The effects of vaccination in immunocompromised pediatric people

Systematic review of research studies on immunogenicity, safety, and efficacy/effectiveness of COVID-19 vaccines in immunocompromised pediatric individuals

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General Disclaimer

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Abbreviations and Definitions

Abbreviations

- BNT162b2 (Pfizer-BioNTech)
- N/A = not applicable
- N/R = not recorded
- Anti-S = antibody to Spike Protein
- Anti-RBD = antibody to Receptor Binding Domain of the Spike Protein
- 95% CI = 95% confidence interval

Key Definitions:

- Age in tables refers to median or mean age (whichever given in the paper)
- Days, weeks and months given in table refers to median or mean (whichever given in the paper)

EXECUTIVE SUMMARY

Objectives: Vaccination against COVID-19 may be less efficacious in immunocompromised pediatric patients. We evaluated this in a systematic review of the efficacy, immunogenicity, and safety of vaccines in the pediatric immunocompromised patients.

Design: This was a rapid systematic review and meta-analysis.

Methods: Two reviewers assessed studies for eligibility and performed data extraction independently. Proportions were calculated for case series and relative risk for comparative studies with 95% confidence intervals and synthesised using a random effects model.

Results: There were five eligible studies evaluating 179 participants that specifically reported in the immunocompromised pediatric population. There were 4 studies involving 152 pediatric immunocompromised patients that reported on seroconversion after the second COVID-19 vaccine. Overall seroconversion occurred in 84% (95% CI = 65% to 97%). 88% seroconverted in the 13 patients with solid organ tumours whilst 100% seroconverted in patients with inflammatory bowel disease on immunosuppressive therapy. The two transplant studies both reported seroconversion rates of 73% with a pooled rate of 73% (95% CI = 62 to 82%). There were two case series evaluating 38 pediatric immunocompromised patients that reported safety outcomes. Overall and individual adverse events were similar that seen in the adult population.

Conclusions: COVID-19 vaccination seems to have similar outcomes in terms of immunogenicity and safety to the adult population. There is, however, limited information in the pediatric immunocompromised population.

Summary of the certainty of the evidence

Outcome	Studies included	Overall certainty of the evidence (GRADE)	Key findings
Immunogenicity of vaccination pediatric immunocompromised patients	Second vaccination efficacy evaluated in 4 case series 152 participants	⨁◯◯◯ Very low[1]	84% (95% CI = 65 to 97%) seroconverted.
Safety of vaccination in immunocompromised pediatric patients	10 cohort studies with 3,132 patients	⨁◯◯◯ Very low[1]	Adverse events similar to that seen in the adult population.

[1]The GRADE approach gives the quality of evidence of observational studies as low and further downgraded because of risk of bias of many of the included studies, small studies and clinical heterogeneity.

Introduction

Research Question

What is the effectiveness, immunogenicity, and safety of COVID-19 vaccines in immunocompromised pediatric patients?

Rationale

COVID-END finds and uses the best available evidence available to support decision-making about COVID-19 pandemic response. To this end, this report summarizes the current evidence regarding the effects of vaccinations in immunocompromised paediatric patients. Specifically, this rapid review synthesizes the body of evidence on the immunogenicity, safety, and efficacy/effectiveness of COVID-19 vaccines in immunocompromised pediatric patients to inform decisions regarding booster vaccinations.

PICOST Framework

	Inclusion Criteria	Exclusion Criteria
Population	Immunocompromised pediatric patients (patients <19 years of age), as defined by persons with HIV infection, primary immune or complement deficiency, malignancy, transplant, or on immunosuppressive therapy.	Patients > 18 years of age
Intervention	COVID-19 vaccines which Canada has currently authorized for use: BNT162b2 (Pfizer-BioNTech); mRNA-1273 (Moderna); AZD1222 (ChAdOx1) (AstraZeneca-Oxford) and Ad26.COV2.S (Johnson & Johnson).	Vaccines not approved in Canada
Comparisons	Healthy controls or disease controls (for immunosuppression e.g. inflammatory bowel disease – outcome of vaccines in those with and without immunosuppressive therapy). Controls can be pediatric or adult.	
Outcomes	1. Immunogenicity:	

	• Humoral immune responses (e.g. binding antibodies, neutralizing antibodies); 2. Safety: • Overall adverse events • Individual events of interest 3. Effectiveness: • confirmed SARS-CoV-2 infection (PCR or serologic); • asymptomatic infection, symptomatic COVID-19 disease; • hospitalizations due to COVID-19; ICU admissions due to COVID-19; • deaths due to COVID-19	
Setting	Population through to tertiary care	
Study designs	Interventional trials, cohort, case-control, or before after studies. Case series with at least 100 participants for efficacy and 10 participants for immunogenicity and safety	Case reports Case series with <100 participants for efficacy and <10 participants for immunogenicity and safety

Methods

Search

On December 21st 2021, the Public Health Agency of Canada's database of COVID-19 literature scan was searched. The search strategy for this database included the following databases and cross-referenced with the COVID-19 information centers run by Lancet, BMJ, Elsevier, Nature, and Wiley.using key terms COVID-19, SARS-CoV-2, SARS-Coronavirus-2, nCov, "novel CoV", (novel AND coronavirus) for published and pre-print studies from January 28, 2021 through December 21st, 2021. The search terms immunocompromised OR immunosuppressed OR immunosuppression OR immunosuppressive OR immunosuppressives OR autoimmune OR cancer OR cancers OR solid tumor OR solid tumors OR solid tumour OR solid tumours OR chemotherapy OR malignancies OR leukemia OR HIV OR rheumatic OR rheumatoid arthritis OR multiple sclerosis OR dialysis OR hemodialysis OR hemodialysis OR transplant OR transplants OR biologic OR biologics OR anti-interleukins OR anti-interleukin OR corticosteroids OR kinase inhibitors OR kinase inhibitor OR calcineurin inhibitors OR calcineurin inhibitor OR mTOR inhibitor OR mTOR inhibitors OR IMDH inhibitors OR IMDH inhibitor OR monoclonal antibodies OR immunotherapy OR immunotherapies OR immunodeficiency* OR immune deficienc* OR anti-CD38 OR anti-CD20 OR calcineurin inhibitor OR calcineurin inhibitors OR disease-modifying OR DMT OR DMTs OR cytotoxic. We also searched the database for specific drug names ending in "mab", "mib", "nib", mycophenolate, prednisone, tacrolimus, dexamethasone (steroid names ending in "sone").

- PubMed
- Scopus
- BioRxiv preprint server
- MedRxiv preprint server
- SSRN
- Research Square

Furthermore, the following bibliographic databases were searched: Medline (OVID), EMBASE, Scopus, SSRN, Research Square, and Cochrane Controlled trials register. All titles were limited to pediatric populations.

Study Selection Criteria

English-language, peer-reviewed sources and sources published ahead-of-print before peer review were included. The types of studies that were eligible to be considered in this rapid review included Interventional trials, cohort, case-control, or before after studies. Case series were also included provided they included at least 100 participants for efficacy and at least 10 for immunogenicity and safety.

After a pilot test, two reviewers independently screened titles as potentially eligible and all studies that at least one reviewer considered eligible was formally assessed. This was again

be done by two independent reviewers according to eligibility criteria and any disagreements were resolved by the senior lead.

Data Extraction

Data relevant to the research question, such as study design, setting, location, population characteristics, interventions or exposure and outcomes were extracted when reported.

Data were extracted by one reviewer and the second reviewer verified key elements related to the outcomes of interest after pilot testing. Data that were extracted included, setting, countries, population (type of immunocompromised patients), intervention (stratified by vaccine platform (e.g. mRNA, viral vector), vaccine product, dose: after 1 dose and/or 2 doses of a 2-dose series; 3rd dose (booster dose), interval between dose 1 and 2 of a 2-dose series (manufacture-recommended interval vs extended interval), and interval between completed vaccination series and additional booster dose.

Data Synthesis

We synthesized the results narratively due to the variation in methodology and outcomes for the included studies.

We synthesized data calculating relative risk (for comparative studies) and synthesizing with a random effects model. Case series data were presented as rates and again were synthesized with a random effects model.

Appraisal of Evidence Quality

We evaluated the quality of included evidence using critical appraisal tools as indicated by the study design below. Quality assessment was completed by one reviewer and verified by a second reviewer. Conflicts were resolved through consensus.

The Grading of Recommendations, Assessment, Development and Evaluations (GRADE) (Schünemann et al., 2013) approach was used to assess the certainty in the findings based on eight key domains.

In the GRADE approach to quality of evidence, observational studies, as included in this review, provide low quality evidence, and this assessment can be further reduced based on other domains:

- High risk of bias
- Inconsistency in effects
- Indirectness of interventions/outcomes
- Imprecision in effect estimate
- Publication bias

and can be upgraded based on:

- Large effect

• Dose-response relationship
• Accounting for confounding.

The overall certainty in the evidence for each outcome was determined taking into account the characteristics of the available evidence (observational studies, some not peer-reviewed, unaccounted-for potential confounding factors, different tests and testing protocols, lack of valid comparison groups). A judgement of 'overall certainty is very low' means that the findings are very likely to change as more evidence accumulates.

Risk of Bias Assessment

The tools used for assessing risk of bias were the Cochrane Risk of Bias (ROB 2) for randomized controlled trials and the Cochrane ROBINS-I tool for observational studies.

Completed quality assessments for each included study are available on request.

Results

There were 29 titles screened (1-29). Of these, 24 studies were excluded (5 were excluded for not reporting the pediatric population data separately, 7 were case reports, 5 had inappropriate designs, 4 evaluated the adult population and 3 did not evaluate relevant populations). The remaining 5 titles were eligible to be included in the review. A list of included and excluded studies are given in Tables 1 and 2.

Figure 1: Flow Diagram of Study Selection

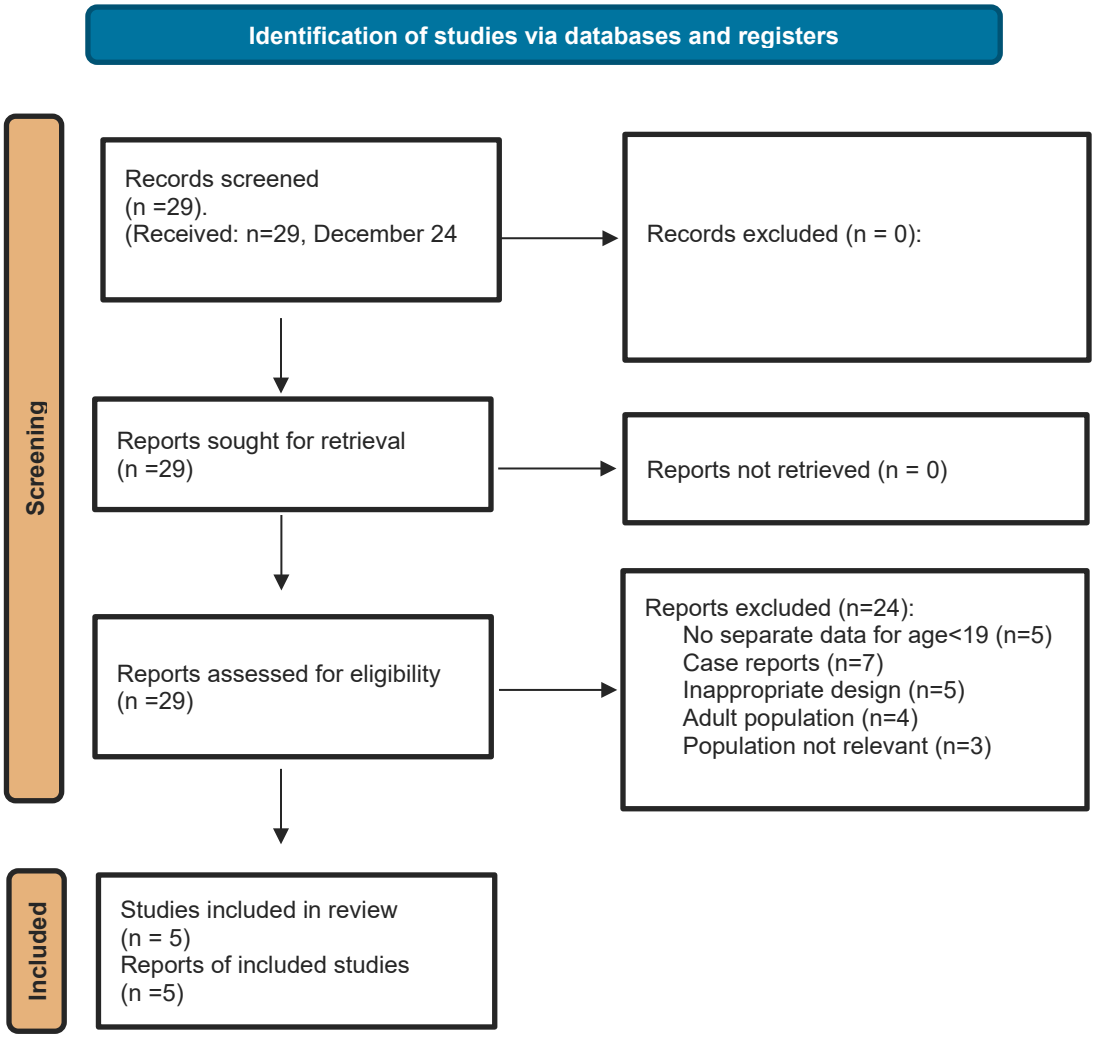


Table 1. Ineligible studies

Reference	Author	Reasons for exclusion
1	Hanna 2021	Case report
3	Haskin 2021	Age range 10-26 years, pediatric not separate
4	Spencer 2021	Inappropriate design, evaluated those that had turned up for a COVID test and tested +ve - don't know denominator
5	Dimopoulou 2021	Age range 16-21 years, pediatric not separate
6	Ruether 2021	Population not relevant – adults with cirrhosis
8	Dailey 2021	Age range 2-26 years, pediatric not separate
9	Crane 2021	Median age 19 years (IQR = 18-20), pediatric not separate
10	Cotugno 2021	Labelled as pediatric but that is when transplanted – now mean age =29 years
11	Kim 2021	Adult population
12	Chadeau-Hyam 2021	Not immunocompromised
13	Matkowska-Kocjan 2021	Adult population
14	Niel 2021	Case report
15	Buchhorn 2021	Case report
17	Dimopoulou 2021	Age range 16-21 years, pediatric not separate
18	Ketres 2021	Adult population
20	Underdown 2021	Case report
21	Das 2021	Inappropriate design – evaluating myocarditis relating to vaccine only
22	Kirpalani 2021	Case report
24	Mark 2021	No relevant data, inappropriate design
25	Das 2021	Inappropriate design – evaluating myocarditis relating to vaccine only – duplicate of 21
26	Nakazawa 2021	Case report
27	Meyer-Szary 2021	Inappropriate design – evaluating myocarditis relating to vaccine only – denominator uncertain
28	Dowell 2021	Inappropriate population – not immunocompromised
29	Larkin 2021	Case report

Note: Some studies have more than one excluded reason and we chose the first applicable one in our assessment form. Duplicate data could be preliminary / interim data, early or duplicate publications.

Table 2. Eligible studies

Reference	Author	Outcome assessed
2	Revon-Riviere 2021	Immunogenicity and safety
7	Qin 2021	Immunogenicity
16	Shire 2021	Immunogenicity
19	Spinner 2021	Immunogenicity
23	King 2021	Safety

Summary of eligible studies

There were five case series (2, 7, 16, 19, 23) evaluating 179 pediatric participants. Almost all participants in these studies received the BNT162b2 vaccine. There were 4 studies (2, 7, 16, 19) evaluating immunogenicity in 152 pediatric participants whilst there were two studies (2, 23) involving 40 participants that reported on safety. The summary of these studies is given in Tables 3.

Table 3. General summary of observational studies evaluating SARS-CoV2 vaccination in the general population

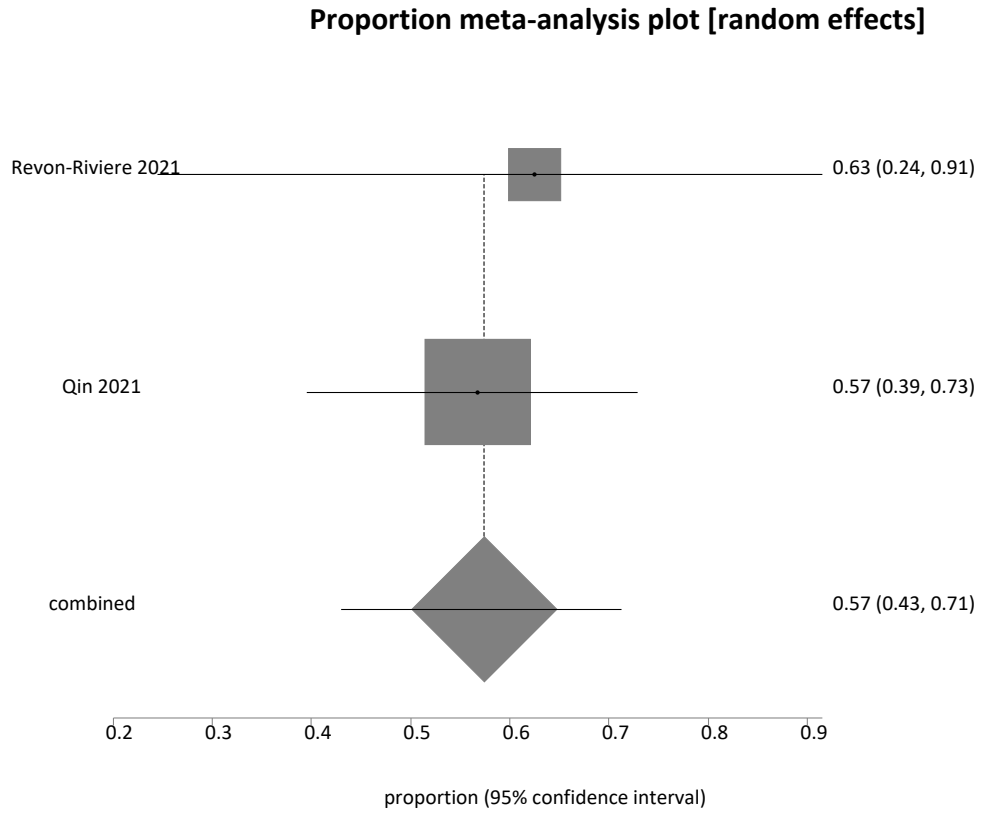
Author	Population	Country	Median age*	Vaccine	No.	Outcome
Revon-Riviere 2021	Solid tumor within 6 months of treatment	France	17 (16 to 18)	BNT162b2	13	Immunogenicity, safety
Qin 2021	Solid organ transplant – median 10 years post transplant	US	14 (12-18)	BNT162b2	45	Immunogenicity
Shire 2021	IBD patients receiving anti-TNF	Canada	17 (12-17)	BNT162b2	68	Immunogenicity
Spinner 2021	Heart transplant	US	17 (16-18)**	BNT162b2 (90%)	26	Immunogenicity
King 2021	Children with severe neurodisabilities	UK	Unclear – aged 12-15 years	BNT162b2	27	Safety

**Median age in years with range in brackets except **= IQR*

Immunogenicity of first COVID-19 vaccination in the immunocompromised pediatric patients

Two studies (2, 7) reported on the immunogenicity of the first COVID-19 vaccine in 45 pediatric participants. One French study (2) evaluated pediatric patients with solid tumours (10 undergoing active therapy for the tumour), 2/13 were female with an age range of 16-21 years and a median age of 17 years. Seven patients had Ewing or other sarcoma and the other six had a variety of other solid tumours. Anti-Spike S1 antibodies (Euroimmun®, Luebeck, Germany) were evaluated 21 days after the fist vaccine. The other US study (7) evaluated solid organ transplant patients with 60% being female and 74% were white. 44% were liver transplants and overall were a median of 10 years post-transplant. 5/57 had had previous COVID-19 infection. Anti-spike-RBD antibodies (Roche Elecsys) were evaluated 14 days after the first vaccine. Overall, 57% (95% CI = 43 to 71%) had seroconverted with both studies giving similar conversion rates (Figure 2).

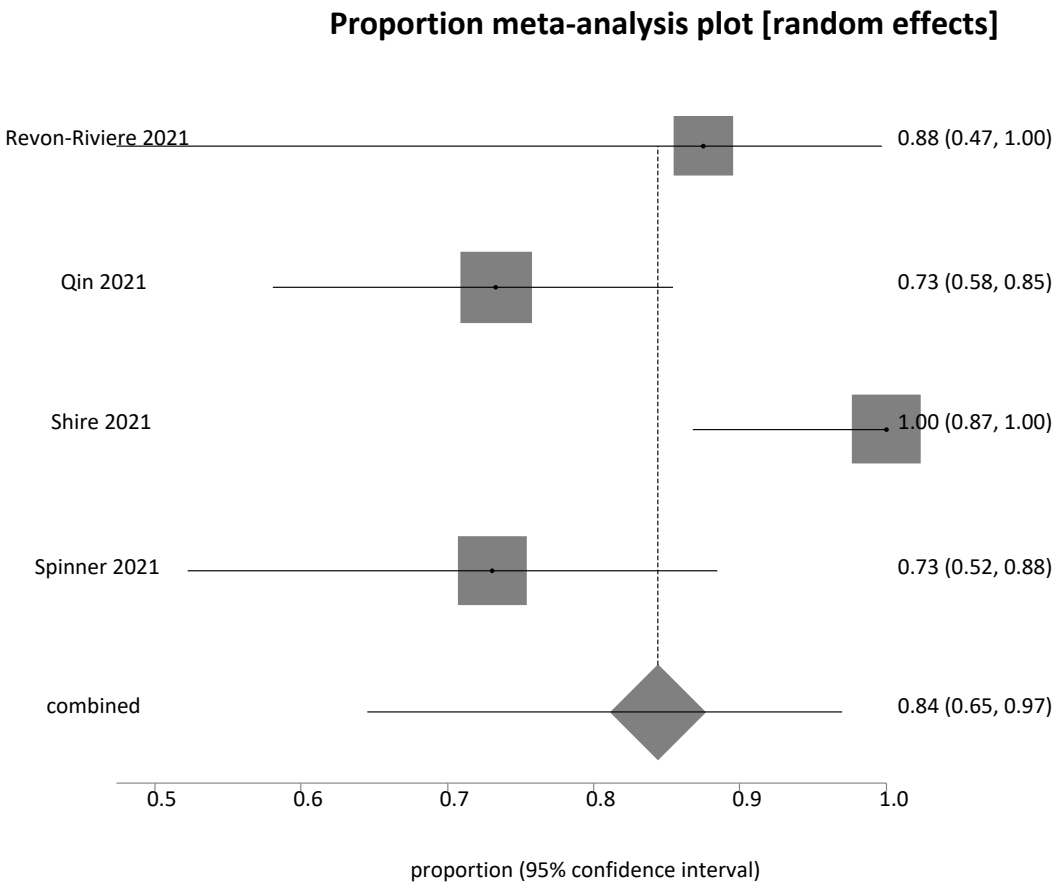
Figure 2. Immunogenicity after the first vaccine in immunocompromised pediatric patients.



Immunogenicity of the second COVID-19 vaccination in the immunocompromised pediatric patients

There were four studies that evaluated the immunogenicity after the second vaccine in 152 pediatric participants. Two studies (2, 7) have been described above. The third Canadian study (16) evaluated pediatric inflammatory bowel disease (IBD) patients on infliximab monotherapy or combined with other immunosuppressive therapy. They also reported on a healthy adult control group. 43% of the IBD participants were female and 79% had Crohn's disease. Anti-S and anti-RBD IgG (mesoscale diagnostics) were measured 28 days and three months after the second vaccine. The study did report that those on infliximab plus other immunosuppressive therapy had lower antibody titres at 28 days compared to healthy controls, but this was not apparent by 3 months. The fourth US study (19) evaluated paediatric heart transplant patients. 13/40 were female and 15/40 were white and were a median of 10 years post-transplant. Anti-spike IgG (Vitros 5600) was measured a median of 118 days after the second vaccination. Overall, there was a seroconversion of 84% (95% CI = 65 to 97%) (Figure 3). It may be inappropriate to combine different immunocompromised groups but the two transplant studies (7, 19) gave seroconversion rates of 73% with a pooled rate of 73% (95% CI = 62 to 82%).

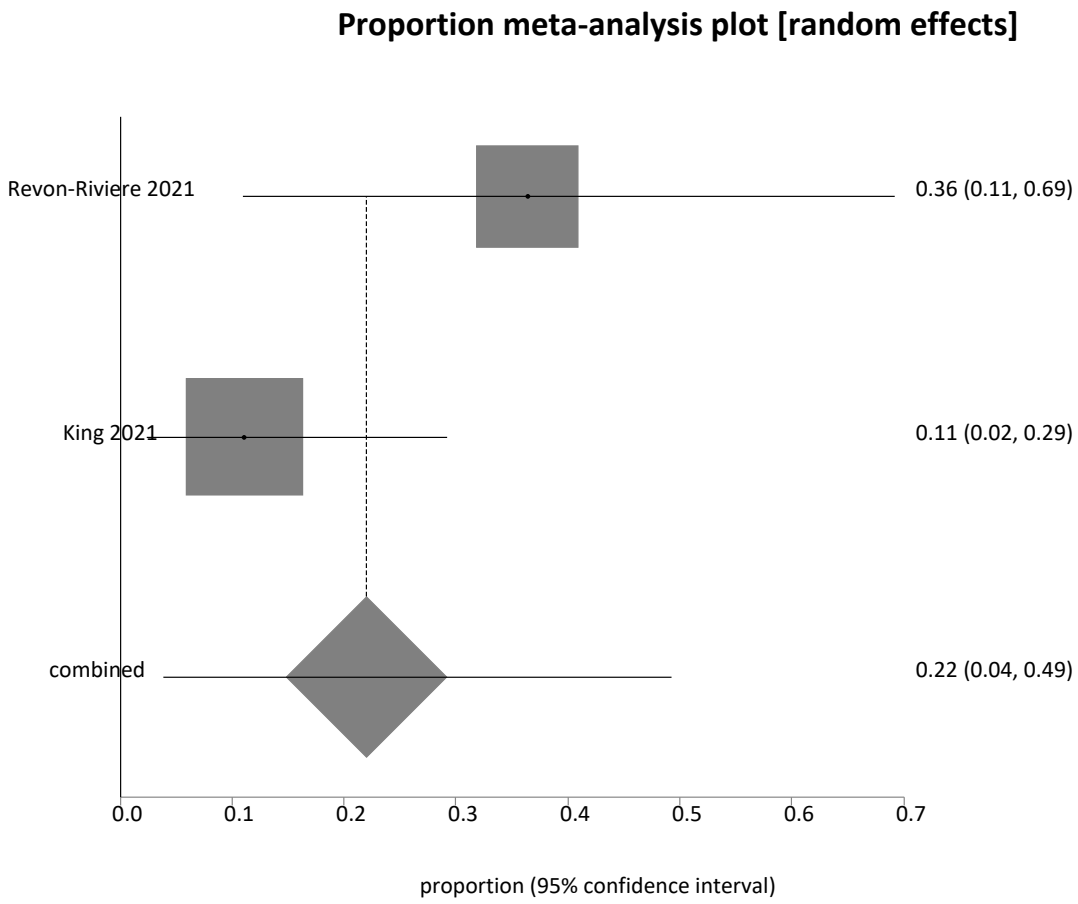
Figure 3. Immunogenicity after the second vaccine in immunocompromised pediatric patients.



Safety of COVID-19 vaccination in the pediatric population

There were two case series (2, 23) that reported on adverse events related to COVID-19 vaccination in 38 pediatric participants. Both reported after the second vaccination and reported on overall adverse events as well as local pain, reactions and fever. There was no suggestion that harms were any different from the adult population. Myocarditis was flagged as a concern in excluded papers (21, 25, 27), but these are difficult to interpret as they reported on cases of myocarditis without giving an indication of the denominator that these cases came from. Fever was described in both studies (2, 23) as an example of a systemic adverse event and was present in 22% (95% CI = 4 to 49%) (Figure 4)

Figure 4. Fever after the second vaccine in immunocompromised pediatric patients.



Conclusion

There are limited data on the immunogenicity and safety of COVID-19 vaccination in the pediatric population with no data of efficacy. Immunogenicity and safety appear similar to the adult population, but more data are needed in this population. In particular, more information on different immunocompromising conditions such as immunosuppressive therapy and transplantation would be helpful to compare with the adult population.

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