National Collaborating Centre for Methods and Tools

Centre de collaboration nationale des méthodes et outils

School of Nursing | McMaster University

Rapid Review: What are the risk factors associated with severe COVID-19 outcomes in children 12 years and under?

Prepared by: The National Collaborating Centre for Methods and Tools

Date: October 25, 2021

Suggested Citation:

National Collaborating Centre for Methods and Tools. (2021, October 25). *What are the risk factors associated with severe COVID-19 outcomes in children 12 years and under? https://www.nccmt.ca/pdfs/res/risk-factors-children*

Please Note: An update of this review may be available. Access the most current version of this review by visiting the National Collaborating Centre for Methods and Tools COVID-19 Rapid Evidence Service at the above link.

The National Collaborating Centre for Methods and Tools (NCCMT) is hosted by McMaster University and funded by the Public Health Agency of Canada. The views expressed herein do not necessarily represent the views of the Public Health Agency of Canada.

The authors declare they have no conflicts of interest to report.

Project Contributors: Michael Scott and Dr. Tayaba Khan of the SPOR Evidence Alliance Patient Partners Rapid Review Panel.

Executive Summary

Background

At the outset of the coronavirus disease 2019 (COVID-19) pandemic and during the ensuing first waves, the data from countries worldwide suggested children had much lower incidence of infection, and when infected were much less likely to experience hospitalization, severe illness, and death. As vaccines became available, large proportions of populations over age 12 have been vaccinated and some public health measures have been relaxed, leaving those under age 12 vulnerable to infection and severe illness. With the approval of COVID-19 vaccines for children under 12 years expected shortly, there is a need to develop efficient and equitable immunization prioritization strategies for this age group. Similar to the strategy used with adults, one approach for an immunization strategy may be to offer immunization first to those with underlying health conditions who may be at greater risk for severe COVID-19 outcomes. Another approach may be to offer immunization first to children with the greatest risk of exposure as a result of high rates of infection in the communities in which they live or go to school, or as a result of their living arrangement (e.g., family members at high risk of infection due to occupation). An understanding of risk factors associated with severe COVID-19 outcomes among those 12 years and under will support decisions about optimal immunization strategies.

This rapid review was produced to support public health decision makers' response to the COVID-19 pandemic. This review seeks to identify, appraise, and summarize emerging research evidence to support evidence-informed decision making.

This rapid review includes evidence available up to October 12, 2021 to answer the question: **What are the risk factors associated with severe COVID-19 outcomes in children 12 years and under?**

Key Points

- Based on 3 studies, the evidence is very uncertain about the association between comorbidities and severe COVID-19 outcomes in children 12 years and under. The certainty of the evidence is very low (GRADE); findings are very likely to change as new data become available.
- Based on 1 study, the evidence is very uncertain about the association between age and severe COVID-19 outcomes in children 12 years and under. The certainty of the evidence is very low (GRADE) and very likely to change as more data become available.
- No studies reported the association between comorbidities and severe COVID-19 outcomes in those 12 years and under specific to those living with social and structural inequities, such as Indigenous or racialized communities. Further research is required to ensure representation of these populations for decision making.

Overview of Evidence and Knowledge Gaps

- The evidence reporting on the association between risk factors and severe COVID-19 outcomes is extremely limited, with only 4 studies reporting data specifically for children 12 years and under. Studies of pediatric populations generally include participants aged

0-18 years. While studies tend to report the number of participants with severe COVID-19 outcomes by age group (i.e., <1, 2-5, 6-12, 13-18), analyses assessing the association between risk factors and severe COVID-19 outcomes are generally reported for the sample as a whole.

- Of 3 studies reporting on the association between comorbidities and severe COVID-19 outcomes, one study reported that the association was not statistically significant, although it is likely this study was underpowered to observe a statistically significant association; another reported a statistically significant finding that those 1 year or less who died were less likely to have a comorbidity; and a third study reported statistically significant associations between some comorbidities and severe illness in multiple age groups (<1, 2-5 and 6-11 years). Specifically, this study reported that for children 1 year and under there were statistically significant associations between prematurity or cardiac and circulatory congenital anomalies and severe COVID-19 outcomes; for children aged 2-5 years there were statistically significant associations between epilepsy and/or convulsions or cardiac and circulatory congenital anomalies and severe COVID-19 outcomes; and for children aged 5-11 years there were statistically significant associations between epilepsy and/or sleep disorders or sleep/wake disorders and severe COVID-19 outcomes.
- One study reporting the association between age and severe COVID-19 outcomes found that those with severe illness (admitted to the ICU) were statistically significantly older than those not admitted.
- Future studies of pediatric populations should report data separately for those 12 years and under, when the sample includes those older than 12 years.
- Given that a relatively small number of children with COVID-19 have experienced severe outcomes, most studies are underpowered to observe statistically significant associations that may exist between risk factors and outcomes. Larger, longitudinal cohort studies are needed to ensure studies are adequately powered to explore associations between risk factors and severe illness in those 12 years and under. Feedback from parent representatives of children with underlying health conditions suggest that the data be reported for specific age groups such as <1, 2-5, 6-11. In order for such studies to be adequately powered to observe associations for these specific age groups, data from studies conducted in multiple countries will be needed.
- While one large study reported statistically significant associations between some comorbidities and severe illness, the small number of affected individuals included may mean that the study had insufficient power to find a statistically significant association, even if one did exist. Furthermore, parent representatives indicated that they may not disclose comorbidities to avoid stigmatization; underreporting of comorbidities could mask associations that actually exist. Strategies to reduce stigma associated with comorbidities are needed if more accurate data on their presence is to be collected. Parent representatives also suggested improved communication with parents articulating how important the collection of accurate data is to studying the association between comorbidities and serve COVID-19 outcomes among children under 12 years.
- Among included studies data were collected up to March 2021; therefore, the findings of this review may not reflect current rates of severe illness and associated risk factors among those 12 years and under, particularly due to the high proportion of current global cases that are attributed to the Delta variant of concern.

Further Considerations for Vaccine Programs for Children 12 and under: Perspectives of Parents of Children with Underlying Health Conditions

- Feedback provided by parent representatives highlights the importance of demonstrating the safety of COVID-19 vaccines for those 12 years and under generally, and specifically for those with underlying health conditions, and/or those receiving specific treatments (e.g., steroids, immunosuppressants).Parents of these children require assurance that the safety of COVID-19 vaccines has been assessed taking into account the medical complexities associated with their children's underlying health conditions and treatments.
- Parent representatives also indicated that immunization programs offering vaccines first to children with underlying health conditions may stigmatize these children and their families, not only in regards to disclosing the underlying conditions, but also in regards to attention and stigma that focuses on the visibility of accepting vaccines vs. anti-vaccination sentiments that are present in some parts of the population. Such a program could pressure parents into disclosing an underlying health condition that they otherwise might not have done and may force people into difficult situations in decision-making and unwanted attention due to the stigma surrounding vaccinations. Parent representatives suggested a preferred alternative would be to immunize first those at greatest risk of exposure, but could include vaccinating willing higher-risk families first.
- Parent representatives indicated that jurisdictional differences (e.g., country to country variation) in vaccine approaches will negatively impact parents' confidence in a given strategy. For example, it is possible that some countries would decide not to vaccinate children 12 years and under, citing safety concerns, but Canada would decide the opposite. In such an instance a communication plan will be needed that clearly articulates what evidence was used to inform the decision and demonstrates the safety of the vaccine for children 12 years and under and for children with specific underlying conditions and who are receiving specific treatments.

Methods

Research Question

What are the risk factors associated with severe COVID-19 outcomes in children 12 years and under?

Search

On October 12, 2021, the following databases were searched using key terms: child*, pediatric, paediatric, infant*, coronavirus, nCoV, CoV, 2019-nCoV, COVID-19, and SARS-CoV-2.

- MEDLINE database
- COVID-19 Evidence Alerts from McMaster PLUS™
- COVID-19 Living Overview of the Evidence (L·OVE)
- McMaster Health Forum
- Cochrane Rapid Reviews Question Bank
- Prospero Registry of Systematic Reviews
- NCCMT COVID-19 Rapid Evidence Reviews
- MedRxiv preprint server
- Morbidity and Mortality Weekly Report (MMWR)
- Public Health Agency of Canada
- ICES
- Statistics Canada: Coronavirus
- European Centre for Disease Prevention and Control: Publications & Data
- Public Health England
- United States Center for Disease Control and Prevention
- John Hopkins Center for Health Security
- World Health Organization

A copy of the full search strategy is available in Appendix 1.

The lists of included studies from several recently published systematic reviews were also screened.

Study Selection Criteria

The search results were first screened for recent guidelines and syntheses. When available, findings from syntheses and clinical practice guidelines are presented first, as these take into account the available body of evidence and, therefore, can be applied broadly to populations and settings.

Single studies were included if no syntheses were available, or if single studies were published after the search was conducted in the included syntheses. English-language, peer-reviewed sources and sources published ahead-of-print before peer review were included. Surveillance sources were excluded.

	Inclusion Criteria	Exclusion Criteria
Population	-Children aged 0-12 years -≥50 participants	-Ages 13 or older
Exposure	-Risk factors: comorbidities, socio-demographic	
Comparisons	No risk factors	
Outcomes	Serious outcomes attributed to COVID-19 including: -Hospitalization -ICU admission -Mechanical ventilation -Death	-Measures of viral load -Long COVID symptoms -COVID-19 symptoms (e.g., cough, fatigue, fever, etc.)

Data Extraction and Synthesis

Data relevant to the research question, such as study design, setting, location, population characteristics, interventions or exposure and outcomes were extracted when reported. We synthesized the results narratively due to the variation in methodology and outcomes for the included studies.

Citizen Engagement in the Review Process

COVID-END in Canada issued an open call for patient and public partners to be involved in COVID-19 evidence synthesis. Of 80 applicants, 20 partners from diverse backgrounds and with a variety of COVID-19 lived experiences join research teams to provide their perspectives.

Two parent representatives from the SPOR Evidence Alliance Patient Partners Rapid Review Panel agreed to participate in this rapid review. Each provided feedback on the initial draft and approved the final report. Their comments were summarized and added to the Overview of Evidence and Knowledge Gaps section. In addition, to adequately represent their feedback a new section was created and labelled: Further considerations for vaccine programs for children 12 and under: Perspectives of parents of children with underlying health conditions.

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 discussion.

Study Design	**Critical Appraisal Tool**
Cross-sectional	Joanna Briggs Institute (JBI) Checklist for Analytical Cross Sectional Studies

The Joanna Briggs Institute Checklist for Analytical Cross Sectional Studies was used to appraise all studies as this was deemed the most appropriate tool given the methods described for included studies. This is despite some authors identifying the design of their study as a cohort study.

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

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.

Findings

Summary of Evidence Quality

This document includes five single studies reported in five publications. The quality of the evidence included in this review is as follows:

Outcome	Studies included			Overall certainty in evidence (GRADE)
	Study design	n	Key findings	
Comorbidities as a risk factor for severe COVID-19 outcomes in children 12 years an under	Observational	3	The evidence is very uncertain about the association between comorbidities and severe outcomes, as well as age and severe outcomes No studies reported associations about sociodemographic factors and severe outcomes in those 12 years and under Studies are likely under powered to observe statistically significant associations.	⨁◯◯◯ Very low*
Age as a risk factor for severe COVID-19 outcomes in children 12 years and under	Observational	1		⨁◯◯◯ Very low*
Sociodemographic variables as a risk factor for severe COVID-19 outcomes in children 12 years and under	Observational	0		

*In the GRADE approach to quality of evidence, **observational studies,** as included in this review, provide **low quality** evidence, and this assessment was further reduced to **very low** based on inconsistency in effects.

Warning

Given the need to make emerging COVID-19 evidence quickly available, many emerging studies have not been peer reviewed. As such, we advise caution when using and interpreting the evidence included in this rapid review. We have provided a summary of overall certainty of the evidence to support the process of decision making. Where possible, make decisions using the highest quality evidence available.

Question: What are the risk factors associated with severe COVID-19 outcomes in children 12 years and under?

Table 1: Findings for Children Ages 0-12

Reference	Date	Study Design	Setting	Data Collection Dates	Participants ≤ 12 years	Risk factors (comorbidities and/or PROGRESS+ factors); number of participants with risk factor	Outcome	Effect estimate	Notes	Quality Rating:
Sharma, A., Kumar, V., Sodani, R., Spare, A., Singh, P., Saha, A., … Pemde, H. (2021). Predictors of mortality in children admitted with SARS-CoV-2 infection in tertiary care hospital in North India. *Journal of Pediatrics and Child Health.* Epub ahead of print.	Sep 21, 2021	Cross-sectional	India	Apr 16-Nov 15, 2020	n=8 aged <1 year who died	Comorbidities (anemia, hematological malignancy, rheumatological condition, cerebral palsy, diabetes, tuberculosis, nephrotic syndrome); n=0	Death	0/0 (0%) who died had comorbidities vs. 8/8 (100%) who died did not have comorbidities, p=0.001		Moderate
					n=10 aged 1-10 years who died	Comorbidities (anemia, hematological malignancy, rheumatological condition, cerebral palsy, diabetes, tuberculosis, nephrotic syndrome); n=5		5/10 (50%) who died had comorbidities vs. 5/10 (50%) who died did not have comorbidities, p=0.08		

Guzman, B., Elbel, B., Jay, M., Messito, M., & Curado, S. (2021). Age-dependent association of obesity with COVID-19 severity in paediatric patients. *Pediatric Obesity*. Epub ahead of print.	Sep 1, 2021	Cross-sectional	USA	Mar 1, 2020-Jan 3, 2021	n=214 aged 0-12	Obesity; n=38	Hospitalization	aRR 0.95 (95% CI=0.56, 1.61)		Moderate
							ICU admission	aRR 1.01 (95% CI=0.36, 2.87)		
						Comorbidities (asthma, any malignancy or metastatic solid tumour, congenital malformations, deformations and chromosomal abnormalities, and diabetes); n=76	Hospitalization	aRR 1.08 (95% CI=0.72, 1.62)		
							ICU admission	aRR 1.98 (95% CI=0.82, 4.782)		

Kompaniyets, L., Agthis, N., Nelson, J., Preson, L., Ko, J., Belay, B., … Goodman, A. (2021). Underlying medical conditions associated with severe COVID-19 illness among children. *JAMA Network Open 1*(4): e2111182.	Jun 7, 2021	Cross-sectional	USA	Mar 1, 2020-Jan 31, 2021	n=7904 aged ≤1 year	Prematurity; n=479	Hospitalized with severe illness	aRR: 1.83 (95% CI=1.47, 2.29)	Additional comorbidities assessed (not statistically significant) include: other congenital anomalies, esophageal disorders, musculoskeletal disorders, genitourinary disorders, asthma, implant device or graft related encounters, other upper respiratory disease, obesity and anxiety and fear related disorders.	Moderate
						Cardiac and circulatory congenital anomalies; n=306		aRR: 1.89 (95% CI=1.48, 2.41)		
						Digestive congenital anomalies; n=132		aRR: 0.52 (95% CI=0.28, 0.96)*		
					n=5034 aged 2-5 years	Neurodevelopmental disorders; n=195	Hospitalized with severe illness	aRR: 0.61 (95% CI=0.43, 0.88)		
						Epilepsy and/or convulsions; n=111		aRR: 1.95 (95% CI=1.40, 2.74)		
						Cardiac and circulatory congenital anomalies; n=84		aRR: 1.50 (95% CI=1.05, 2.16)		
					n=7552 aged 6-11 years	Epilepsy and/or convulsions; n=110	Hospitalized with severe illness	aRR: 1.54 (95% CI=1.05, 2.26)		
						Sleep/wake disorders; n=80		aRR:1.82 (95% CI=1.35, 2.45)		
Haslak, F., Barut, K., Durak, C., Aliyeva, A., Yildiz, M., Guliyeva, V., … Kasapcopur, O. (2021). Clinical features and outcomes of 76 patients with COVID-19-related multi-inflammatory syndrome in children. *Clinical Rheumatology 40*(10): 4167-4178.	Jun 5, 2021	Cross-sectional	Turkey	Jul 2020-Mar 2021	n=76 aged <18 years children with multi-system inflammatory syndrome	Age	ICU admission; n=62	aOR: 1.277 (95% CI: 1.089, 1.498) p=0.003; for every 1-year increase in age	Mean age±SD for ICU-admitted patients was 10.44±4.87 years. Mean age±SD for patients not admitted to ICU was 6.92±3.63 years.	Moderate

References

Guzman, B., Elbel, B., Jay, M., Messito, M., & Curado, S. (2021). Age-dependent association of obesity with COVID-19 severity in paediatric patients. *Pediatric Obesity*. Epub ahead of print.

Haslak, F., Barut, K., Durak, C., Aliyeva, A., Yildiz, M., Guliyeva, V., … Kasapcopur, O. (2021).Clinical features and outcomes of 76 patients with COVID-19-related multi-inflammatory syndrome in children. *Clinical Rheumatology 40*(10): 4167-4178.

Kompaniyets, L., Agthis, N., Nelson, J., Preson, L., Ko, J., Belay, B., … Goodman, A. (2021).Underlying medical conditions associated with severe COVID-19 illness among children. *JAMA Network Open 1*(4): e2111182.

Schünemann, H., Brożek, J., Guyatt, G., & Oxman, A. (2013). *Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach*.

Sharma, A., Kumar, V., Sodani, R., Spare, A., Singh, P., Saha, A., … Pemde, H. (2021). Predictors of mortality in children admitted with SARS-CoV-2 infection in tertiary care hospital in North India. *Journal of Pediatrics and Child Health.* Epub ahead of print.