than 90 are still under development and exploration.[17] Even with the approval and clearance by regulatory health agencies, legal guardians or parents of children still have doubts about the safety and possible adverse reactions.[18 19]

In a systematic review of the safety and efficacy of vaccinations against COVID-19 in children and adolescents, local reactions had a low occurrence, with some reports of myocarditis and pericarditis.[20] However, this review only evaluated English-language publications and did not include children younger than 1 year.

Currently, vaccinations continue to develop for younger age groups (from the age of 6 months), as new cases and virus variants continue to emerge every day.[21]

It is not possible to measure all the effects of the SARS-CoV-2 pandemic on the paediatric population. The suspension of face-to-face classes and social distancing has damaged cognitive and social development. In addition, the WHO warns of a reduction in childhood vaccination coverage; in 2021, about of 25 million children were not vaccinated.[22] Non-adherence to the schedule of other vaccines may affect susceptibility to other diseases. During the pandemic outbreak, some children developed multisystem inflammatory syndrome after contact with the SARS-CoV-2 virus, which had symptoms similar to incomplete Kawasaki disease; it was reported in several countries[23–25] with a mortality rate of approximately 1%–2%.[16]

Postmarketing pharmacovigilance, especially in the paediatric population, will help parents or guardians in decision-making. This protocol is designed to include large numbers of vaccinated paediatric patients across all age groups and different vaccines, to provide reliable results on childhood COVID-19 vaccination.

Contributors Conceptualisation: CLF, ACAS, KSM and AKG. Data curation: CLF, NS and MLN. Formal analysis: CLF, KSM, APFC and ACAS. Methodology: CLF, KSM, APFC and ACAS. Supervision: CLF, KSM and AKG. Validation: CLF, KSM, ACAS and AKG. Writing–original draft: CLF, NS, MLN and KSM. Writing–review and editing CLF, ACAS, KSM and AKG.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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REFERENCES

1 Coronavirus COVID-19 global cases by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU). 2022. Available: https://coronavirus.jhu.edu/map.html
2 Xu W, Tang J, Chen C, *et al*. Safety and efficacy of the COVID-19 vaccine in children and/or adolescents: a meta-analysis. *J Infect* 2022;84:722–46.
3 World Health Organization (WHO). Improving the quality of care for maternal, newborn and child health: implementation guide for national, district and facility levels. Geneva WHO; 2022.
4 Dong Y, Dai T, Wei Y, *et al*. A systematic review of SARS-Cov-2 vaccine candidates. *Signal Transduct Target Ther* 2020;5:237.
5 Pormohammad A, Zarei M, Ghorbani S, *et al*. Efficacy and safety of COVID-19 vaccines: a systematic review and meta-analysis of randomized clinical trials. *Vaccines (Basel)* 2021;9:5.

6 Chappell KJ, Mordant FL, Li Z, *et al*. Safety and immunogenicity of an MF59-adjuvanted spike glycoprotein-clamp vaccine for SARS-Cov-2: a randomized, doubleblind, placebo-controlled, phase 1 trial. *Lancet Infect Dis* 2021;21:1383–94.
7 Emary KRW, Golubchik T, Aley PK, *et al*. Efficacy of ChAdOx1 Ncov-19 (AZD1222) vaccine against SARS-Cov-2 variant of concern 202012/01 (B. 1.1. 7): an exploratory analysis of a randomized controlled trial. *Lancet* 2021;397:1351–62.
8 Sadarangani M, Marchant A, Kollmann TR. Immunological mechanisms of vaccine-induced protection against COVID-19 in humans. *Nat Rev Immunol* 2021;21:475–84.
9 Walsh EE, Frenck RW, Falsey AR, *et al*. Safety and immunogenicity of two RNA-based COVID-19 vaccine candidates. *N Engl J Med* 2020;383:2439–50.
10 World Health Organization. WHO SAGE road map for prioritizing the use of vaccines against COVID-19. 2023. Available: https://apps.who.int/iris/handle/10665/351138
11 Zimmermann P, Pittet LF, Finn A, *et al*. Should children be vaccinated against COVID-19? *Arch Dis Child* 2022;107:e1.
12 Eberhardt CS, Siegrist CA. Do we need a pediatric COVID-19 vaccine? *Rev Med Suisse* 2021;17:353–7.
13 Shamseer L, Moher D, Clarke M, *et al*. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ* 2015;350:g7647.
14 Higgins JPT, Thomas J, Chandler J, et al., eds. *Cochrane handbook for systematic reviews of interventions. Version 6.2*. Cochrane, 2021.
15 Guyatt G, Oxman AD, Akl EA, *et al*. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol* 2011;64:383–94.
16 Kaushik A, Gupta S, Sood M, *et al*. A systematic review of multisystem inflammatory syndrome in children associated with SARS-Cov-2 infection. *Pediatr Infect Dis J* 2020;39:e340–6.
17 World Health Organization. COVID-19 vaccines with WHO emergency use list. 2023. Available: https://extranet.who.int/pqweb/vaccines/vaccinescovid-19-vaccine-eul-issued
18 Wang Q, Xiu S, Zhao S, *et al*. Vaccine hesitancy: COVID-19 and influenza vaccine willingness among parents in Wuxi, China-A cross-sectional study. *Vaccines (Basel)* 2021;9:342.
19 Nour R. A systematic review of methods to improve attitudes towards childhood vaccinations. *Cureus* 2019;11:e5067.
20 Lv M, Luo X, Shen Q, *et al*. Immunogenicity, and efficacy of COVID-19 vaccines in children and adolescents: a systematic review. *Vaccines (Basel)* 2021;9:1102.
21 Galindo R, Chow H, Rongkavilit C. COVID-19 in children: clinical manifestations and pharmacologic interventions including vaccine trials. *Pediatr Clin North Am* 2021;68:961–76.
22 World Health Organization. Vaccines and immunization. 2023. Available: https://www.who.int/health-topics/vaccines-and-immunization#tab=tab_1
23 Riphagen S, Gomez X, Gonzalez-Martinez C, *et al*. Hyperinflammatory shock in children during COVID-19 pandemic. *Lancet* 2020;395:1607–8.
24 Verdoni L, Mazza A, Gervasoni A, *et al*. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-Cov-2 epidemic: an observational cohort study. *Lancet* 2020;395:1771–8.
25 Whittaker E, Bamford A, Kenny J, *et al*. Clinical characteristics of 58 children with a pediatric inflammatory multisystem syndrome temporally associated with SARS-Cov-2. *JAMA* 2020;324:259–69.