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Rapid Review Update 1: 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

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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.

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

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

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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. With the availability of vaccines, 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, 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 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 December 6, 2021 to answer the question: **What are the risk factors associated with severe COVID-19 outcomes in children 12 years and under?**

What has Changed in This Version?

- This update adds an additional 12 studies to the four synthesized previously; four published since the search date of the initial review completed in November 2021, and eight studies excluded in the initial review because results were not reported specifically for children 12 years and under. We reached out to the authors of 15 studies following the initial review requesting additional analyses be conducted on participants 12 years or younger, or to provide the raw data for those 12 years or younger, and received the requested information from eight. The 12 added studies are from Europe (n = 4), Canada (n = 2), South Africa (n = 2), USA (n = 2), Mexico (n= 1), and Norway (n = 1).
- While the evidence base is growing, evidence continues to be limited for the relationship between risk factors and severe COVID-19 outcomes in children aged 12 and under. Similar to previously reported results, added studies are likely underpowered to observe statistically significant associations between risk factors and severe COVID-19 outcomes, in particular death, due to relatively few children experiencing severe outcomes and even fewer children with comorbidities experiencing severe outcomes.
- The evidence continues to suggest that there is an association between the presence of any comorbidity and severe COVID-19 outcomes.

- Given conflicting results across studies and the likelihood that most studies are underpowered to conduct these analyses, it is not possible to draw definitive conclusions regarding the association between specific comorbidities and severe COVID-19 outcomes.
- There is limited and conflicting evidence on the association between age and severe COVID-19 outcomes either as a sole predictor variable or alongside a comorbidity.
- There is some, albeit very limited, evidence to suggest a relationship between race and ethnicity and/or those living with social and structural inequities and severe COVID-19 outcomes.

Key Points

- Based on 11 studies, it is likely that children 12 years and under with any comorbidity have an increased risk for severe COVID-19 outcomes. The certainty of the evidence is low (GRADE); findings are likely to change as new data become available.
- Based on 4 studies, the relationship between age as a sole predictor, or age along with a comorbidity and severe COVID-19 outcomes is unclear. The certainty of the evidence is very low (GRADE); findings are very likely to change as more data become available.
- Based on 3 studies there is some evidence to suggest race and ethnicity and/or those living with social and structural inequities have an increased risk for severe COVID-19 outcomes. The certainty of the evidence is very low (GRADE); findings are very likely to change as more data become available.

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 16 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. To support decision making future studies should report results separately, at a minimum, for the following age groupings: < 1, < 12, 13-18.
- Of 11 studies assessesing the relationship between any comorbidity and severe COVID-19 outcomes, 7 reported a statistically significant increase in severe outcomes, three reported the association was not statistically significant (although it is likely these studies were underpowered to observe a statistically significant association), and one study reported the proportion of children with any comorbidity with a severe outcome was greater than the proportion of children without a comorbidity with a severe outcome; this study did not assess if this difference was statistically significant. The magnitude of risk ranged from two to three times increased risk to just under 20 times increased risk, and is dramatically higher when the upper limit of the 95% confidence interval is considered (i.e. 34.06).
- For children < 1 year there were statistically significant associations between prematurity or cardiac and circulatory congenital anomalies, and severe COVID-19 outcomes;

- For children aged 1 - 5 years there were statistically significant associations between chronic lung disease, neurological disorders, cardiovascular disease, feeding tube dependence, chronic metabolic disease, hypertension, epilepsy and/or convulsions, cardiac and circulatory congenital anomalies, or immunosuppression and severe COVID-19 outcomes;
- For children aged either 5 or 6 -11 years there were statistically significant associations between obesity, feeding tube dependence, cardiovascular disease, epilepsy and/or sleep disorders or sleep/wake disorders and severe COVID-19 outcomes.
- While two studies found those aged 5 or 6 – 11 were stastically significantly more likely to have a severe COVID-19 outcome, two other studies reported children < 1 were statistically significantly more likely to have a severe COVID-19 outcome.
- 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 eight studies explored associations between specific 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.
- While two studies reported data to December 2021, and two others to October 2021, the majority of studies reported data to July 2021 or prior; 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 Omicron 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.
- Parent representatives reflected on their lived experience accessing emergency care and highlighted the urgent need for better data collection and storage with effective, secure sharing and retrieval of data across the continuum of care. This recommendation comes not only in the context of the pandemic but in the wider generalized scope of healthcare and health research.

Methods

Research Question

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

Search

On December 6, 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 published systematic reviews were screened for the first version of this rapid review in November 2021.

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.

Data Requested and Received from Study Authors

Our search yielded several studies that explored the relationship between risk factors and severe COVID-19 outcomes in pediatric populations, but that did not report results specifically for children under 12 years. We contacted authors of these studies directly requesting additional data. Many authors reran their analyses specifically for children under 12 years and provided us with their data. The results are included in Table 1.

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

In this update, four new single studies were identified. Additionally, eight previously excluded studies were included upon receiving additional data from study authors, for a total of 16 publications addressing the research question. The quality of the evidence included in this review is as follows:

Outcome	Studies included			Overall certainty in evidence (GRADE)
	Study design	n = 16	Key findings	
Comorbidities as a risk factor for severe COVID-19 outcomes in children 12 years an under	Observational	11	The certainty of the evidence is low about the association between comorbidities and severe outcome. The certainty of the evidence is very low about the association between age and those living with social and structural inequities and severe COVID-19 outcomes Studies are likely under powered to observe statistically significant associations.	⊕⊕◯◯ Low*
Age as a risk factor for severe COVID-19 outcomes in children 12 years and under	Observational	5		⊕◯◯◯ Very low*
Sociodemographic variables as a risk factor for severe COVID-19 outcomes in children 12 years and under	Observational	3		⊕◯◯◯ Very low*

*In the GRADE approach to quality of evidence, **observational studies,** as included in this review, provide **low quality** evidence. For age and social and structural inequities 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:
New evidence reported on January 18, 2022										
Shi, T., Pan, J., Katikireddi, S., McCowan, C., Kerr, S., Agrawal, U., … Public Health Scotland & EAVE II collaborators. (2021). Risk of COVID-19 hospital admission among children aged 5–17 years with asthma in Scotland: a national incident cohort study. *The Lancet Respiratory Medicine.* Epub ahead of print.	Nov 30, 2021	Cross-sectional	Scotland	Mar 1, 2020 – Jul 27, 2021	n=416,713 aged 5–11 years	2 years before March 1st, 2020: (n=NR)	COVID-19 hospital admissions	Adjusted hazard ratio: 2.05 (95% CI=1.35, 3.12)	Additional comorbidities assessed (not statistically significant): 2 years and 1 year before March 1st, 2020: Asthma with 1 course of oral corticosteroids.	High
						Asthma without previous hospital admission (n=24973)				
						Asthma with previous hospital admission (n=1142)		Adjusted hazard ratio: 3.78 (95% CI=1.20, 11.93)		
						Asthma with 0 courses of oral Corticosteroids (n=19219)		Adjusted hazard ratio: 2.18 (95% CI=1.36, 3.50)		
						Asthma with 1 course of oral corticosteroids (n=15998)		Adjusted hazard ratio: 1.30 (95% CI=0.61, 2.79)		
						Asthma with 2 courses of oral Corticosteroids (n=3003)		Adjusted hazard ratio: 3.21 (95% CI=1.31,7.87)		
						Asthma with ≥3 courses of oral Corticosteroids (n=2667)		Adjusted hazard ratio: 4.81 (95% CI=2.33, 9.92)		
						1 year before March 1st, 2020: (n=NR)				

						Asthma without previous hospital admission		Adjusted hazard ratio: 2.08 (95% CI=1.38, 3.15)		
						Asthma with previous hospital admission		Adjusted hazard ratio: 4.39 (95% CI=1.08, 17.84)		
						Asthma with 0 course of oral corticosteroids		Adjusted hazard ratio: 2.14 (95% CI=1.38, 3.34)		
						Asthma with 1 course of oral corticosteroids		Adjusted hazard ratio: 1.08 (95% CI=0.40, 2.94)		
						Asthma with 2 courses of oral corticosteroids		Adjusted hazard ratio: 3.33 (95% CI=1.05, 10.54)		
						Asthma with ≥3 courses of oral corticosteroids		Adjusted hazard ratio: 8.11 (95% CI=3.28, 20.04)		
Bundle, N., Dave, N., Pharris, A., Spiteri, G., Deogan, C., & Suk., J. (2021). COVID-19 trends and severity among symptomatic children aged 0-17 years in ten EU countries, 3 August 2020 – 3 October 2021. *Preprint.*	Nov 29, 2021	Cross-sectional	Europe	Aug 3, 2020 – Oct 3, 2021	n=4192 aged <1 year	Any comorbidities including: cancer, diabetes, cardiac disease, lung disease, neuromuscular disease; HIV, asthma, kidney disease, hypertension, liver disease, obesity; smoker/history of smoking	Hospitalization; n=184	aOR: 1.68 (95% CI=0.38, 7.41)		Moderate ***PREPRINT***
							ICU; n=34	aOR: 1.72 (95% CI=0.30, 9.96)		
							Death; n=5	aOR: 9.05 (95% CI=0.70, 117.78)		
					n=97,260 aged 1-4 years		Hospitalization; n=1912	aOR: 8.95 (95% CI=5.02, 15.95) p<0.0001	Additional comorbidities assessed (not statistically significant): Any comorbidities in children less than 1 year and death in children 1-4 years.	
							ICU; n=95	aOR: 10.25 (95% CI=5.70, 18.45) p<0.0001		
							Death; n=7	aOR: 7.02 (95% CI=0.62, 79.09) p=0.44		
					n=281,058 aged 5-11 years		Hospitalization; n=1837	aOR: 11.98 (95% CI=9.02, 15.91) p<0.0001		
							ICU; n=159	aOR: 18.56 (95% CI=10.12, 34.06) p<0.0001		

							Death; n=18	aOR: 158.61 (95% CI=19.06, 1,319.58) p<0.0001		
Woodruff, R., Campbell, A., Taylor, C., Chai, S., Kawasaki, B., Meek, J., … Havers, F. (2021). Risk Factors for Severe COVID-19 in Children. *Pediatrics.* Epub ahead of print.	Oct 22, 2021	Cross-sectional	Children's Hospital Colorado	March to July 2020	n=450 aged <6 months	Prematurity	Severe COVID-19 outcomes (ICU admission, invasive mechanical ventilation, or death)	aRR 2.4 (95% CI 1.7, 3.5)	"Other" includes liver disease, renal disease, rheumatologic autoimmune and inflammatory conditions, chronic metabolic disease, immune-compromised conditions, chronic lung disease, neurologic disorders, airway abnormalities, feeding tube dependence, and blood disorders.	High
						Cardiovascular disease		aRR 2.4 (95% CI 1.3, 4.3)		
						Other		aRR 1.2 (95% CI 1.0, 1.4)		
					n=295 aged 6-23 months	Chronic lung disease		aRR 2.4 (95% CI 1.3, 4.2)		
						Neurologic disorders		aRR 2.3 (95% CI 1.8, 2.9)		
						Abnormality of airway		aRR 1.5 (95% CI 0.8, 2.9)		
						Cardiovascular disease		aRR 1.4 (95% CI 1.2, 1.5)		
						Prematurity		aRR 1.0 (95% CI 0.5, 1.8)		
						Feeding tube dependence		aRR 0.5 (95% CI 0.1, 1.6)		
						Other		aRR 0.9 (95% CI 0.4, 2.0)		
					n=249 aged 2-4 years	Feeding tube dependence		aRR 2.1 (95% CI 1.1, 3.9)		
						Obesity		aRR 1.4 (95% CI 0.9, 2.0)		
						Neurologic disorder		aRR 1.4 (95% CI 1.0, 1.9)		
						Chronic lung disease		aRR 1.3 (95% CI 0.9, 1.7)		
						Chronic metabolic disease		aRR 1.3 (95% CI 1.1, 1.5)		
						Cardiovascular disease		aRR 0.8 (95% CI 0.6, 1.1)		

						Other		aRR 0.6 (95% CI 0.5, 0.7)		
					n=470 aged 5-11 years	Chronic metabolic disease		aRR 1.4 (95% CI 0.9, 2.1)		
						Obesity		aRR 1.4 (95% CI 1.2, 1.6)		
						Feeding tube dependence		aRR 1.3 (95% CI 1.0, 1.7)		
						Neurologic disorder		aRR 1.1 (95% CI 0.9, 1.3)		
						Chronic lung disease		aRR 0.8 (95% CI 0.7, 1.0)		
						Cardiovascular disease		aRR 0.8 (95% CI 0.4, 1.3)		
						Immunocompromised condition		aRR 0.5 (95% CI 0.4, 0.8)		
						Blood disorder		aRR 0.6 (95% CI 0.3, 1.0)		
						Other		aRR 0.6 (95% CI 0.4, 0.7)		
Van der Zalm, M.M., Lishman, J., Verghagen, L.M., Redfern, A., Smit, L., Barday, M., … Rabie, H. (2021). Clinical Experience With Severe Acute Respiratory Syndrome Coronavirus 2–Related Illness in Children: Hospital Experience in Cape Town, South Africa. *Clinical Infectious Diseases, 72*(12), e938–e944.	Jun 15, 2021	Cross-sectional	South Africa	Apr 17, 2020 – Jul 24, 2020	n=159 aged 0 – 12 years	Comorbidities (prematurity Hematology Oncology HIV infection Tuberculosis Cardiac Gastrointestinal Asthma Other) and underlying/ concurrent conditions	Hospitalization	8/11 (73%) were aged <5 years; 7/11 (64%) had underlying/concurrent illnesses, all of whom were aged <5 years. Conditions included: HIV, Wolf-Parkinson-White Syndrome, patent ductus arteriousus, Trisomy-21, Rickets, tuberculosis and asthma.		Moderate

Previously excluded studies; authors have provided additional analysis or data (n=9)										
Kufa, T., Jassat, W., Cohen, C., Tempia, S., Wolter, N., Walaza, S., … Blumberg, L. (2021). Epidemiology of SARS-CoV-2 infection and SARS-CoV-2 positive hospital admissions among children in South Africa. *Influenza and other respiratory viruses.* Epub ahead of print.	Nov 18, 2021	Cross-sectional	South Africa	Mar 1, 2020 – Dec 31, 2021	n=13,219 aged <1-12 years	All chidren aged <1-12	Death	Case fatality risk (CFR): 3.0 (95% CI=2.7, 3.3) aOR (NR)	Additional analysis provided by study authors	Moderate
						< 1year (n=4811)		CFR: 5.0 (95% CI=4.4, 5.6) aOR: 3.33 (95% CI=2.09,5.30)		
						1-4 years (n=4489)		CFR: 1.7 (95% CI=1.4, 2.1) aOR: Ref.		
						5-9 years (n=2739)		CFR: 1.8 (95% CI=1.4,2.4) aOR: 1.02 (95% CI=0.55, 1.92)		
						10-12 years (n=1180)		CFR: 2.6 (95% CI=1.9, 3.7) aOR: 1.19 (95% CI=0.55, 5.70)		
						Asthma/CPD (n=455)		CFR: 1.8 (95% CI=0.9, 3.5) aOR: 1.19 (95% CI=0.43, 3.30)		
						Chronic kidney disease (n=14)		CFR: 14.4 (95% CI=2.9,48.0) aOR: 1.27 (95% CI=0.12, 13.01)		
						Diabetes (n=119)		CFR: 3.4 (95% CI=1.2, 8.7) aOR: 3.59 (95% CI=1.31, 11.36)		
						Cardiac disease (n=51)		CFR: 15.7 (95% CI=7.9, 28.9) aOR: 1.96 (95% CI=0.62, 6.21)		
						HIV (n=204)		CFR: 11.3 (95% CI=7.6, 16.4) aOR: 2.16 (95% CI=1.01, 4.61)		

						Hypertension (n=82)		CFR: 8.5 (95% CI=2.6, 23.9) aOR: 2.23 (95% CI=0.65, 7.64)		
						Malignancy (n=36)		CFR: 8.3 (95% CI=2.6, 23.9) aOR: 3.25 (95% CI=0.68, 15.78)		
						TB active (n=114)		CFR: 3.5 (95% CI=1.3, 9.1) aOR: 1.04 (95% CI=0.22, 4.85)		
						TB past (n=158)		CFR: 2.5 (95% CI=0.6, 6.6) aOR: 2.15 (95% CI=0.48, 9.62)		
						Other (n=326)		CFR: 12.0 (95% CI=8.8, 16.0) aOR: 2.58 (1.46, 4.57)		
						Male		CFR: NR aOR: 0.77 (95% CI=0.54, 1.09)		
						Public hospital , compared to private		CFR: NR aOR: 8.69 (95% CI=5.48, 13.77)		
Schober, T., Caya, C., Barton, M., Bayliss, A., Bitnun, A., Bowes, J., …Papenburg, J. (2021) Risk factors for severe PCR-positive SARS-CoV-2 infection in hospitalized children: a multicenter cohort study. *Preprint*	Nov 8, 2021	Cross-sectional	Canada Iran Costa Rica	Feb 1, 2020 – May 31, 2021	n=308 aged <12 years	Obesity	Severe COVID-19 and/or ICU admission	OR: 2.85 (95% CI=1.45, 5.58)	Additional analysis performed by study authors.	High ***PREPRINT***
						Pulmonary disorders		OR: 2.38 (95% CI=1.17, 4.82)		
						Non-asthma pulmonary disorders		OR: 4.33 (95% CI=1.60, 11.70)		
						Neurological disorders		OR: 2.74 (95% CI=1.33, 5.63)		
						Chromosomal disorders		OR: 4.84 (95% CI=1.06, 22.18)		
						Multiple comorbidities		OR: 2.85 (95% CI=1.45, 5.58)		

Tagarro, A., Cobos-Carrascosa, E., Villaverde, S., Sanz-Santaeufemia, F., Grasa, C., Soriano-Arandes, A., ... Moraleda, C. (2021). Clinical spectrum of COVID-19 and risk factors associated with severity in Spanish children. *European Journal of Pediatrics.* Epub ahead of print.	Nov 5, 2021	Cross-sectional	Spain	Mar 12, 2020 – Mar 22, 2021	n=903 aged <12 years of age	Having any comorbidity (n=201) including: MISC-C, chronic cardiac disease, hypertension, chronic pumonary disease, asthma, chronic kidney disease, moderate or severe liver disease, mild liver disease, chronic neurological disorder, malignant neoplasm, chronic hematologic disease, obesity, diabestes, inflammatory disease, malnutrition	Admission to ICU	aOR: 1.42 (95% CI=0.64, 3.1)		Moderate
Navarro-Olivos, E., Padilla-Raygoza, N., Flores-Vargas, G., Gallardo-Luna, M., León-Verdín, M., Lara-Lona, E., ...Díaz-Martínez, D. (2021). COVID-19-Associated Case Fatality Rate in Subjects Under 18 Years Old in Mexico, up to December 31, 2020. *Frontiers in Pediatrics,* 9, 696425.	Oct 1, 2021	Cross-sectional	Mexico	Mar 2020 – Dec 31, 2021	n=20 935 aged <12 years of age	Age 0-2 (n=5573)	Death	CFR: 3.84 (95% CI=3.32, 4.54)	Additional analysis performed by study authors.	High
						Age 3-5 (n=3666)		CFR: 0.71 (95% CI=0.44, 0.98)		
						Age 6-11 (n=11,696)		CFR: 0.53 (95% CI=0.39, 0.66)		
						Diabetes (n=174)		OR: 7.22 (95% CI=4.37, 11.93)		
						Immunosuppression (n=350)		OR: 5.37 (95% CI=3.49, 8.24)		
						Hypertension (n=179)		OR: 8.32 (95% CI=1.54, 4.09		
						Cardiovascular disease (n=203)		OR: 6.99 (95% CI=4.25, 7.66)		
						Chronic kidney disease (n=62)		OR: 10.35 (95% CI=4.88, 21.93)		
						Pneumonia (n=1217)		OR: 41.65 (95% CI=32.42, 53.49)		
						Obesity (n=559)		OR: 1.38 (95% CI=0.75, 2.54)		
						Asthma (n=596)		OR: 0.33 (95% CI=0.11, 1.05)		

						Having any comorbidity (n=2283)		OR: 4.79 (95% CI=1.56, 2.51)		
						Aged 0-2		Hypertension (n=125) aOR: 4.03 (95% CI= 2.29, 7.19)		
						Aged 3-5		Immunosuppression (n=83) aOR: 14.72 (95% CI=5.73, 37.79)		
						Aged 6-11		Cardiovascular disease (n=61) aOR: 10.65 (95% CI=3.24, 35.02)		
Drouin, O., Hepburn, C., Farrar, D., Baerg, K., Chan, K., Cyr, C., … Morris, S. (2021). Characteristics of children admitted to hospital with acute SARS-CoV-2 infection in Canada in 2020. *Canadian Medical Association Journal, 193*(38), E1483 – E1493.	Sep 27, 2021	Cross-sectional	Canada	Apr 8, 2020 – Dec 31, 2020	n=172 aged <12 years of age	Infant (<1 year) (n=96)	Hospitalization with severe COVID-19; n=47 compared to hospitalization with non-severe COVID-19; n=60	Infants had the highest proportion of severe COVID-19 hospital admissions (44.7% vs. 21.3% vs. 34%), p=0.01.		Moderate
						Preschool (1-4 years) (n=42)				
						School age (5-<12 years) (n=34)				
						Having any comorbidity (n=50)	Hospitalization with severe COVID-19; n=47 compared to hospitalization with non-severe COVID-19; n=60	One or more comorbidities (55.3%) vs. having none (44.7%) p=0.006		
						Chronic encephalopathy (n<15)		Severe (44.7%) vs. non-severe (18.3%); p=0.003		
						Chronic lung disease (excluding asthma) (n=7)		Severe (14.9%) vs. non-severe (0%); p=0.005		
						Epilepsy (n<11)		Severe (12.85%) vs. non-severe (8.7%); p=0.04		

Størdal, K., Ruiz, P., Greve-Isdahl, M., Surén, P., Knudsen, P., Gulseth, H., & Tapia, G. (2021). Risk factors for SARS-CoV-2 infection and hospitalisation in children and adolescents in Norway: A nationwide population-based study. *Preprint.*	Jul 5, 2021	Cross-sectional	Norway	Mar 1, 2020 – Apr 31, 2021	n=835 498 aged <12 years of age	Age (6-11) (n=36)	Hospitalization	aHR:0.23 (95% CI=0.16, 0.34)		High ***PREPRINT***
						Gender (female) (n=69)		aHR:0.91 (95% CI=0.63, 1.30)		
						SES (low) (n=35)		aHR:1.38 (95% CI=0.90, 2.11)		
						Cerebral palsy (n=74)		aHR:0.79 (95% CI=0.63, 1.00)		
						Neurological/muscular disorders (n=53)		aHR: 0.78 (95% CI=0.59, 1.03)		
						Chromosomal conditions (n=81)		aHR: 0.85 (95% CI=0.68, 1.07)		
						Trisomy-21 (n=53)		aHR: 0.79 (95% CI=0.59, 1.04)		
						Cancer (n=32)		aHR:0.52 (95% CI=0.37, 0.74)		
						Transplant and immune disorders (n=33)		aHR: 0.77 (95% CI=0.55, 1.10)		
						Asthma (n=2945)		aHR:0.91 (95% CI=0.88, 0.95)		
						Cardial/Pulmonary disease (except asthma) (n=519)		aHR: 1.08 (95% CI=0.99, 1.18)		
						Diabetes mellitus (n=86)		aHR: 0.88 (95% CI=0.71, 1.09)		
						Rheumatological conditions (n=25)		aHR: 0.77 (95% CI=0.52, 1.13)		
						Inflammatory bowel disease (n=16)		aHR: 0.76 (95% CI=0.46, 1.26)		
						Celiac disease (n=206)		aHR: 0.76 (95% CI=0.46, 1.26)		
						Liver/billary disorders (n=7)		aHR: 0.83 (95% CI= 0.36, 1.90)		
						Kidney disorders (n=80)		aHR: 0.94 (95% CI=0.75, 1.17)		

						Having any chronic condition (n=4210)		aHR: 0.92 (95% CI=0.89,0.95)		
						Age 6-11 and having any chronic condition compared to <5 and having a chronic condition		aHR: 3.27 (95% CI=2.15, 4.97)		
Armann, J., Doenhardt, M., Hufnagel, M., Diffloth, N., Reichert, F., Haas, W., … Berner, R. (2021). Risk factors for hospitalization, disease severity and mortality in children and adolescents with COVID-19: Results from a nationwide German registry. *Preprint.*	Jun 13, 2021	Cross-sectional	Germany	Mar 18, 2020 – Apr 30, 2021	n=1500 aged <12 years of age	Respiratory, pulmonary (n=15), cardiovascular (n=11), gastrointestinal (n=5), hepatic (n=1), renal (n=0) neurological/neuromuscular (n=21), psychiatric (n=1), hematological (n=3), oncological (n=3), organ (n=1), autoimmunological (n=2), primary immunodeficiency (n=4), HIV infection (n=0), tracheostoma (n=4), syndromal disease (n=9), Trisomy-21 (n=4)	ICU admission	RR: 8.6 (95% CI=4.64, 15.97)	Additional data provided by study authors.	Moderate ***PREPRINT***
							Death	RR: 2.4 (95% CI=2.02, 2.9)		
Moreira, A., Chorath, K., Rajasekaran, K., Burmeister, F., Ahmed, M., & Moreira, A. (2021). Demographic predictors of hospitalization and mortality in US children with COVID-19. *European Journal of Pediatrics,* 180, 1659-1663.	Jan 20, 2021	Cross-sectional	United States	Mar 2, 2020 – Jul 16, 2020	n=8121 <10 years of age	American Indian/Alaska Native, NH (n=45)	Hospitalization	Risk factors for hospitalization due to COVID-19 among children <10 are being Black, NH [OR 2.28 (95% CI: 1.93, 2.70)] or mixed race, NH [OR 2.95 (95% CI: 2.28, 3.82)] ethnicity and having an underlying medical condition	Additional data provided by study authors.	Moderate
						Asian, NH (n=385)				
						Black, NH (n=1354)				
						Hispanic/Latino (n=4014)				
						Multiple/Other/NH (n=311)				
						Native Hawaiian, Pacific Islander, NH (n=202)				

						Female (n=215)		[OR 3.55 (95% CI: 3.14, 4.01)].		
						Comorbidities (asthma, autoimmune disease, cardiovascular disease, chronic lung disease, neurologic disease, obesity, renal disease, other) (n=3004)				
						American Indian/Alaska Native, NH (n=27)	Death	Risk factors for death due to COVID-19 among children <10 are being Black, NH [OR 2.96 (95% CI: 1.30, 6.73)] and having an underlying medical condition [OR 8.8 (95% CI: 3.7, 21.1)].		
						Asian, NH (n=259)				
						Black, NH (n=1047)				
						Hispanic/Latino (n=3028)				
						Multiple/Other/NH (n=212)				
						Native Hawaiian, Pacific Islander, NH (n=109)				
						Female (n=2974)				
						Comorbidities (asthma, autoimmune disease, cardiovascular disease, chronic lung disease, neurologic disease, obesity, renal disease, other) (n=2149)				

Previously reported evidence										
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, 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, 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

MIS-C: Multisysyem inflammatory syndrome in children
NH : Non-Hispanic
NR: Not Reported

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