



MEDICINE

# Covid-19 in Children

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## Topics I want to cover:

- Burden of disease
- Severity of Covid-19 in children
- Management of Covid-19 in children
- Coinfections in confirmed cases
- MISC



### Prevalence of COVID-19 Reported in Children – 13 Countries



Country (date of data)	Total # cases	0-19	0-19 Years		0-9 Years		10-18 Years	
Africa (June 6) <sup>1</sup>	124,289	469	0.4%	189	0.2%	280	0.2%	
China (Feb 11) <sup>2</sup>	44,672	965	2.1%	416	0.9%	549	1.2%	
Mexico (June 6) <sup>3</sup>	110,026	3,008	2.7%	1,038	0.9%	1,970	1.8%	
Brazil (May 23) <sup>4</sup>	117,598	4,019	3.4%	1,973	1.7%	2,046	1.4%	
United States (June 6) 5	1,516,175	64,177	4.2%		-		-	
EU/EEA/UK (June 4) <sup>6</sup>	635,274	26,817	4.2%	8,906	1.4%	17,911	2.8%	
Australia (June 5) 7	7,173	336	4.4%	104	1.3%	232	3.1%	
Canada (June 5) <sup>8</sup>	92,264	6,025	6.5%		-		-	
Japan (May 28) <sup>9</sup>	11,344	799	7.1%	155	1.4%	644	5.7%	
South Korea (May 22) 10	11,402	806	7.1%	156	1.4%	650	5.7%	
Moscow (new cases May 21) 11	2,830	201	7.1%		-		-	
New Zealand (May 22) 12	1,504	157	10.4%	36	2.4%	121	8.0%	
India (April 26) 13	2,344	326	13.9%	98	4.2%	228	9.7%	
TOTAL	2,676,982	108,105	4.0%	13,071	1.2%*	24,631	2.3%*	
<u>1 https://www.afro.who.int/health-topics/coronavirus-covid-19</u> <u>2 https://www.statista.com/statistics/1095024/china-age-distribution-of-wuhan-coronavirus-covid-19-patients/</u> <u>3 https://coronavirus.gob.mx/datos/</u> <u>4 https://portalarguivos.saude.gov.br/images/pdf/2020/May/21/2020-05-19BEE16Boletim-do-COE-13h.pdf</u> <u>5 https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/cases-in-us.html</u> § bttps://ovid19-surveillance-report ecdc.guvona.gu/			h-infobase.canada.ca/c 3.nhk.or.jp/news/specia v.statista.com/statistics/ v.statista.com/statistics/ v.health.covt.nz/our-wov	ovid-19/epidemiolog //coronavirus (d(ຜ້າວ) 1102730/south-kore 1109859/covid-19-c k/diseases-and-con	ical-summary-covid-19- id 2: a-coronavirus-cases-by ases-by-age-group-mos ditions/covid-19-novel-d	<u>-cases.html</u> - <u>-age/</u> scow/ coronavirus/covid-1	* denominator 1,065,6	

<sup>7</sup> https://www.health.gov.au/news/health-alerts/novel-coronavirus-2019-ncov-health-

alert/coronavirus-covid-19-current-situation-and-case-numbers#cases-and-deaths-by-age-and-sex

19 https://www.covid19india.org/deepdive

# Pediatric Mortality

#### International heterogeneity in coronavirus disease 2019 pediatric n

Heterogeneidad internacional en las tasas de mortalidad pediátrica por COVID-19

Nadia González-García<sup>1</sup>, América L. Miranda-Lora<sup>2</sup>, Juan Garduño-Espinosa<sup>3</sup>, Javier T. Granados-Riveró

<sup>1</sup>Laboratorio de Investigación en Neurociencias; <sup>2</sup>Unidad de Investigación en Medicina Basada en Evidencias; <sup>3</sup> Investigación en Enfermedades Emergentes; <sup>6</sup>Dirección General. Hospital Infantil de México Federico Gómez, Mexico

Paediatric mortality rate is 1-10% that of the adult population Table 1. Mortality indices by COVID-19 and neonatal mortality in 2018 by country.

Country	COVID- 19 Deaths in populati on < 15 years of age	COVID- 19 Mortality rate in <15 years of age, per million people	COVI D-19 Mortal ity rate in gener al popul ation per millio n peopl e (23/08/ 20)	Pediatr ic/ Genera I COVID -19 mortali ty rate ratio (%)	Neonatal mortality (every cause) per 1000 alive newborns in 2018	Date of d a t a
Peru	94	12.1	852	1.4	7.3	09/08/2020
Brazil <sup>ab</sup>	405	8.8	541	1.6	8.1	02/08/2020
Ecuador <sup>b</sup>	25	5.5	367	1.5	7.2	13/08/2020
Mexico	169	5.1	472	1.5	7.5	18/08/2020
India <sup>a</sup>	1622	4.35	42	10.4	22.7	05/08/2020
Chile	15	4.1	576	0.7	4.9	05/08/2020
Colombia	29	2.9	334	0.9	7.8	05/08/2020
Indonesia ad	88	1.3	25	5.2	12.7	05/05/2020
Philippines <sup>ac</sup>	40	1.2	29	4.3	13.5	05/08/2020
Argentina <sup>a</sup>	13	1.1	153	0.7	6.4	10/08/2020
Spain <sup>a</sup>	5	0.8	616	0.1	1.7	21/05/2020
United States of America <sup>a</sup>	46	0.8	533	0.1	3.5	01/08/2020
United Kingdom	7	0.6	623	0.1	2.6	05/08/2020
Sweden <sup>a</sup>	1	0.6	571	0.1	1.5	05/08/2020
Italy	4	0.6	586	0.1	2	28/07/2020
France	4	0.35	454	0.1	2.54	12/07/2020
Canada <sup>a</sup>	1	0.1	245	0.1	3.4	26/08/2020
Germany <sup>a</sup>	1	0.1	111	0.1	2.2	05/08/2020
Australia <sup>a</sup>	0	0	19	0	2.3	05/08/2020
Austria	0	0	83	0	2.1	05/08/2020
Finland	0	0	61	0	1	05/08/2020
Greece	0	0	22	0	2.6	05/08/2020
Republic of Korea	0	0	6	0	1.5	05/08/2020

# **Indonesia Current Situation**

### July 23, 2021



https://covid19.go.id/peta-sebaran

# Mortality by Age

**79,032** DEATHS 2.6 % From Confirmed

NUMBER of Pediatric Death Case 1.0% from all death cases = 790

CFR of Pediatric Case 790 from all death cases (388.276) = 0.20%





#### Consistent with Less Severe Disease, Children Were Less Likely to Require ICU or Significant Treatments

Liguoro I et al. Eur J Pediatr. 2020 May 18



Systematic Review - Liguoro I et al. Eur J Pediatr. 2020 May 18

Guan W et al. N Engl. J Med. 2020 Feb 28 (China data)

## Hypothetical reasons why children less affected





angiotensin-converting enzyme 2 (ACE2) and transmembrane serine protease 2 (TMPRSS2)

# Clinical Presentation Covid-19 in Children



Sore throat - Nasal congestion - Running nose - Cough

Cough - Tachypnea - Shortness ofbreath - Dyspnea - Cyanosis - Oxygen saturation < 92% - Acute respiratory distress syndrome

Nausea/vomiting - Abdominal pain - Diarrhea - Trouble feeding

Headache-Dizzines-Seizures

Fever – Fatigue – Myalgia - Skin rash - Multiple organ failure - Multisystem inflammatory syndrome



# Management of Covid-19 in Children

Klasifikasi	Definisi					
Asimtomatik	Hasil uji SARS-CoV-2 positif tanpa ada tanda dan gejala klinis.					
Ringan	Gejala infeksi saluran napas atas seperti demam, fatigue, mialgia, batuk, nyeri tenggorokan, pilek, dan bersin. Beberapa kasus mungkin tidak disertai demam, dan lainnya mengalami gejala saluran pencernaan seperti mual, muntah, nyeri perut, diare, atau gejala non-respiratori lainnya.					
Sedang	Gejala dan tanda klinis pneumonia. Demam, batuk, takipnu*, dapat disertai ronki atau wheezing pada auskultasi paru tanpa distres napas dan hipoksemia. *Takipnu= Frekuensi napas <2 bulan: ≥60x/menit, 2–11 bulan: ≥50x/menit, 1–5 tahun: ≥40x/menit, >5 tahun: ≥30x/menit					
Berat	<ul> <li>Gejala dan tanda klinis pneumonia berat berupa napas cuping hidung, sianosis, retraksi subkostal, desaturasi (saturasi oksigen &lt;94%).</li> <li>Adanya tanda dan gejala bahaya umum seperti kejang, penurunan kesadaran, muntah profuse, tidak dapat minum, dengan atau tanpa gejala respiratori.</li> </ul>					
Kritis	Pasien mengalami perburukan dengan cepat menjadi acute respiratory distress syndrome (ARDS) atau gagal napas atau terjadi syok, ensefalopati, kerusakan miokard atau gagal jantung, koagulopati, gangguan ginjal akut, dan disfungsi organ multiple atau manifestasi sepsis lainnya.					

MANAGEMENT	Confirmed cases with no symptom, suspected, probable and confirmed with mild symptoms case	Suspected, probable and confirmed with moderate symptoms case	Suspected with severe symptoms and critical	Probable/ Confirmed case with severe symptoms and critical, MIS-C
Self isolation and monitoring	+	+ After discharge from hospital, still do protocol COVID for infection prevention	+ If confirmed (+) After discharge from hospital, , do protocol COVID for infection prevention	+ After discharge from hospital, still do protocol COVID for infection prevention
Isolation at hospital	-	+ Isolation room and continue to self- isolation if already stated outpatient	+ Isolation room and if confirmed (+) have to continue to self-isolation if already stated outpatient	+ Isolation room and continue to self- isolation if already stated outpatient
Blood test	- Except children w/ comorbid	+ (Complete blood count test, CRP, D- Dimer and other test based on indication / Comorbid)	+ (Routine blood count test, blood gas analysis, CRP. SGOT/SGPT, ur/cr, coagulation factors, inflammation markers, cardiac markers, and others)	+(Routine blood count test, blood gas analysis, CRP. SGOT/SGPT, ur/cr, coagulation factors, inflammation markers, cardiac markers, and others)
Xray – test	- Except children w/ comorbid	+	+	+
Vitamin C, D3, and Zink	+ Oral	+ Oral / Enteral	+ Oral / Enteral	+ Oral / Enteral

Treatment	Comfirmed cases w/o symptom, suspected, probable and confirmed w/ mild symptoms case	suspected, probable and confirmed w/ moderate symptoms case	Suspected w/ severe symptoms and critical	Probable/ Confirmed case ww/severe symptoms and critical, MIS-C
Specific Antiviral	<ul> <li>In special condition in children w/ comorbid :</li> <li>Favipiravir</li> </ul>	+ - Remdesivir - Favipiravir	+ - Remdesivir - Favipiravir	+ - Remdesivir - Favipiravir
Antibiotic	-	-/+	-/+	-/+
- Ceftriaxone	-	If there is sign of bacterial infection	If there is sign of bacterial infection	If there is sign of bacterial infection
Other Antiviral : - Oseltamivir	- Not for COVID-19	- Not for COVID-19	If there is co-infection w/ Influenza	If there is co-infection w/ Influenza
Steroid	- (Only in patient w/ comorbid )	+	+	+

# Antivirus for Covid-19

- Main management of Covid-19 is supportive
- Not all children with Covid-19 needs specific antivirus
- Limited evidence / clinical trial on efficacy of antivirus in pediatric population, however, children with comorbidity show higher mortality
- Recommendation of prescribing antivirus:
  - Clinical severity
  - Comorbidity/underlying chronic diseases
  - Progressive deterioration

# Can we predict severity ?

### Risk Factors for Severe COVID-19 in Children

Kelly Graff, MD, \* Christiana Smith, MD, \* Lori Silveira, PhD, \* Sarah Jung, PhD, † Shane Curran-Hays, MS, \* Jane Jarjour, MD, \* Lauren Carpenter, BS, ‡ Kasey Pickard, BA, ‡ Michael Mattiucci, MD, \* JoEllen Fresia, BA, ‡ Elizabeth J. McFarland, MD, \* Samuel R. Dominguez, MD, PhD, \*† and Lisa Abuogi, MD\*

- Extremes of age, comorbid conditions, and elevated CRP are predictors of severe disease in children.
- Preterm birth history (aOR, 3.7; P = 0.03), comorbidities [including immunocompromise (aOR, 3.5; P = 0.004), gastrointestinal condition (aOR, 2.7; P = 0.009), diabetes (aOR, 6.6; P = 0.04), asthma (aOR, 2.2; P = 0.04)]
- Elevated C-reactive protein was associated with the need for critical care with median of 17.7 mg/dL (IQR, 5.3–22.9) versus 1.95 mg/dL (IQR, 0.7–5.5) among patients requiring critical versus no critical care (OR, 1.2; P = 0.02)



Contents lists available at ScienceDirect

International Journal of Infectious Diseases



journal homepage: www.elsevier.com/locate/ijid

Severe COVID-19 Infection and Pediatric Comorbidities: A Systematic Review and Meta-Analysis



Boyan K. Tsankov<sup>a,b,d,e</sup>, Joannie M. Allaire<sup>a,b,d</sup>, Michael A. Irvine<sup>d</sup>, Alison A. Lopez<sup>a,c,d</sup>, Laura J. Sauvé<sup>a,c,d</sup>, Bruce A. Vallance<sup>a,b,d</sup>, Kevan Jacobson<sup>a,b,d,f,\*</sup>

- •42 studies : 275,661 children without comorbidities and 9,353 children with comorbidities were included.
- Severe COVID-19 was present in 5.1% of children with comorbidities, and in 0.2% without comorbidities. Random-effects analysis revealed a higher risk of severe COVID-19 among children with comorbidities than for healthy children; relative risk ratio 1.79 (95% CI 1.27 – 2.51; I<sup>2</sup> = 94%).
- Children with underlying conditions also had a higher risk of COVID-19-associated mortality; relative risk ratio 2.81 (95% CI 1.31 6.02; I<sup>2</sup> = 82%). Children with obesity had a relative risk ratio of 2.87 (95% CI 1.16 7.07; I<sup>2</sup> = 36%).

Conclusions: Children with comorbidities have a higher risk of severe COVID-19 and associated mortality than children without underlying disease.



Contents lists available at ScienceDirect

International Journal of Infectious Diseases

FOR INFECTIOUS DISEASES

journal homepage: www.elsevier.com/locate/ijid

Mortality in children with positive SARS-CoV-2 polymerase chain reaction test: Lessons learned from a tertiary referral hospital in Dewi R,

RSCM STUDY

Dewi R, Kaswandani N, Karyanti MR, et al

NTERNATIONAL

- . 490 patients were admitted and diagnosed with suspected and probable COVID-19.
- •Of these patients, 50 (10.2%) were confirmed to have COVID-19, and 20 (40%) had a fatal outcome.
- The fatality rate higher in patients aged >10 years, categorized as severe disease at admission and chronic underlying diseases.
- •19 out of 20 fatal cases had more than 1 comorbidities, only 1 death case had only 1 comorbidity
- •The most common clinical manifestations were generalized symptoms, while acute respiratory distress syndrome (8/20) and septic shock (7/20) were the two most common causes of death.
- Increased procalcitonin, D-dimer, lactate dehydrogenase and presepsin levels were found in all fatal cases. One patient met the criteria of multisystem inflammatory syndrome in children.

#### Mortality of Children with Confirmed COVID-19: Report from Indonesian Pediatric Society COVID-19 Data Registry

Pudjiadi AH, et al. (in press)



# **Superinfection and Coinfection**

### **Superinfections and Coinfections in COVID-19**

Zhongnan Hospital:

- 57/221 (25.8%) patients have coinfections, includes secondary infections that were present on admission
- Viral 57.9% (33/57), bacterial 29.8% (7/57), fungal 12.3% (7/57)
- 19 (8.6%) developed nosocomial infections during hospitalization
- 55 severe and 166 non-severe cases
- Patients with severe illness are much more likely (10x) to have bacterial/fungal secondary infections than viral (2x)





https://www.medpagetoday.com/infectiousdisease/covid19/86192

## Coinfection and Other Clinical Characteristics of COVID-19 in Children

Qin Wu, MD,<sup>a,\*</sup> Yuhan Xing, MD,<sup>b,\*</sup> Lei Shi, MB,<sup>a,\*</sup> Wenjie Li, MS,<sup>a</sup> Yang Gao, MS,<sup>a</sup> Silin Pan, PhD, MD,<sup>a</sup> Ying Wang, MS,<sup>c</sup> Wendi Wang, MS,<sup>a</sup> Quansheng Xing, PhD, MD<sup>a</sup>

Coinfection, n (%)	19 (51.4)
Mycoplasma	16 (84.2)
RSV	3 (15.8)
EBV	3 (15.8)
CMV	3 (15.8)
Influenza A and B	1 (5.3)

15 patients with confirmed Mycoplasma infection were treated with azithromycin orally or intravenously, and the other 12 children received empirical antibiotic therapy.

Only the 13-year-old with a severe case was given systematic corticosteroids for 5 days and g-globulin for 3 days. No patient required mechanical ventilation, except 1 child with a severe case who received noninvasive ventilation for 5 days. All 74 patients were discharged with good prognosis.

### World map of national pediatric COVID-19 deaths (/1,000,000 children)



https://datacatalog.worldbank.org/dataset/world-bank-official-boundaries



This article is made available via the <u>ACS COVID-19 subset</u> for unrestricted RESEARCH re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for the duration of the World Health Organization (WHO) declaration of COVID-19 as a global pandemic.



pubs.acs.org/journal/aidcbc

Viewpoint

#### Detection of Bacterial Coinfection in COVID-19 Patients Is a Missing Piece of the Puzzle in the COVID-19 Management in Indonesia

Anggia Prasetyoputri\*



Figure 1. Proposed workflow for detection of bacterial coinfection from swabs of COVID-19 positive patients.



#### Multisystem inflammatory syndrome in children



Major symptoms similar to those of Kawasaki disease and toxic

> 2 Red eyes/bloodshot eyes or a "strawberry tongue"

Abdominal pain

Swollen hands and feet

O Low blood pressure

Graphic by Nam Kyung-don don@heraldcorp.com

**Multisystem** Inflammatory Syndrome in Children (MISC)

Henderson LA. Arthritis & Rheumatology. 2020;72:1791–1805

										64-
	Criteria		RCPCH†			CDC			WHO‡	
MIS	Age	All c	children ge not defined)	<21	years			0–19 years		
	Fever	Per	sistent fever (≥38.5°C)	Terr fe	Temperature ≥38.0°C for ≥24 hours <i>or</i> subjective fever for ≥24 hours		Fever for ≥	23 days		
	Clinical symptoms	Bot 1. s d 2. a	h of the following: ingle or multiorgan lysfunction; <i>and</i> idditional features	Botl 1. s 2. ≥	<ul> <li>3oth of the following:</li> <li>. severe illness (hospitalized); and</li> <li>2. ≥2 organ systems involved</li> </ul>			At least 2 of 1. rash, con mucocur 2. hypoten 3. cardiac i 4. coagulo 5. acute Gl	of the following: njunctivitis, and taneous inflammatio sion or shock; nvolvement; oathy; symptoms	n;
	Inflammation	All 3 1. n 2. ir 3. ly	B of the following: neutrophilia; <i>and</i> ncreased CRP; <i>and</i> ymphopenia	Lab 1.↑ 2.↑ 3.↑ 4.↑ 5.↑ 7.↑ 8.↑ 9. n 10. 11.	<ul> <li>Laboratory evidence of inflammation including, but not limited to, 1 or more of the following:</li> <li>1. ↑CRP;</li> <li>2. ↑ESR;</li> <li>3. ↑fibrinogen;</li> <li>4. ↑procalcitonin;</li> <li>5. ↑p-dimer;</li> <li>6. ↑ferritin;</li> <li>7. ↑LDH;</li> <li>8. ↑IL-6;</li> <li>9. neutrophilia;</li> <li>10. lymphopenia;</li> </ul>		Elevated in including 1. ↑ESR; 2. ↑CRP; 3. ↑procal	nflammation markers g any of the following citonin	5,	
	Link to SARS-CoV-2	Pos	itive or negative by PCR	Cur 1. p 2. p 3. p 4. C	ositive by ositive by ositive by ositive by OVID-19 es	t or recent findings of the following: tive by PCR; tive by serology; tive by antigen test; <i>or</i> D-19 exposure within prior 4 weeks		Evidence of 1. positive 2. positive 3. positive 4. likely CO	of COVID-19 by the fo by PCR; by antigen test; by serology; <i>or</i> VID-19 contact	llowing:
THE ADD DOLLARS	Exclusion	Oth	er infections	No	alternative	diagnosis		No obviou	s microbial cause	>



#### Possible mechanism of inflammatory process for MIS-C

Antibody enhancement

Antibody / T-CMI attack host-expressing antigen

Jiang L. Lancet Infect Dis 2020; 20: e276-88





### **MIS-C:**

Respiratory symptoms typically reported in COVID-19 may not be present in MIS-C.

When present, breathing difficulties are often linked to shock, and are suggestive of heart failure.

European Centre for Disease Prevention and Control. American Academy of Pediatrics. July 2020.



M. Ahmed et al. EClinicalMedicine 26 (2020) 100527

#### EClinicalMedicine 26 (2020) 100527

Contents lists available at ScienceDirect



EClinicalMedicine

journal homepage: https://www.journals.elsevier.com/eclinicalmedicine

#### **Research Paper**

Multisystem inflammatory syndrome in children: A systematic review

Mubbasheer Ahmed<sup>a</sup>, Shailesh Advani<sup>b,c,1</sup>, Axel Moreira<sup>a</sup>, Sarah Zoretic<sup>d</sup>, John Martinez<sup>d</sup>,

M. Ahmed et al. / EClinicalMedicine 26 (2020) 100527

Signs and Symptoms in MIS-C vs. COVID-19



#### Medications.

Total $n = 662$	N (%)
Intravenous immunoglobulin	506 (76.4)
Vasoactive support	347 (52.3)
Corticosteroids	347 (52.3)
Antibiotics	108 (16.3)
Anticoagulants	172 (25.9)
Aspirin	111 (16.8)
Interleukin-1ra inhibitor	56 (8.5)
Interleukin-6 inhibitor	40 (6.0)
Remdesivir	6 (0.9)
Hydroxychloroquine	5 (0.8)

MIS-C COVID-19

	Royal College of Paediatrics and Child Health <sup>39</sup>	US Centers for Disease Control and Prevention <sup>37</sup>
Supportive care	Only recommended for mild to moderate disease; discuss early with paediatric intensive care unit and paediatric infectious disease, immunology, and rheumatology team; if clinically deteriorating or in cases of severe disease, discuss transfer with paediatric intensive care unit retrieval teams	Fluid resuscitation, inotropic support, respiratory support, and in rare cases, extracorporeal membranous oxygenation
Directed care against underlying inflammatory process	Immunotherapy should be discussed with a paediatric infectious diseases unit and experienced clinicians on a case-by-case basis and used in the context of a trial if eligible and available	Intravenous immunoglobulin, steroids, aspirin, and anticoagulation treatment
Antiviral therapy	Should be given only in the context of a clinical trial and should be discussed at multidisciplinary team meetings with a clinician from an external trust	
Antibiotics for sepsis		Given while waiting for bacterial cultures
Other	All children treated as if they have COVID-19 and all should be considered for recruitment in research studies	

Table 2: Published guidance on the management of multisystem inflammatory syndrome in children associated with COVID-19

# SUMMARY

- Even Covid-19 in children considered less and milder, evidence showed that Covid-19 can be fatal esp in children with comorbidity
- Majority of fatal cases had risk factors such as younger age, severity at admission and comorbidities
- Management of Covid-19 in children mostly are supportives, antivirus be given in severe cases or patients with comorbidity
- Clinician should aware of coinfection, but antibiotics are given if bacterial co-infections are proven or highly suspected
- Despite of lower incidence and mortality of Covid-19 in children, a fatal condition of MIS-C should be anticipated and managed carefully