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Rapid Review: What are the risk factors associated with severe COVID-19 outcomes in children 5 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: Tamy Bell and Marion Knutson of COVID-END in Canada's citizen pool; and 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 5 have been vaccinated and some public health measures have been relaxed, leaving those under age 5 vulnerable to infection and severe illness. Pending the approval of COVID-19 vaccines for children under 5 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 5 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 February 10, 2022 to answer the question: **What are the risk factors associated with severe COVID-19 outcomes in children 5 years and under?**

What has Changed in This Version?

- This review builds on a previous review of risk factors associated with severe COVID-19 outcomes in children aged 0-12 released in January 2022, adding four new studies. In the previous review, six included studies reported results specifically for children aged 5 years and under; resulting in a total of 10 studies included in this update. The 10 studies were conducted in the United States (n=3), South Africa (n=2), Canada (n=1), Scotland (n=1), Mexico (n=1), Europe (Austria, Cyprus, Finland, Germany, Ireland, Italy, Luxembourg, Malta, Slovakia and Sweden) (n=1) and multi-national; United States, United Kingdom, Italy, France, Turkey, United Arab Emirates and Iran (n=1). These studies include data collected from early 2020 to the end of 2021.
- There is limited but increasing evidence exploring the association between severe COVID-19 outcomes and age as a sole predictor variable, including among neonates (≤ 28 days old).
- The evidence continues to grow for the association between severe COVID-19 outcomes and the presence of any comorbidity in children aged 5 years and under;
- Given there are few studies, inconsistent results across studies and that studies are small and underpowered, it is not possible to draw definitive conclusions regarding the association between specific comorbidities and severe COVID-19 outcomes.

- There is some, albeit very limited, evidence suggesting a relationship between race and ethnicity and those living with social and structural inequities and severe COVID-19 outcomes.

Key Points

- Based on 6 studies, the evidence demonstrates age as a sole predictor of severe COVID-19 outcomes, with neonates at the highest risk for severe outcomes. The certainty of the evidence is low (GRADE); findings are very likely to change as more data become available.
- Based on 8 studies, there is consistent evidence that children 5 years and under with any comorbidity have an increased risk for severe COVID-19 outcomes. The certainty of the evidence is moderate (GRADE); findings are unlikely to change as new data become available. Neonates and those under 1 year with one or more comorbidities may experience the highest risk for severe outcomes; (based on 6 studies). The certainty of the evidence is low (GRADE); findings are likely to change as new data become available.
- Based on 5 studies, the evidence suggests there is an association between age, having any comorbidity and severe outcomes. The certainty of the evidence is low (GRADE); findings are very likely to change as new evidence emerged.
- Based on 5 studies, the evidence suggests there is an association between age and specific comorbidities. The certainty of the evidence if very low (GRADE); findings are very likelyt o change as new evidence emerges. Furthermore, based on 3 studies, prematurity (<34 weeks gestation) statistically significantly increases the risk for severe COVID-19 outcomes among neonates and those 1 year and under. The certainty of the evidence is very low (GRADE); findings are very likely to change as new data become available.
- Based on 2 studies there is limited evidence to suggest race and ethnicity and 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 for the association between risk factors and severe COVID-19 outcomes is limited, with only 10 studies reporting data specifically for children 5 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, 1-5, 6-12, 13-18), analyses of risk factors for severe COVID-19 outcomes are generally reported for the sample as a whole. Given the results of this review illustrate differences in risk for severe outcomes among the very young (neonates) compared to infants, toddlers and pre-schoolers, future studies should report results for the following age groupings: ≤28 days, 1-3 months, 3-6 months, <1 year, 1-5, <12 and 13-18 years.
- Similar to previously reported results, studies are generally underpowered to observe statistically significant associations between specific risk factors and severe COVID-19 outcomes. This is due to relatively few children experiencing severe outcomes.
- This review includes a recently published moderate quality meta-analysis of 17 studies. While the overall finding reported the association between age and severe COVID-19 outcomes was not statistically significant among those 1 year and under, sub-group

analysis demonstrates a statistically significant increased risk for severe outcomes among neonates compared to those aged 1-3 months; RR: 2.69 (95% CI=1.83, 3.97), p<0.00001.

- Of 4 single studies reporting statistical significance for the relationship between any comorbidity and severe COVID-19 outcomes, 1 reported a statistically significant difference between those with a severe outcome with any comorbidity versus those without a severe outcome and any comorbidity; and 3 reported statistically significant increased risk for severe outcomes in the presence of any comorbidity, compared to those without a comordibity. The magnitude of risk (relative risk; RR) across studies ranged from 4.53 to 17.92, with confidence intervals (95%) ranging from 2.06 to 44.55).
- 5 studies assessed the relationship between specific comorbidities and severe outcomes in children aged 0-2 months, 3-5 months, <12 months, 6-23 months and 2-5 years . Overall, statistically significant associations with severe outcomes were reported for the following comorbidities: cardiac and circulatory congenital anomalies; chronic lung conditions; and feeding tube dependence.
- For children <2 years, statistically significant assocations were reported for prematurity, cardiovascular condition, respiratory condition, abnormality of airways, neurologic disorder, feeding tube dependence and hypertension.
- For children 2-5 years, statistically significant assocations were reported for neurodevelopmental disorders, epilepsy and/or convulsions, obesity, chronic metabolic disease and immunosuppression.
- Overall, four studies reported a statistically significant increased risk among younger children for severe COVID-19 outcomes compared to older children (e.g., neonates vs. 0-3, 4-6, 6-12 months and 1 year vs. 1-5, 3-5 years). One study found more severe outcomes for slightly older infants; age range 1-4 months vs. 0-2 months.
- While 2 studies reported data to the end of December 2021, and one other to October 2021, the majority of studies reported data to August 2021 or prior; therefore, the findings of this review may not reflect current rates of severe illness and associated risk factors among those 5 years and under related to the Omicron variant of concern.

Further Considerations for Vaccine Programs for Children 5 and under: Perspectives of Parents of Children with Underlying Health Conditions

- Feedback provided by a parent representative suggested a further breakdown of severe outcomes (i.e. hospitalization, admittance to the intensive care unit, death). Significantly larger studies are required in order for statistically significant associations between risk factors and specific severe outcomes to be observed. Collaboration between researchers internationally to combine data sets is needed in order to address this issue.
- Parent representatives expressed interest in hearing how children under 5 with underlying health conditions who experienced severe outcomes presented at the outset of getting COVID-19, and what the disease progression looked like (i.e. was it a sudden escalation, or long, drawn-out illness). Parents are also interested in hearing more about long COVID-19 among children with underlying health conditions.
- Parents also had questions about vaccination status among children under 5 with underlying health conditions. Specifically they wanted to know if vaccinated children with underlying health conditions had less severe outcomes than unvaccinated children. They also wanted to know how effective one dose of the vaccine was in comparison to

two doses. Future studies should report results by vaccination status, when possible (i.e. vaccines available for children under 5).
- As reported previously for children 12 and under, parents of children 5 and under recommend vaccines be made as accessible as possible taking into account the unique challenges faced by these children, such as running vaccine clinics that cater to sensory needs, curbside vaccination, so as to avoid crowds, particularly as these children may be unmasked.

Perspectives of Parents of Children 12 and under with Underlying Health Conditions (collected previously for January 2022 update)

- 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.
- Alternatively, 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. 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.
- 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. 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.

- 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 5 years and under?

Search

On February 10, 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 studies included in a previous review on risk factors for severe COVID-19 outcomes in children 12 years and under, published January 18, 2022, were screened for inclusion in this review. 6 studies were subsequently included.

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 0-5 years -≥50 participants	-Ages 6 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

Six studies identified in a previous review on risk factors for severe outcomes in children 12 years and under met the eligibility requirements for this review. For the review on children under 12 years, 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 re-ran their analyses specifically for children under 12 years and provided us with their data. Some (n = 2) provided results specific to ages 0-5 and therefore are included in this review. 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 a new section of the review entitled: 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
Systematic Review	Assessing the Methodological Quality of Systematic Reviews (AMSTAR) AMSTAR 1 Tool

The Joanna Briggs Institute Checklist for Analytical Cross Sectional Studies was used to appraise all single 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, three new single studies and one synthesis were identified. Six studies from the previous update were included with results for ages 0-5. for a total of 10 publications addressing the research question. Studies may be captured in more than one outcome. The quality of the evidence included in this review is as follows:

Outcome	Studies included			Overall certainty in evidence (GRADE)
	Study design	n = 10	Key findings	
Age as a risk factor for severe COVID-19 outcomes in children 5 years and under	Observational	6	The evidence is uncertain about the association between age and severe outcomes.	⊕⊕◯◯ Low
Any comorbidity as a risk factor for severe COVID-19 outcomes in children 5 years and under	Observational	8	Children with any comorbidity likely have the highest risk for severe outcomes.	⊕⊕⊕◯ Moderate
Age and comorbidities as risk factors for severe COVID-19 outcomes in children 5 years and under	Observational	5	Younger children may experience the highest risk for severe outcomes.	⊕⊕◯◯ Low

Specific comorbidities and age as risk factors for severe COVID-19 outcomes in children 5 years and under	Observational	5	The evidence is very uncertain about age and specific comorbidities.	⊕◯◯◯ Very low*
Prematurity and age as risk factors for severe COVID-19 outcomes in children 5 years and under		3		
Sociodemographic variables as a risk factor for severe COVID-19 outcomes in children 5 years and under	Observational	2	The evidence is very low about the association of age and those living with social and structural inequities and severe outcomes.	⊕◯◯◯ Very low*

*In the GRADE approach to quality of evidence, **observational studies,** as included in this review, provide **low quality** evidence. For any comorbidity this assessment was upgraded to **moderate quality** based on large effect. For specific comorbidities this assessment was reduced to **very low** based on inconsistency in effects. For sociodemographic variables this assessment was 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 5 years and under?

Table 1: Synthesis

Reference	Date released	Risk factors (comorbidities and/or PROGRESS+ factors)	Review conclusion	Quality Rating:
New evidence reported on March 7, 2022				
Choi, J. H.,Choi, S. H.,& Yun, K. W. (2022). Risk Factors for Severe COVID-19 in Children: A Systematic Review and Meta-Analysis. *Journal of Korean Medical Science. 37*(5): e35.	Jan 21, 2022 (Search completed Aug 25, 2021)	Age (≤1 year)	This systmatic review and meta-analysis included 17 studies that estimated the association between risk factors and severe COVID-19 in children, particularly neonates (≤ 28 days old) and those infants younger than 3 months. Studies that included severe outcomes (i.e., ICU admission, invasive mechanical ventilation and/or death) in children of young age (n=6) identified 1699 cases aged ≤1 year; pooled risk ratio (RR) was 1.03 (95% Confidence interval (CI))I=0.74, 1.41), p=0.87 with high heterogeneity across studies (I^2=86%). Estimates differed significantly across age groups: • ≤1 year (n=354); RR: 0.45 (95% CI=0.18, 1.16), p=0.10 • ≤3 months (n=274); RR: 0.26 (95% CI=0.11, 0.66), p=0.004 • ≤28 days (n=1071); RR: 2.69 (95% CI=1.83, 3.97), p<0.00001 While additional risk factors (i.e., prematurity, obesity, diabetes, complex genetic disorders, respiratory disease, heart disease, neurologic disease and immunocompromised disease) were assessed, analyses were not reported specifically for children < 5 years.	Moderate

Table 2: Single study findings for Children Ages 0-5

Reference	Date	Study Design	Setting	Data Collection Dates	Participants ≤ 5 years	Risk factors (comorbidities and/or PROGRESS+ factors); number of participants with risk factor	Outcome	Effect estimate	Notes	Quality Rating:
New evidence reported on March 7, 2022										
Piché-Renaud, P-P., Panetta, L., Farrar, D.S., Moore-Hepburn, C., Drouin, O., Papenburg, J., … the Canadian Paediatric Surveillance Program COVID-19 Study Team. (2022). Clinical manifestations and disease severity of SARS-CoV-2 infection among infants in Canada. *Preprint.*	Feb 7, 2022	Cross-sectional	Canada	Apr 8, 2020 – May 31, 2021	n=531 aged <1 year	Age <1 month (compared to age 1-3 months) n=81	Hospitalized with severe disease (ICU admission, acute respiratory distress syndrome, severe neurological symptoms, ventiliation or vasopressors) n=20	adjusted odds ratio (aOR): 3.78 (95% CI=1.97, 7.26)	Population groups with the highest proportion of infants hosptalized with COVID-19 were White (31.9%), Arab/West Asian (14.9%), Indigenous (3.5-5.7%) or unknown (24.8%) p<0.001. * * * The dataset for this study is the Canadian Paediatric Surveillance Program (CPSP).	High ***PREPRINT***
						Age 4-6 months (compared to age 1-3 months) n=151		aOR: 0.24 (95% CI= 0.12, 0.47)		
						Age 7-12 months (compared to age 1-3 months) n=181		aOR: 0.13 (95% CI=0.06, 0.25)		
						Having ≥1 comorbidity compared to none n=59		aOR: 4.53 (95% CI=2.06, 9.97)		
						Prematurity (<34 weeks gestation) n=27		aOR: 3.54 (95% CI=1.19, 10.46)		

Hardelid, P., Favarato, G., Wijlaars, L., Fenton, L., McMenamin, J., Clemens, T., ... Wood, R.(2022). Risk of SARS-CoV-2 testing, PCR-confirmed infections and COVID-19--related hospital admissions in children and young people: birth cohort study. *Preprint.*	Jan 5, 2022	Cross-sectional	Scotland	Feb 1 – Dec 31, 2020	n=299,216 aged 1-4 years	Age 1-4 compared to age <1 year	Hospitalization; n=104	adjusted hazard ratio (aHR): 0.13 (95% CI= 0.09, 0.19)	Comorbidities include: developmental/ mental health, blood/cancer, chronic infections, respiratory, metabolic/ gastrointestinal/ endocrine/ genitourinary, musculoskeletal /skin, neurological/ sensory, and cardiac conditions.	High ***PREPRINT***
					n=92,539 aged <1 year	Having >1 comorbidity compared to none		aHR: 17.92 (95% CI=7.21, 44.55)		
					n=206,677 aged 1-4 years	Having >1 comorbidity compared to none		aHR: 12.87 (95% CI=5.12, 32.40)		
Hobbs, C.V., Woodworth, K., Young, C.C., Jackson, A.M., Newhams, M.M., Dapul, H., ... Overcoming COVID-19 Investigators. (2022). Frequency, Characteristics and Complications of COVID-19 in Hospitalized Infants. *The Pediatric Infectious Disease Journal. 41*(3): e81–e86.	Dec 24, 2021	Cross-sectional	United States	Mar 15 – Aug 13, 2020	n=206 aged >7 days to <1 year	Age	Hospitalized severe COVID-19 (n=104) compared to non-severe COVID-19 (n=102)	Infants with severe outcomes were older than infants with non-severe outcomes (age range 1–4 months vs. 0-2 months), p= 0.001.	Infants who are Black NH, Hispanic and other NH accounted for the majority of severe outcomes (69.2%), p=0.20 * * * Neurologic conditions were assessed but found to be not-significant.	Moderate
						≥1 comorbiditiy n=40		Severe outcomes (31.7%) vs. non-severe (6.9%), p< 0.001.		
						Respiratory condition n=9		Severe outcomes (8.7%) vs. non-severe (0%), p=0.003		
						Cardiovascular condition n=14		Severe outcomes (12.5%) vs. non-severe (1%), p=0.001		

						Other conditions (including oncologic, immunosuppressive, rheumatologic, autoimmune, hematologic, renal, urologic, gastrointestinal, hepatic, endocrine and metabolic conditions) n=32		Severe (26%) vs. non-severe (4.9%), p<0.001	Obesity is excluded.	
Previously reported evidence										
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. *Eurosurveillance 26*(50), 2101098.	Dec 16, 2021	Cross-sectional	Europe; Austria, Cyprus, Finland, Germany, Ireland, Italy, Luxombourg, Malta, Slovakia, Sweden	Aug 3, 2020 – Oct 3, 2021	n=4192 aged <1 year n=97,260 aged <5 years	Any comorbidities including: cancer, diabetes, cardiac disease, lung disease, neuromuscular disease; HIV, asthma, kidney disease, hypertension, liver disease, obesity; smoker/history of smoking compared to none.	Hospitalization; n=184 ICU; n=34 Death; n=5 Hospitalization; n=1912 ICU; n=95 Death; n=7	aOR: 1.68 (95% CI=0.38, 7.41) aOR: 1.72 (95% CI=0.30, 9.96) aOR: 9.05 (95% CI=0.70, 117.78) aOR: 8.95 (95% CI=5.02, 15.95) p<0.0001 aOR: 10.25 (95% CI=5.70, 18.45) p<0.0001 aOR: 7.02 (95% CI=0.62, 79.09)	Additional comorbidities assessed (not statistically significant): Any comorbidities in children less than 1 year and death in children 1-4 years.	Moderate
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	United States	Mar 1, 2020-Jan 31, 2021	n=7904 aged ≤1 year n=5034 aged 2-5 years	Prematurity; n=479 Cardiac and circulatory congenital anomalies; n=306 Digestive congenital anomalies; n=132 Neurodevelopmental disorders; n=195 Epilepsy and/or convulsions; n=111	Hospitalized with severe illness	adjusted relative risk (aRR): 1.83 (95% CI=1.47, 2.29) aRR: 1.89 (95% CI=1.48, 2.41) aRR: 0.52 (95% CI=0.28, 0.96) aRR: 0.61 (95% CI=0.43, 0.88) aRR: 1.95 (95% CI=1.40, 2.74)	Additional comorbidities assessed (not statistically significant) include: other congenital anomalies, esophageal disorders,	Moderate

						Cardiac and circulatory congenital anomalies; n=84		aRR: 1.50 (95% CI=1.05, 2.16)	musculoskeletal disorders, genitourinary disorders, asthma, implant device or graft related encounters, other upper respiratory disease, obesity and anxiety and fear related disorders.	
Woodruff, R., Campbell, A., Taylor, C., Chai, S., Kawasaki, B., Meek, J., … Havers, F. (2021). Risk Factors for Severe COVID-19 in Children. *Pediatrics* 149(1).	Oct 22, 2021	Cross-sectional	United States	Mar – Jul 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)		
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=87 aged ≤5 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

Studies with additional analysis or data provided by authors (n=2)										
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 16*(1) p34-47.	Nov 18, 2021	Cross-sectional	South Africa	Mar 1, 2020 – Dec 31, 2021	n=9300 aged <1-4 years	<1 year (n=4811) 1-4 years (n=4489)	Death	Case fatality rate (CFR): 5.0 (95% CI=4.4, 5.6) aOR: 3.33 (95% CI=2.09,5.30) CFR: 1.7 (95% CI=1.4, 2.1) aOR: Ref.	Additional analysis provided by study authors.	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=9239 aged 0-5	Age 0-2 (n=5573) Age 3-5 (n=3666) Aged 0-2 Hypertension (n=125) Aged 3-5 Immunosuppression (n=83)	Death	CFR: 3.84 (95% CI=3.32, 4.54) CFR: 0.71 (95% CI=0.44, 0.98) aOR: 4.03 (95% CI = 2.29, 7.19) aOR: 14.72 (95% CI=5.73, 37.79)	Additional analysis performed by study authors.	High

ICU: Intensive Care Unit
MIS-C: Multisysyem inflammatory syndrome in children
NH: Non-Hispanic
NR: Not Reported

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