COVID-19 in Infants and Children: Lessons From Italy

Pediatric Nutrition
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Presented by
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This activity is supported by an educational grant from
Mead Johnson Nutrition.

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Disclosures

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Speakers Bureau	AbbVie, Janssen, Mead Johnson Nutrition, Sodilac
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Learning Objectives

- Recognize symptoms of COVID-19 in pediatric and neonatal patients
- Review practical approaches for perinatal care, as well as delivery room and NICU procedures suggested during the COVID-19 pandemic

Overview

Module 1

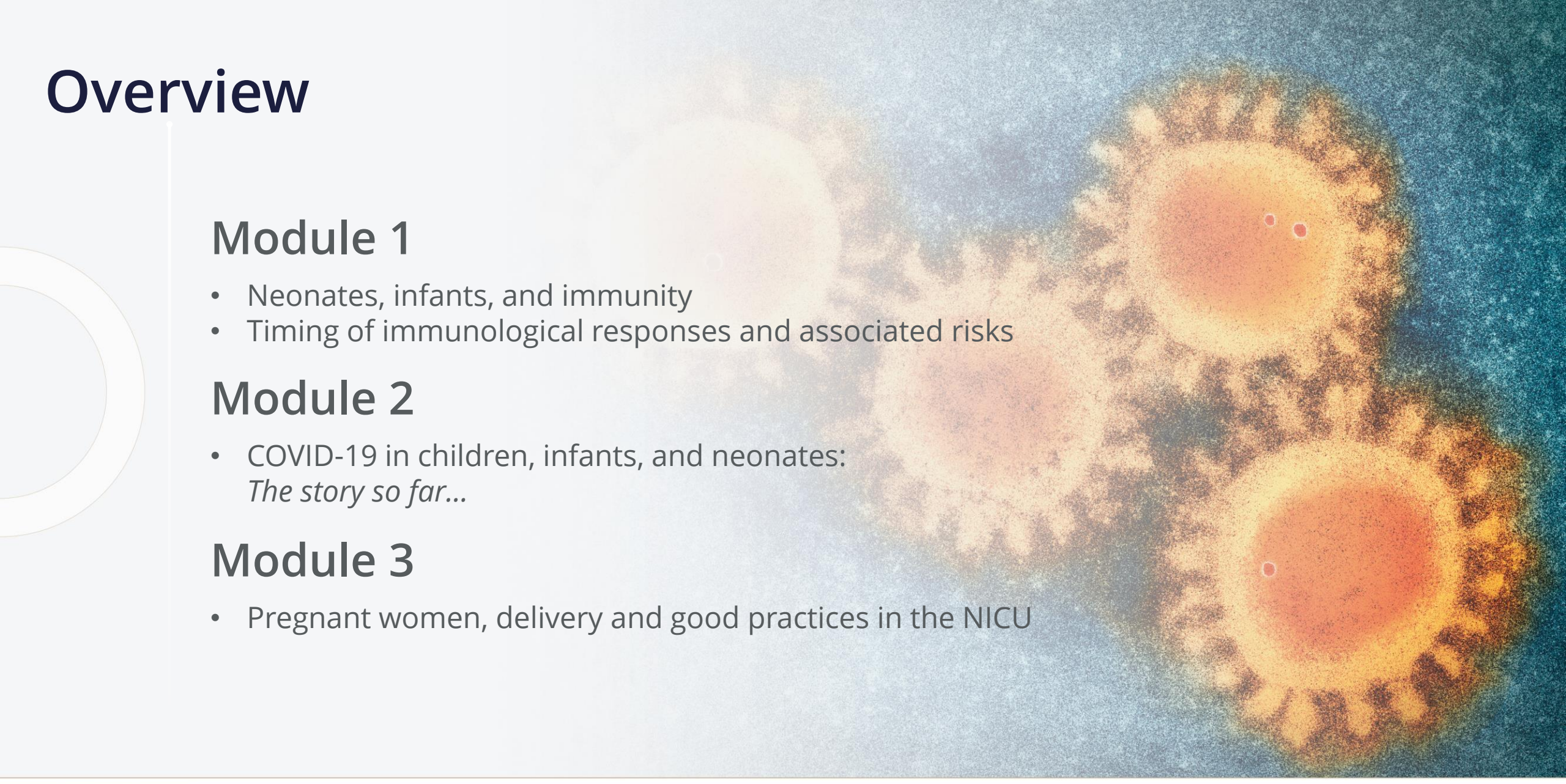
- Neonates, infants, and immunity
- Timing of immunological responses and associated risks

Module 2

- COVID-19 in children, infants, and neonates:
  The story so far…

Module 3

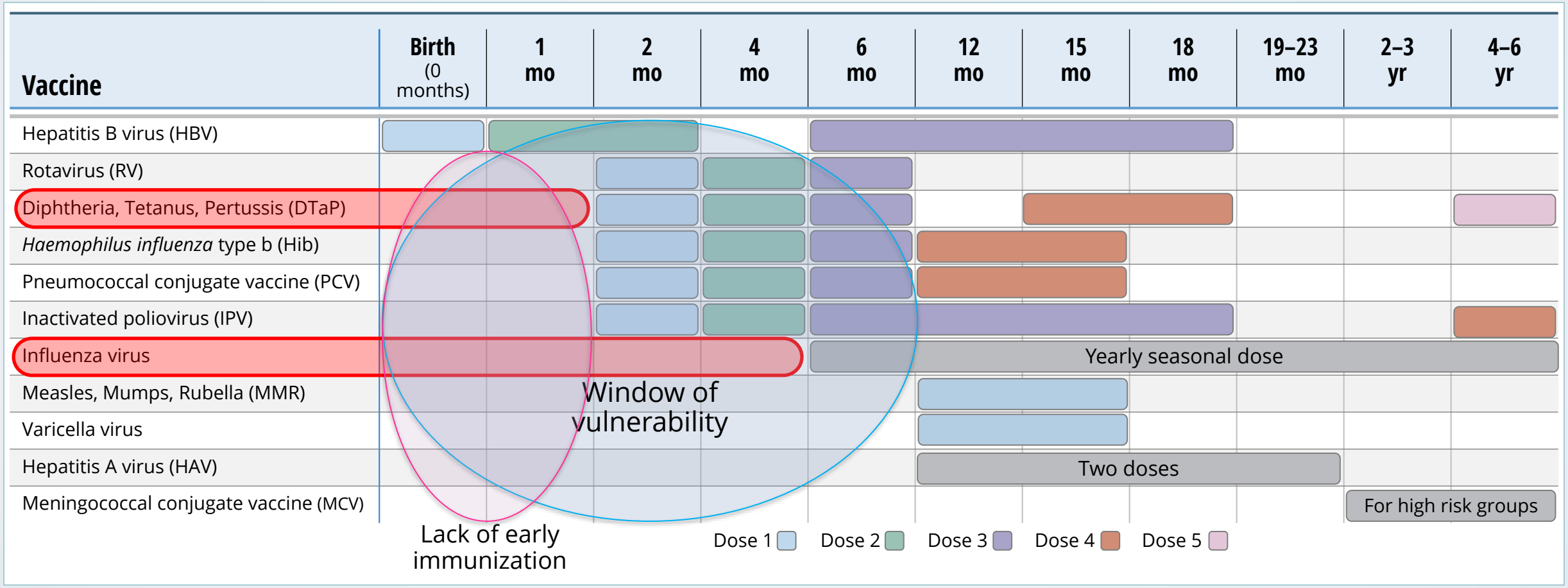
- Pregnant women, delivery and good practices in the NICU



Module 1

- Neonates, infants, and immunity
- Timing of immunological responses and associated risks

Period of Vulnerability for Infant Infectious Diseases



Jones C, et al. *Hum Vaccin Immunother*. 2014;10:2118-2122.

Neonates and Infants Immunity

Period of life	Is the child immune competent?	How can he/she be defended? (1)	How can he/she be defended? (2)
0–3 months	No	Maternal antibodies passed through placenta (natural + boosted by maternal vaccine in pregnancy)	Breastfeeding + passive immunization
3–6 months	No/Yes	Breastfeeding	Initial response to vaccines
6–24 months	Yes	Complete response to vaccines	Breastfeeding + infection experience
24 months—late childhood	Yes	Vaccine-derived immunity	Infection experience

Example of the most frequent respiratory virus = RSV

RSV-Hospital Admissions, ICU Admissions, and Need for Mechanical Ventilation

Show same time peaks = 2–3 months of age

Figure. Distribution of community-acquired RSV-confirmed hospitalizations[1]

How to protect?

1. Maternal vaccine (?)
2. Infant passive immunization
3. Breastfeeding

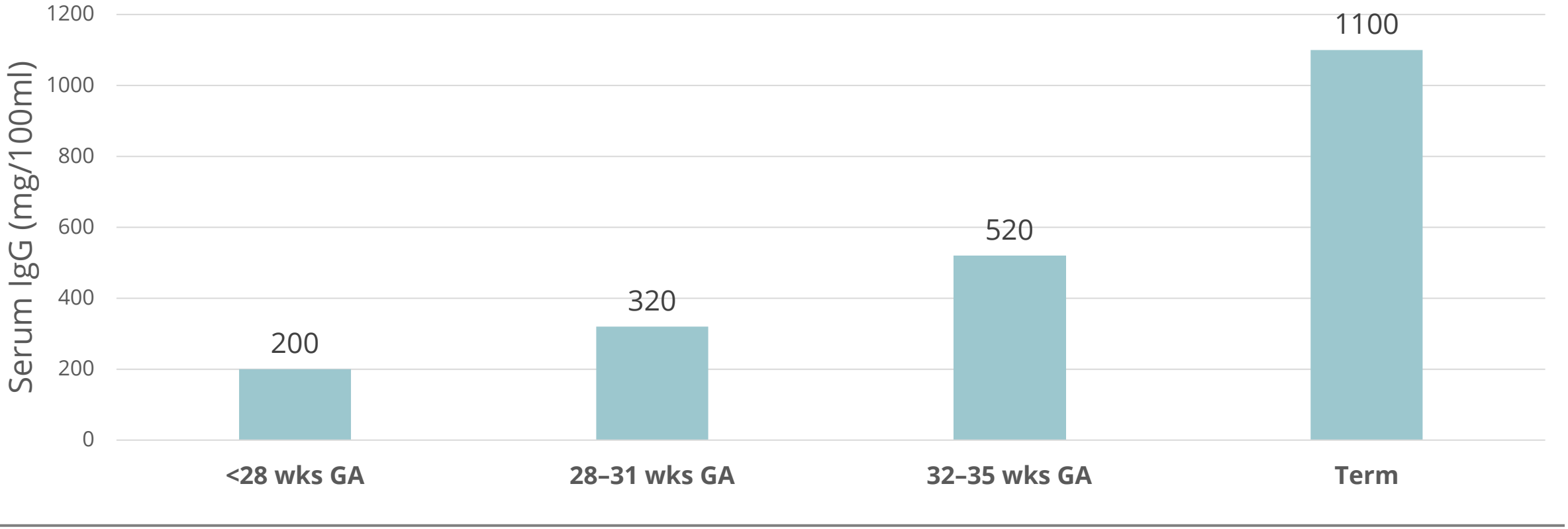
RSV, respiratory syncytial virus.

1. Anderson E, et al. *Am J Perinatol*. 2017;34:51-61. Used under the terms of the Creative Commons Attribution License.

Importance of Maternal Transfer of Antibodies to the Fetus

- The first 3–4 months are the MOST CRITICAL
- The neonate and young infant are protected ONLY through ANTIBODIES FROM THE MOTHER:
  1. Transfer through placenta during pregnancy from immune mothers
  2. Transfer through placenta during pregnancy after boosting with a maternal vaccine
  3. Transfer through fresh breast milk

Prematurity Interrupts Optimal Transfer of Maternal IgG



GA, gestational age.

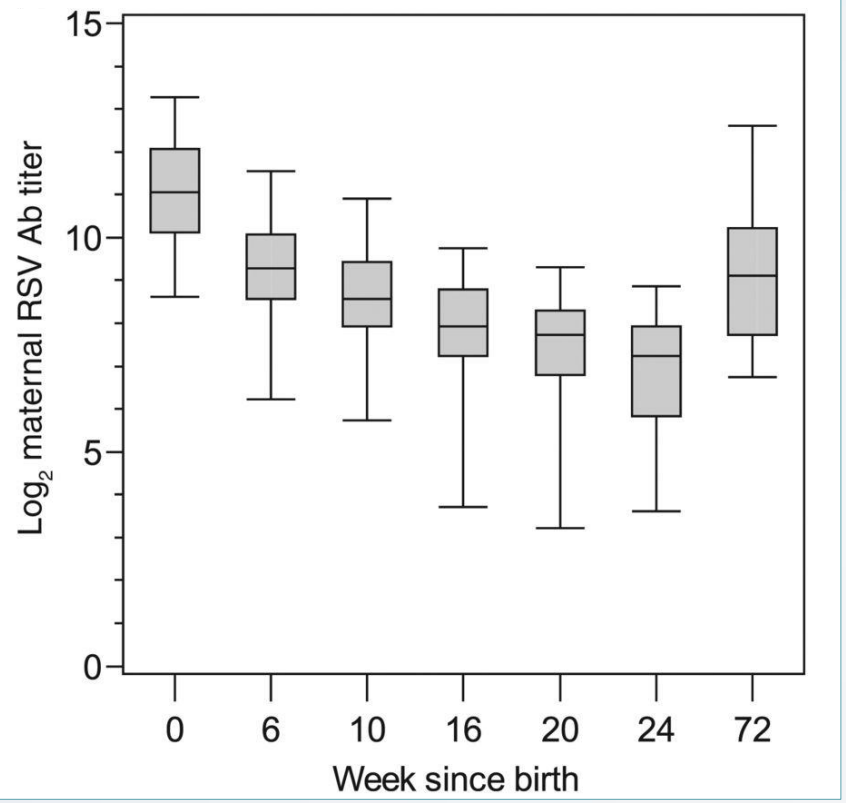
Adapted from data and formulas as published by Yeung CY, Hobbs, JR. *Lancet*. 1968;7553:1167-70.

Serum concentrations of specific anti-RSV antibodies in the newborn: A serum concentration of specific antibodies 2 to 4 times lower in infants who have RSV disease is observed, compared with those who do not get sick from RSV

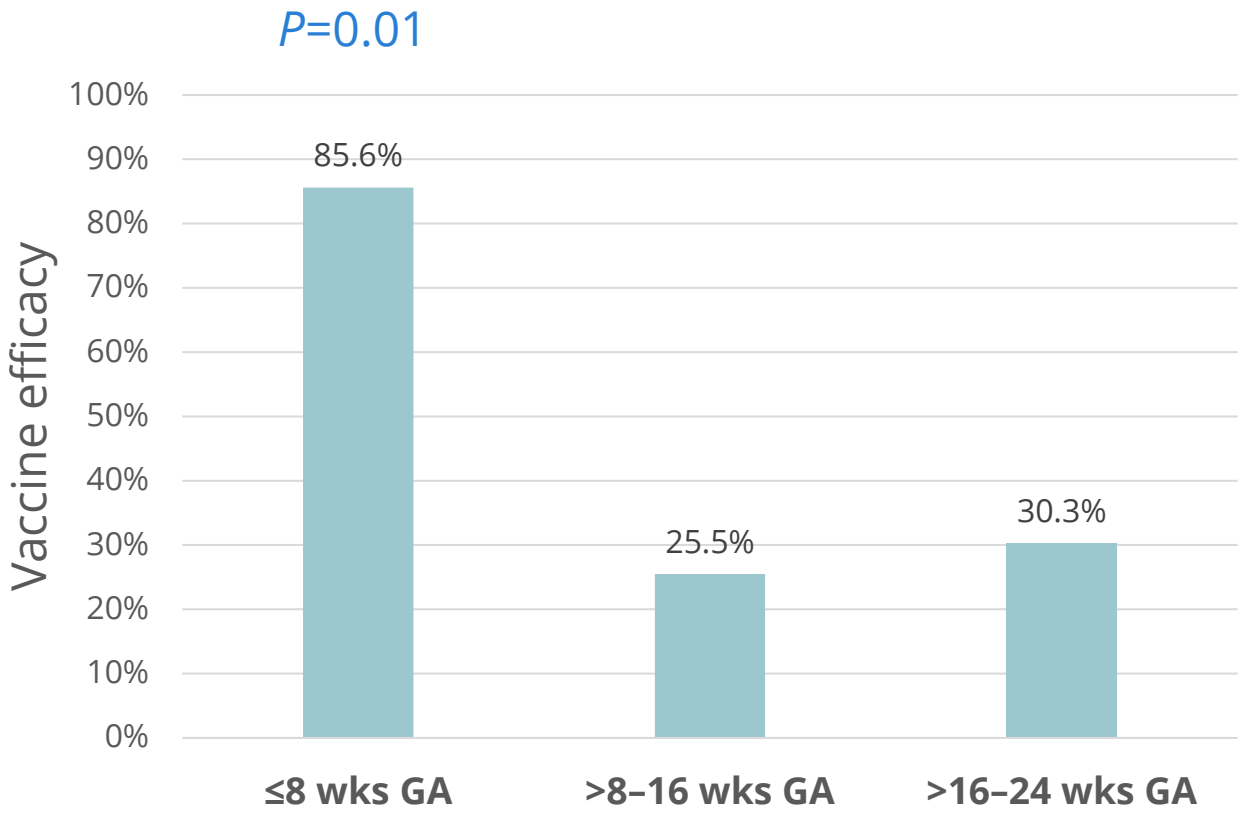
RSV Antibody Titer		Assay Method	Article
No RSV disease	RSV disease		
652.6	198.1	Membrane Fluorescent Antibody Test	Ogilvie. Maternal Ab & RSV. *J Med Virol*. 1981;7:263-71.
92	9.5	Neutralizing Ab	Glezen. *J Pediatr*. 1981;98:708-15.
40.00 44.16	11.08 11.37	MFAT Neutralizing Ab	Roca. IgG Mozambique. *J Med Virol*. 2002;67:616.
238.9	68.6	Neutralizing Ab	Piedra. Correlates of immunity. *Vaccine*. 2003;21:3479.
538.0	392.1	Neutralizing Ab	Eick. Native American Infants. *Pediatr Infect Dis J*. 2008 27:207.
1047	646	ELISA	Ochola. Infants in Kenya. *PLOS One*. 2009;4:e8088.

What is the duration of passive protection in the offspring born to a mother who is already immune for RSV?

Figure 1. Infant log_2 RSV Ab titers at birth and 6, 10, 16, 20, 24, and 72 weeks of age[1]



What is the duration of passive protection in the offspring born to a mother vaccinated for RSV during pregnancy?



Median time to reduction of titer below a potentially protective level → 17 weeks (3–4 months)

RSV, respiratory syncytial virus; Ab, antibody; GA, gestational age.

1. Chu HY, et al. *J Infect Dis.* 2014;210:1582–1589. Used by permission of Oxford University Press
2. Madhi SA, et al. *N Engl J Med*. 2014;371:918-931. Nunes MC, et al. *JAMA Pediatr*. 2016;170:840-847.

In Summary…

- The first 3–4 months are the most critical.
- Maternal antibodies → need to be fully provided through a TERM delivery!
- Duration of protection can be precisely calculated → 17 weeks.
- The more antibodies received, the more you are protected.
- Infants who get infected have fewer maternal antibodies.
- Maternal vaccination in pregnancy might be a good option for some preventable diseases that may be very severe in the first weeks of life (eg, pertussis, influenza, RSV, etc).
- Breastfeeding is currently the best possible option after birth.

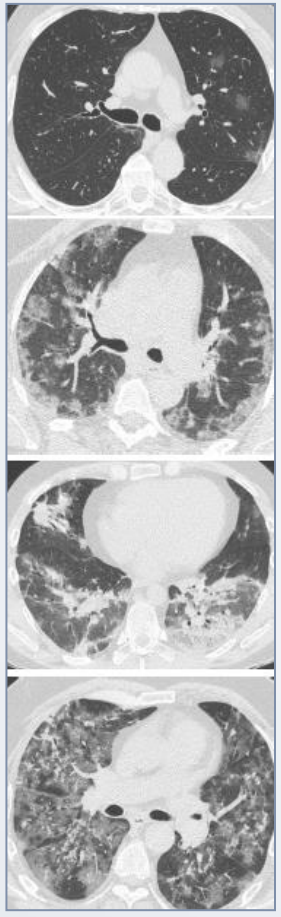
Module 2

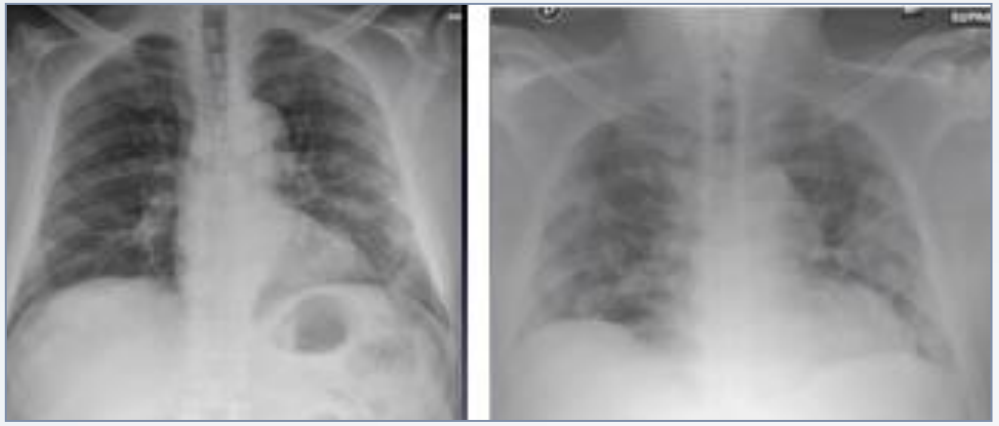
COVID-19 in children, infants, and neonates:
The story so far, and the lesson from the Italian epidemic.

What about COVID-19 Infections? Risk Factors and Severity

- People with COVID-19 can have no symptoms or develop mild, severe, or fatal illness
- The ACE2 cellular receptor is critical, since COVID-19 adheres to enter the cell
- Kids may have less severe disease (only 2% of confirmed cases in China occurred among those <20 yrs; in Italy, so far only 1.6% are <19 yrs)
- Current case fatality rate in COVID-19 adults 2%–8%, <1% in children
- Risk factors for severe illness may include:
  - Older age
  - Underlying chronic medical condition(s)
  - Obesity

COVID-19 Pneumonia





Typical interstitial lesions, evolving with X-rays and CT-confirmed ground-glass (or frosted-glass) lesions and multiple consolidations

Diagnosis through COVID-19 RT-PCR on nasopharyngeal swab

RT-PCR, reverse transcription polymerase chain reaction.

Is COVID-19 also a problem in children, infants, neonates, and/or pregnant mothers?

CHILDREN

Limited Burden, Limited Severity

- In China, a review of 72,314 cases by the Chinese Center for Disease Control and Prevention showed that <1% of the cases were in children <10 years of age
- In the same report, no ICU cases occurred in children
- In Korea, only 0.7% of cases occurred in children <9 yrs
- In Italy, only 1.2% of COVID cases occurred in children <18 yrs
- The course of infection is generally mild to moderate
- No confirmed deaths attributed to COVID-19 so far in Italian children, except a debated case of a 16-yr-old female adolescent
- Severe disease requiring ICU admission and mechanical ventilation mainly in children affected by pre-existing complex disorders and comorbidities (ie, BMT, leukemia, immunodeficiencies, etc)

BMT, bone marrow transplant.

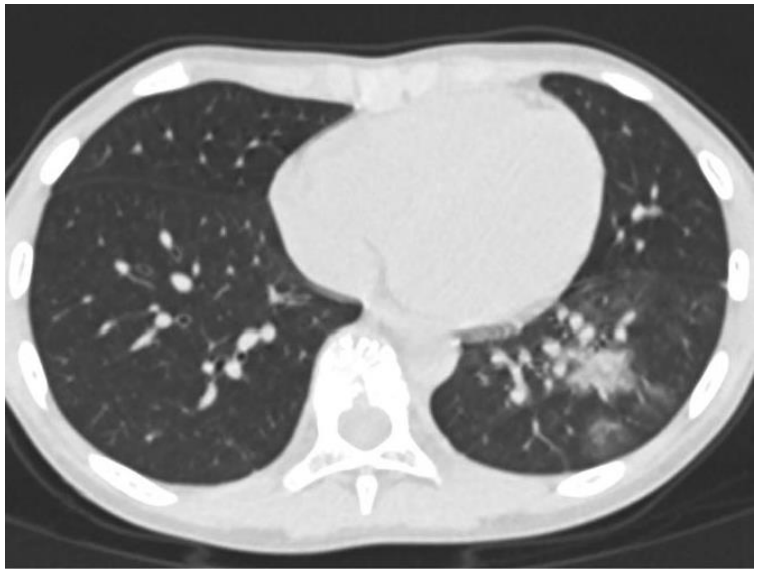
Demographic and Clinical Characteristics of Patients in the First 24 Hours of ICU Admission for COVID-19 in Lombardy, Italy: only 0.3% were children

- Retrospective, huge case series that involved 1,591 critically ill patients admitted from February 20–March 18, 2020, to one of the ICUs of the Lombardy network for severe COVID-19 infection
- 99% of them required respiratory support, including endotracheal intubation in 88% and noninvasive ventilation in 11%; ICU mortality was 26%
- Out of 1,591 patients, only 4 were <20 yrs old
- None of those 4 adolescents died, none had significant comorbidities

Grasselli G, et al. *JAMA*. 2020. [published online ahead of print April 6, 2020]

Clinical and CT features in pediatric patients with COVID-19 infection: Different points from adults[1]

- Consolidation with surrounding halo sign is considered a typical sign in pediatric patients
- Coinfections are more common than in adults



Male, 10 years old. Chest CT showed consolidation with halo sign in the inferior lobe of the left lung surrounded by ground-glass opacities

COVID, coronavirus disease; CT, computed tomography.

Table. CT imaging findings in 20 patients with COVID-19 pneumonia in early stage

Findings	Number of Patients (%)
Pulmonary lesions	
Null	4 (20%)
Unilateral	6 (30%)
Bilateral	10 (50%)
Subpleural lesions	
Seen	20 (100%)
Not seen	0 (0%)
Consolidation with surrounding halo sign	10 (50%)
Ground-glass opacities	12 (60%)
Fine mesh shadow	4 (20%)
Tiny nodules	3 (15%)

1. Xia W, et al. *Pediatr Pulmonol*. 2020;55(5):1169-1174. [published online ahead of print March 5, 2020]

Epidemiological and Clinical Characteristics of COVID-19 Pediatric Cases in China (n=171)[1]

Table 1. Epidemiologic Characteristics, Clinical Features, and Radiologic Findings of 171 Children with SARS-CoV-2 Infection.*

Characteristic	Value
Age	
Median (range)	6.7 yr (1 day–15 yr)
Distribution — no. (%)	
<1 yr	31 (18.1)
1–5 yr	40 (23.4)
6–10 yr	58 (33.9)
11–15 yr	42 (24.6)
Sex — no. (%)	
Male	104 (60.8)
Female	67 (39.2)
Diagnosis — no. (%)	
Asymptomatic infection	27 (15.8)
Upper respiratory tract infection	33 (19.3)
Pneumonia	111 (64.9)
Exposure or contact information — no. (%)	
Family cluster	154 (90.1)
Confirmed family members	131 (76.6)
Suspected family members	23 (13.5)
Unidentified source of infection	15 (8.8)
Contact with other suspected case	2 (1.2)
Signs and symptoms	
Cough — no. (%)	83 (48.5)
Pharyngeal erythema — no. (%)	79 (46.2)
Fever — no. (%)	71 (41.5)
Median duration of fever (range) — days	3 (1–16)
Highest temperature during hospitalization — no. (%)	
<37.5°C	100 (58.5)
37.5–38.0°C	16 (9.4)
38.1–39.0°C	39 (22.8)
>39.0°C	16 (9.4)
Diarrhea — no. (%)	15 (8.8)
Fatigue — no. (%)	13 (7.6)
Rhinorrhea — no. (%)	13 (7.6)
Vomiting — no. (%)	11 (6.4)
Nasal congestion — no. (%)	9 (5.3)
Tachypnea on admission — no. (%)†	49 (28.7)
Tachycardia on admission — no. (%)‡	72 (42.1)
Oxygen saturation <92% during period of hospitalization — no. (%)	4 (2.3)
Abnormalities on computed tomography of the chest — no. (%)	
Ground-glass opacity	56 (32.7)
Local patchy shadowing	32 (18.7)
Bilateral patchy shadowing	21 (12.3)
Interstitial abnormalities	2 (1.2)

1. Lu X, et al. *N Engl J Med*. 2020. [published online ahead of print March 18, 2020]

Epidemiological and Clinical Characteristics of COVID-19 Pediatric Cases in Italy (n=168)[1]

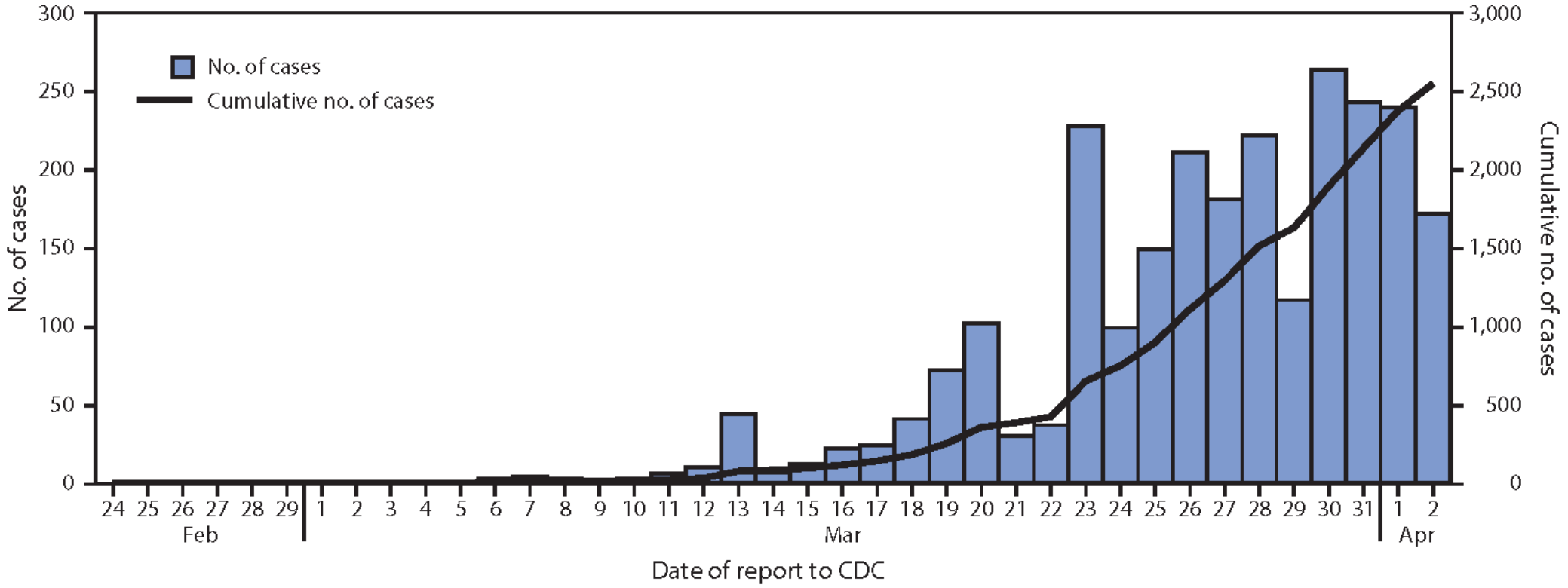
Characteristic	Value
Age	
Median age, years (IQR)	2.3 (0.3–9.6)
Age groups	**n (%)**
< 1 yr	66 (39.3)
1–5 yrs	38 (22.6)
6–10 yrs	24 (14.3)
11–17 yrs	40 (23.8)
Gender	**n (%)**
Males	94 (55.9)
Females	74 (44.1)
Signs and symptoms	**n (%)**
Fever	138 (82.1)
Cough	82 (48.8)
Rhinitis	45 (26.8)
Diarrhea	22 (13.1)

Characteristic	Value
Signs and symptoms *(continued)*	**n (%)**
Dyspnea	16 (9,5)
Pharyngitis	9 (5,4)
Vomiting	9 (5.4)
Conjunctivitis	6 (3.6)
Chest pain	4 (2.4)
Fatigue	3 (1.8)
Non-febrile seizures	3 (1.8)
Febrile seizures	2 (1.2)
Hospital admission	**110 (65.1)**
Age groups	**n (%)**
< 1 yr	52 (47.3)
1–5 yrs	24 (21.8)
6–10 yrs	13 (11.8)
11–17 yrs	21 (19.1)

1. Italian Pediatric Registry, the Italian SITIP-SIP SARS-Cov-2 pediatric infection study group (reported as of April 11, 2020) {Badolato R., Meini A., Plebani A. (Brescia), Garazzino S., Denina M. (Torino), Venturini E., Montagnani C., Galli L. (Firenze), Giaquinto C., Donà D. (Padova), Pierantoni L., Lanari M. (Bologna), Manno EC, Santilli V., Lancella L., Cursi L., Bernardi S., Campana A., Bozzola E., Krzysztofiak A., Villani A. (Roma), Felici E. (Alessandria), Vergine G. (Rimini), Giacchero R. (Lodi), Lo Vecchio A., Pecoraro C (Napoli), Rabbone I. (Novara), Marchisio P., Bosis S. (Milano), Nicolini G. (Belluno), Banderali G. (Milano S. Paolo), Abbagnato L. (Como), Nicastro E., Ghitti C., Lippi P. (Bergamo), Salvini F. (Milano Niguarda), Del Barba P. (Milano S. Raffaele), Agostiniani R. Pistoia), Cherubini S. (Busto Arsizio), Gianino P. (Asti), Vaccaro A. (Lucca), Manzoni P (Biella), Verna P. (Casale), Comberiati P. (Pisa), Di Filippo P (Pescara), Gallia (Milano PLS), Battezzati G. (S. Croce), Fiore L (Moncalieri), Tappi E. (Cuneo), Valentini P. (Roma) Esposito S., Dodi I. (Parma), Lazzerini M. (Trieste), Zuccotti GV (Milano), Castagnola E. (Genova), Corsello G. (Palermo), Cardinale F. (Bari), Tocco AM (Pescara), Ballardini G. (Verbania), Zavarise G. (Verona).

Epidemiological and Clinical Characteristics of a Series of COVID-19 Pediatric Cases in USA (n=291)[1]

Figure. COVID-19 cases in children[a] aged <18 years, by date reported to CDC (N = 2,549)[b] — United States, February 24–April 2, 2020[c]



a. Includes infants, children, and adolescents.
b. Excludes 23 cases in children aged <18 years with missing report date.
c. Date of report available starting February 24, 2020; reported cases include any with onset on or after February 12, 2020

1. CDC COVID-19 Response Team. Coronavirus Disease 2019 in Children — United States, February 12–April 2, 2020 Weekly / April 10, 2020 / 69(14);422–426. On April 6, 2020, this report was posted online as an MMWR Early Release. Available at https://www.cdc.gov/mmwr/volumes/69/wr/mm6914e4.htm#contribAff.

Epidemiological and Clinical Characteristics of a Series of COVID-19 Pediatric Cases in USA[1] *(continued)*

Main differences in children compared with adults:

- Less fever
- Less cough
- Less dyspnea
- Less headache
- Less myalgia
- Similar incidence of gastrointestinal symptoms

IN USA as of April 2: 2,572 cases in children <17 yrs (1.7% of all ages)

Table. Signs and symptoms among 291 pediatric (age <18 years) and 10,944 adult (age 18–64 years) patients[a] with laboratory-confirmed COVID-19 — United States, February 12–April 2, 2020

Sign/Symptom	No. (%) with sign/symptom	
	Pediatric	Adult
Fever, cough, or shortness of breath[b]	213 (73)	10,167 (93)
Fever[c]	163 (56)	7,794 (71)
Cough	158 (54)	8,775 (80)
Shortness of breath	39 (13)	4,674 (43)
Myalgia	66 (23)	6,713 (61)
Runny nose[d]	21 (7.2)	757 (6.9)
Sore throat	71 (24)	3,795 (35)
Headache	81 (28)	6,335 (58)
Nausea/Vomiting	31 (11)	1,746 (16)
Abdominal pain[d]	17 (5.8)	1,329 (12)
Diarrhea	37 (13)	3,353 (31)

a. Cases were included in the denominator if they had a known symptom status for fever, cough, shortness of breath, nausea/vomiting, and diarrhea. Total number of patients by age group: <18 years (N = 2,572), 18–64 years (N = 113,985).
b. Includes all cases with one or more of these symptoms.
c. Patients were included if they had information for either measured or subjective fever variables and were considered to have a fever if "yes" was indicated for either variable.
d. Runny nose and abdominal pain were less frequently completed than other symptoms; therefore, percentages with these symptoms are likely underestimates.

1. CDC COVID-19 Response Team. Coronavirus Disease 2019 in Children — United States, February 12–April 2, 2020 Weekly / April 10, 2020 / 69(14);422–426. On April 6, 2020, this report was posted online as an MMWR Early Release. Available at https://www.cdc.gov/mmwr/volumes/69/wr/mm6914e4.htm#contribAff.

Main Clinical Characteristics in Children A Comparison: CHINA vs USA vs ITALY[1]

Characteristic	CHINA	USA[a]	ITALY
Median age	6.7 yrs	11 yrs	2.5 yrs
Asymptomatic	15%	NA	2.4%
Underlying chronic diseases and comorbidities	NA	NA	19.6%
Pneumonia	70%	67%	40%
Gastrointestinal symptoms (vomiting, diarrhea, etc)	15%	29%	19%
Lymphopenia (lymphocyte count <1.200/liter)	3.6%	NA	2%
Fever	42%	56%	82%
Conjunctivitis	NA	NA	3.6%
Seizures	NA	NA	3%

a. This US report includes only symptomatic cases.

1. Manzoni P. [unpublished, submitted to *NEJM*]

Tips to Limit Spread in Infants and Children

1. From experimental decay and virus survival models, we know **aerosol and fomite transmission** of SARS-CoV-2 is plausible, because the virus can remain viable and infectious in aerosols for hours and on surfaces up to days (depending on the inoculum shed), thus possibly producing nosocomial spread and super-spreading events. (van Doremalen, et al. *N Engl J Med*. 2020)
   → **SOCIAL DISTANCING AND HYGIENE**
2. Although the predominant symptoms of COVID-19 are respiratory, gastrointestinal (GI) manifestations can occur and may be overlooked, as well as **fecal-oral transmission**. A meta-analysis of 60 studies with data on GI symptoms + stool viral RNA (n=4243), pooled prevalence of GI manifestations was 18%. Anorexia (27%), diarrhea (12%), nausea and vomiting (10%), abdominal pain (9%) were the most common symptoms. Prevalence of GI symptoms was similar among adults, children, and pregnant women. The overall concomitant viral RNA positivity rate of stool and respiratory samples was 48%, and very frequent positivity of stool RNA was persistent even after respiratory tests had become negative. (Cheung KS, et al. *Gastroenterology*. 2020.)
   → **HYGIENE + PRECAUTIONS WITH DIAPERS AND STOOLS**

1. van Doremalen N, et al. *N Engl J Med*. 2020: NEJMc2004973. [published online ahead of print March 17, 2020]
2. Cheung KS, et al. *Gastroenterology*. 2020. pii: S0016-5085(20)30448-0. [published online ahead of print April 3, 2020]

Peculiar Presentations in Children

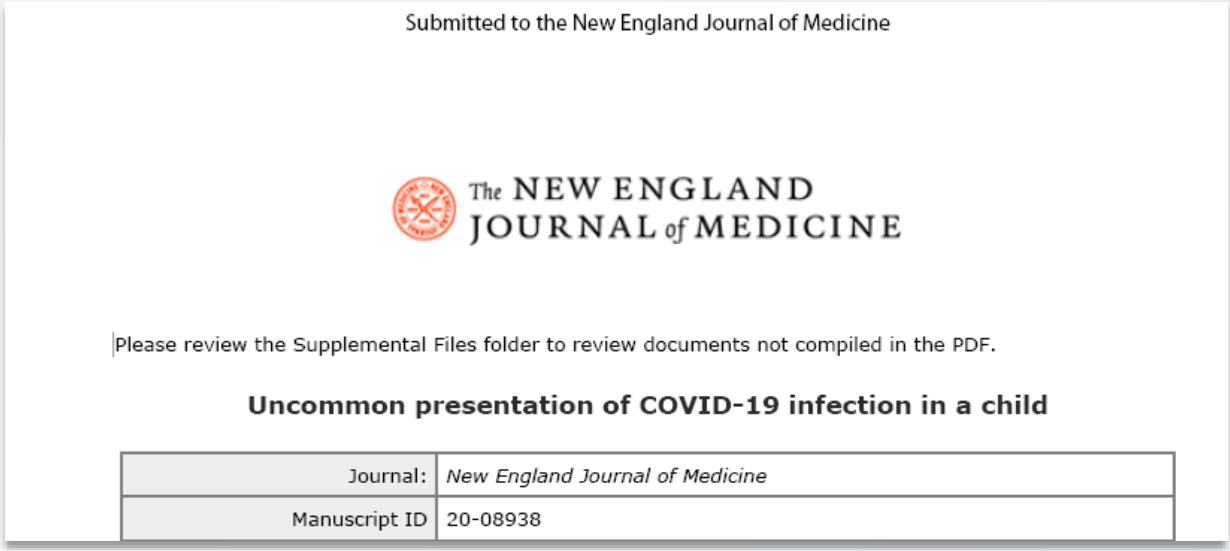
Gastrointestinal symptoms and morbidities

Peripheral vasculitis

Possible presentation as severe gastrointestinal disorders ultimately leading to acute ischemic gastrointestinal disease

Uncommon presentation in a 7-year-old child with no underlying comorbidities, hospitalized for persistent diarrhea and increasingly severe abdominal pain, but no history of cough or fever

- A complete workup was performed, including nasopharyngeal swab that disclosed positivity for COVID-19.
- Chest X-rays showed typical viral pneumonia patterns.
- She was referred to surgery and underwent exploratory laparoscopy revealing phlegmonous appendicitis with Peritonitis.
- No pathogens grew from any cultures.
- The child was treated empirically and recovered well
- She became negative to COVID-19 after 17 days.
- Vomiting, diarrhea, and gastrointestinal symptoms are frequently described in Italian COVID-19 patients, including children.



Submitted to the New England Journal of Medicine

The NEW ENGLAND JOURNAL of MEDICINE

Please review the Supplemental Files folder to review documents not compiled in the PDF.

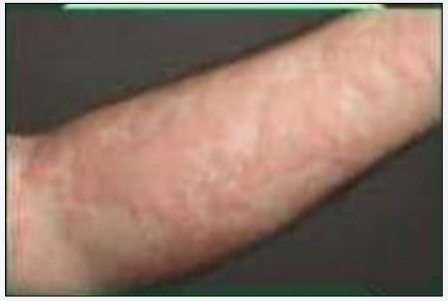
Uncommon presentation of COVID-19 infection in a child

Journal:	*New England Journal of Medicine*
Manuscript ID	20-08938

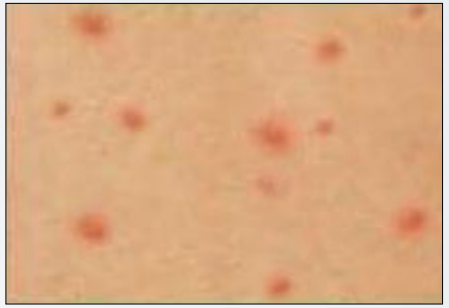
Manzoni P. [unpublished, submitted to *NEJM*]

Possible Association of COVID-19 With Skin Lesions

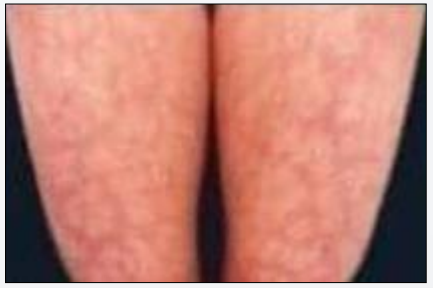
- COVID-19 associated rashes and skin lesions are being reported in Northern Italy in up to 20% of patients
- The skin lesions are mainly of 5 types:
  1. Urticaria
  2. Livedo reticularis
  3. Vesicular → chickenpox-like vesicles on erythematous base
  4. Petechiae
  5. Acral ischemia
- The common denominator of these lesions is occurrence of Microthrombi and Ischemia of peripheral vessels



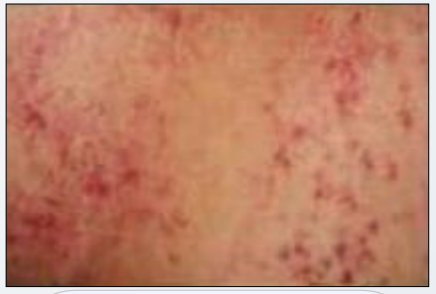
1. Urticaria



3. Vesicular



2. Livedo reticularis

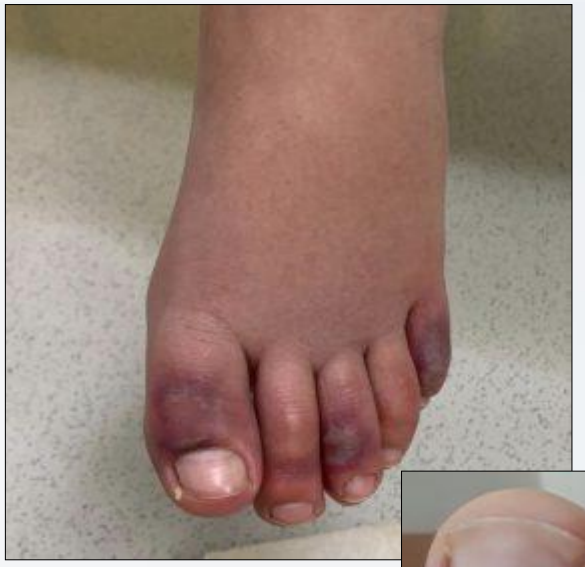


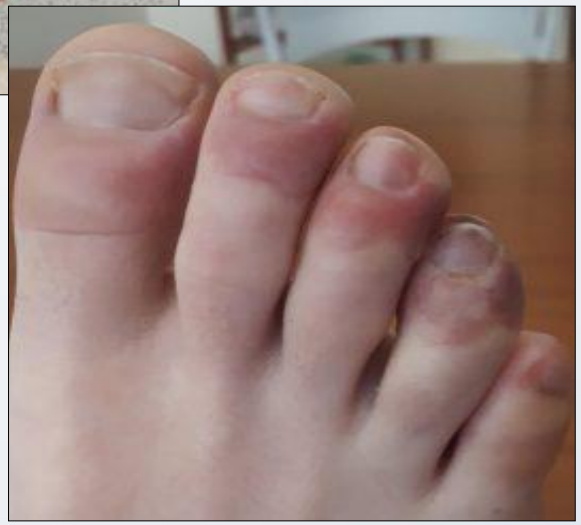
4. Petechiae

The main feature of skin involvement in COVID-19 infection: Acral ischemic lesions in asymptomatic children

- The first report appeared in Italy on March 29, 2020, ie, 5 weeks after the first COVID-19 case
- In the last 3 weeks, there was an epidemic of reports of acral ischemic lesions in asymptomatic children ~10 yrs of age throughout Italy, with dozens of overlapping cases of intensely painful, new cases reported weekly, to date
- The lesions usually affect feet, sometimes the hands; the fingers are typically affected, not all concomitantly, but usually 3 fingers, often separated by fingers not affected; the lesions have initially a purplish-red or bluish color; they can evolve with bullae or blackish crusts
- *Restitutio ad integrum* typically occurs within 2 weeks
- Limited testing for COVID-19 has been done, but many cases are reported as family clusters, or swab positives, or both

Rationale → COVID-19 disease is emerging as a SYSTEMIC VASCULITIS disease associated with abnormal inflammatory response





https://www.faropediatrico.com/editoriali/covid-19-e-arrossamenti-dita-in-bambini-acrovasculite-acuta/
https://www.faropediatrico.com/wp-content/uploads/2020/04/acroischemia.pdf.pdf

In Summary

- Data from China, Italy, and the USA suggest pediatric coronavirus disease 2019 (COVID-19) cases might be less severe than cases in adults, and children might experience different symptoms than adults.
- In these preliminary descriptions of pediatric COVID-19 cases, relatively few children with COVID-19 are hospitalized.
- Pediatric COVID-19 patients might not have fever or cough. In general, fewer children than adults experience fever, cough, or shortness of breath.
- Severe outcomes have been very rarely reported in children, and only 3 deaths in the USA have been described.
- Nonetheless, patients with less serious illness and those without symptoms (ie, children) likely play an important role in disease transmission. Consider fecal transmission from carrier children!

Module 3

Pregnant women, delivery and good practices in the NICU

Is COVID-19 also a problem in children, infants, neonates, and pregnant women?

INFANTS and NEONATES

Very Limited Burden, Very Limited Severity

Two main case series, so far:

- China → 37 neonates
- Italy → 12 neonates
- 80% to 90% are asymptomatic
- 10% to 20% have only mild respiratory distress, feeding instability, sometimes fever and rash

Characteristics of infants born to mothers with positive SARS-CoV-2 infection

Study	N	Region, Country	GA Range	Infant Testing	Respiratory Support	Adverse Events
Infants with negative testing, pending testing or not tested for SARS-CoV-2						
Chen H et al.	9	Wuhan, China	36 to 39^{+4}	Negative (6/6)	None	Increased myocardial enzymes (1/9)
Chen S et al.	3	Wuhan, China	$35/37^{+3}/38^{+6}$	Negative	None	None
Chen Y et al.	4	Wuhan, China	37^{+2} to 39	Negative (3/3)	CPAP for TTN (1/4)	None
Fan C et al.	2	Wuhan, China	$37/36^{+5}$	Negative	None	Mild neonatal pneumonia (2/2)
Iqbal S et al.	1	Washington, DC	39	Negative	None	None
SIN-ISN	7	Northern Italy	34^{+1} to 40^{+2}	Negative (4/4)[a]	NIV for prematurity (1/7)	None
Li Y et al.	1	Zhejiang, China	35	Negative	None	None
Liu D et al.	11	Wuhan, China	34 to 38	Not done	None	None
Liu H et al.	16	Shanghai, China	Not specified	Not done	None	None
Liu W et al.	3	Wuhan, China	38^{+4} to 40	Negative	None	None
Liu Y et al.	10	Outside Wuhan	32 to 38^{+3}	Not specified	None	Stillbirth for maternal ARDS and shock (1/10)
Wang X et al.	1	Suzhou, China	30	Negative	None	None
Yu N et al.	6[b]	Wuhan, China	37 to 41^{+2}	Negative (2/2)	None	None
Zeng H et al.	4	Wuhan, China	Not specified	Negative	None	None
Zeng L et al.	30	Wuhan, China	T (27), PT (3)	Negative	None	RDS (3/30), cyanosis (2/30), asphyxia (1/30)
Zhang L et al.	10	Wuhan, China	35^{+5} to 41	Negative (10/10)	Not reported	Bacterial pneumonia (3/10)
Zhu H et al.	10	Wuhan, China	31 to 39	Negative (9/9)[b]	IMV on DOL 8 (1/10) NIV after birth then IMV on DOL 3 (1/10)	Shortness of breath (6/10); pneumothorax (1/10); RDS (2/10); Shock, multiple organ failure, DIC and death on DOL 8-9 (1/10); respiratory distress after birth then DIC on DOL 3 (1/10)
Infants with equivocal test results for SARS-CoV-2						
Dong L et al.	1	Wuhan, China	34^{+2}	Negative RT-PCR High IgM/IgG	None	None
Zeng H et al.	2	Wuhan, China	Not specified	Negative RT-PCR High IgM/IgG (2/6)	None	None
Infants with positive testing for SARS-CoV-2						
Wang S et al.	1	Wuhan, China	39^{+6}	Positive at 36h [c]	None	Lymphopenia and transaminitis
Zeng L et al.	3	Wuhan, China	Term (2/3) Preterm (1/3)	Positive at ~48h	NIV for prematurity (1/3)	1 infant: 31^{+2} wks, fetal distress, asphyxia, low Apgar scores, RDS, pneumonia, bacteremia

Shalish W, et al. *Am J Perinatol*. 2020. [in press]

Characteristics of neonates and infants <1 year of age with positive COVID-19 testing

Study	N	Region, Country	Age range	Need for Respiratory Support	Symptoms/Outcomes
Cai J et al.	2	Shanghai and Haikou, China	3 and 7 months	None	Fever and mild URTI symptoms
Cui Y et al.	1	Guiyang, China	55 days	Oxygen therapy	Pneumonia, increased myocardial/liver enzymes
Dong Y et al.	379	Mainland China	0 to 1 year	Not specified	7 (2%) asymptomatic 205 (54%) mild 127 (34%) moderate 33 (9%) severe 7 (2%) critical
SIN-ISN	5	Northern Italy	2 to 44 days	Oxygen (1/5)	Fever and/or mild URTI symptoms conjunctivitis
Le HT et al.	1	Hanoi, Vietnam	3 months	None	Mild URTI symptoms
Li W et al.	1	Zhuhai, China	10 months	No	Asymptomatic
Liu H et al.	2	Shanghai, China	2 and 11 months	Not specified	Both had mild pneumonia, one infant also had pleural effusion and was RSV positive
Lu X et al.	31	Wuhan, China	0 to 1 year	1 infant required IMV due to intussusception and multi-organ failure (4 weeks after admission)	0 asymptomatic 6 (19%) URTI symptoms 25 (81%) pneumonia 1 (3%) death
Qiu H et al.	10	Zhejiang, China	0 to 5 years	Oxygen therapy (1/10)	4 (40%) asymptomatic/mild 6 (60%) moderate
Wei M et al.	9	Mainland China	28d to 1y	None	Fever or mild URTI symptoms
Xia W et al.	9	Wuhan, China	0 to 1 year	Not specified	Neonates: asymptomatic (3/3) Others: asymptomatic or mild pneumonia
Zeng L et al.	1	Wuhan, China	17 days	None	Mild symptoms (fever, vomiting, diarrhea)
Zhang Y et al.	1	Haikou, China	3 months	None	Mild URTI symptoms

Shalish W, et al. *Am J Perinatol*. 2020. [in press]

COVID-Positive Mothers and Neonatal Outcomes

- In the literature noted, there are reports of **140 COVID-positive mothers** who gave birth to only **8 COVID-positive neonates** (5 from China and 3 from Italy)
- Infected neonates were mostly asymptomatic
- A few had mild respiratory distress, instability, sepsis-like symptoms, likely attributable to concomitant conditions (such as prematurity or sepsis)

Shalish W, et al. *Am J Perinatol*. 2020. [in press]

Can we continue to use current respiratory strategies with neonates born to COVID-19-positive mothers?

- Yes, with a few suggested modifications to address the possibility of aerosol generation and exhaled air dispersion during oxygen administration and ventilatory support.

- To date, the only recommended modification for contemporary respiratory care is the use of **bacterial/viral hydrophobic** filters located at the expiratory part of the systems.

- Any strategy in such neonates should be tailored to the individual patient, rather than to the disease.

Shalish W, et al. *Am J Perinatol*. 2020. [in press]

Practical Approach in the Delivery Room

Bag and mask/ T-piece and mask ventilation	**Delivery room and NICU** should continue to be used as recommended by the NRP with all protective measure in place for suspected or confirmed COVID-19 cases. A small viral/bacterial filter should be placed in between the T-piece resuscitator or anesthesia bag and the mask or in the expiratory limb (before the PEEP valve) of a self-inflating bag. Normally, the filter should be replaced every 8–12 hours. **NOTE**: When placed between the T-piece or anesthesia bag and mask, the filter adds significant dead space. For that reason, the smallest available filter should be used and prolonged ventilation using this apparatus should be avoided.
Suction (oropharyngeal area and ETT)	**Non-intubated infant**—continuous suctioning reduces aerosol spread better than several episodes of intermittent suctioning. In this respect, open airway toileting should be performed with continuous suctioning. **Mechanically ventilated infants:** a closed-circuit suction should always be inline and used for endotracheal suctioning.
Continuous positive airway pressure	**Delivery room and NICU** should continue to be used as recommended by the NRP with all protective measures in place for suspected or confirmed COVID-19 cases. A viral/bacterial filter should be placed in the expiratory limb (before the water reservoir for the bubble system) or before the ventilator exhalation valve. Normally, the filter should be replaced every 8–12 hours.
Non-invasive positive pressure ventilation	**Delivery room and NICU** is acceptable as long as all protective measures are in place for suspected or confirmed COVID-19 cases. A viral/bacterial filter placed in the expiratory limb of the system. **Note:** If those measure are not available or reliable, then intubation and invasive mechanical ventilation is a reasonable option.
Endotracheal intubation	**Delivery room and NICU** is the procedure associated with higher risk of contamination. Therefore, the operator should have experience and be properly protected. If possible, use a video laryngoscopy system to maintain some distance from the patient airway.
Mechanical ventilation	**NICU**—Should continue to be used in the NICU as per unit protocols as long as all protective measures are in place for suspected or confirmed COVID-19 cases. There are no data to recommend a specific mode. A viral/bacterial filter should be placed in the expiratory limb before the ventilator exhalation valve (not feasible with but high-frequency oscillatory ventilation). Normally, the filter should be replaced every 8–12 hours. A closed ETT suction apparatus should be used.

ETT, endotracheal tube; NRP, Neonatal Resuscitation Program®.

Shalish W, et al. *Am J Perinatol*. 2020. [in press]

Is COVID-19 a Problem During Pregnancy or Delivery?

We do not know at this time if COVID-19 would cause problems during pregnancy or affect the health of the baby after birth.

Can COVID-19 be passed from a pregnant woman to the fetus or newborn?

No confirmed maternal-neonatal vertical transmission, so far:
We still do not know if a pregnant woman with COVID-19 can pass the virus that causes COVID-19 to her fetus or baby during pregnancy or delivery.
No infants born to mothers with COVID-19 have tested positive for the COVID-19 virus. In these cases, which are a small number, the virus was not found in samples of amniotic fluid or breast milk.

If a pregnant woman has COVID-19 during pregnancy, will it hurt the baby?

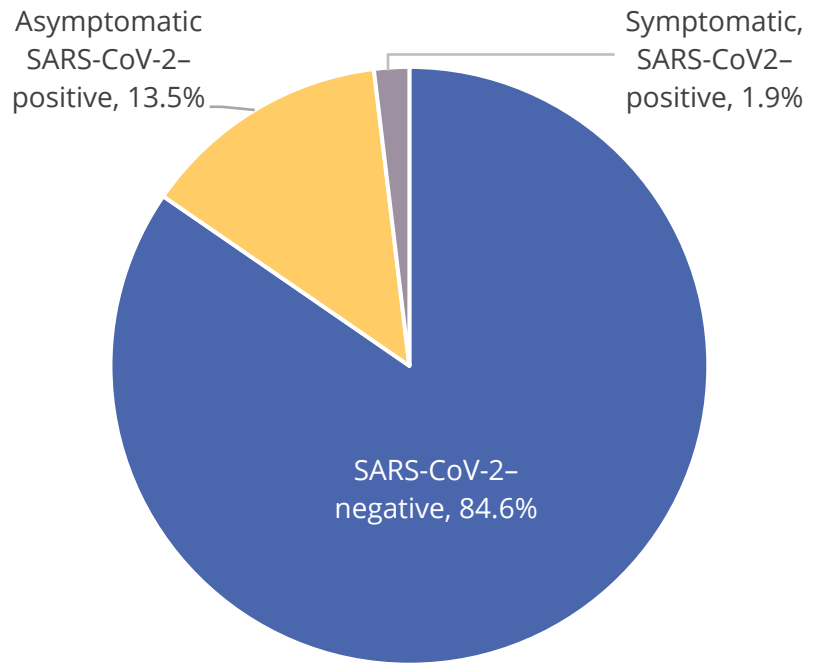
We do not know at this time if any risk is posed to infants of a pregnant woman who has COVID-19.
There have been a small number of reported problems with pregnancy or delivery (eg, preterm birth) in babies born to mothers who tested positive for COVID-19 during their pregnancy.
It is not clear, however, that these outcomes were related to maternal infection.

Procianoy RS, et al. *J Pediatr (Rio J)*. 2020.

What is the current prevalence of COVID-19 in pregnant women at delivery?[1]

- Universal screening in a New York academic setting during 2 consecutive weeks in late March–early April
- 215 pregnant women tested at admission for delivery
- Main findings:
  15.4% COVID-positive
  but only
  1.9% COVID-symptomatic

Figure. Symptom Status and SARS-CoV-2 Test Results among 215 Obstetrical Patients Presenting for Delivery[1]



Key Takeaway: Risk of underestimating COVID-19 positivity in women delivering

1. Sutton D, et al. Universal Screening for SARS-CoV-2 in Women Admitted for Delivery. *NEJM*. April 13, 2020.

Guidance for Neonatal Management in the Nursery and for Breastfeeding

- **AAP document (USA)** → Recommends to consider separating mother and neonate in many situations (Puopolo KM, et al. *Pediatrics*. 2020)
- **SIN-UENPS document (ITALY-EUROPEAN UNION)** → Recommends not to separate mother and neonate, unless in very limited situations (Davanzo R, et al. *Matern Child Nutr*. 2020, in press) (Davanzo, ADCFN 2020, in press)
- **BRAZILIAN PEDIATRIC SOCIETY document** → the same as Europe (Procianoy, Silveira, Manzoni, Sant'Anna. *J Pediatr*. 2020, in press)

Breastfeeding and COVID-19[1]

Health status of the mother	Pharyngeal swab for COVID-19 on the mother	Pharyngeal swab for COVID-19 on the neonate	Isolations of the mother	Management of the neonate during hospital stay	Advice on direct breastfeeding	Preventative measures for mother-neonate transmission
Asymptomatic or paucisymptomatic to be COVID-19 positive	Already done	Yes	Yes In an isolated and dedicated area of postpartum ward	In a rooming-in regimen, in an isolated and dedicated area of postpartum ward	Yes	Yes
COVID-19 paucisymptomatic mother under investigation	Yes	Only if maternal test is positive	Yes In an isolated and dedicated area of postpartum ward, pending result of lab test	In a rooming-in regimen, in an isolated and dedicated area of postpartum ward, at least until result of the lab test	Yes	Yes
Mother with symptoms of respiratory infection (fever, cough, secretions) and too sick to care for newborn, COVID-19+ or under investigation	Yes or already being done	Only if maternal test is positive	Yes In an isolated and dedicated area of postpartum ward, pending result of lab test	Neonate isolated and separated from the mother at least until the result of the lab test. Neonate placed in a dedicated and isolated area in the Neonatology Unit (if asymptomatic) or in the NICU (if symptomatic; eg, with respiratory disease)	No; use of expressed milk. Pasteurization not recommended	Yes

Davanzo R, et al. *Matern Child Nutr*. 2020:e13010. doi: 10.1111/mcn.13010. [published online ahead of print April 3, 2020]

How to manage a tertiary-level NICU in the time of COVID-19? A summary of the lessons learned from a high-risk zone in Italy

- Official policy issued by the Academic and Institutional Committees of a large tertiary NICU in Northern Italy
- NICU, Department of Women's and Children's Health, University Hospital of Padua, Venetian Region

Table. Checklist of preventive measures in our NICU during COVID-19 pandemic

Maternity service	Mother	Tested if symptomatic or with a recent history of close contact with an individual testing positive for COVID-19
		Isolation of mother and baby until swab test results are available
		Pumping milk without breastfeeding until swab test results are available
NICU	Newborn	Nasopharyngeal swabs on admission and weekly thereafter
		More frequent repetition of tests in the event of contact with an individual testing positive for COVID-19 or showing symptoms
		Quarantine zone for symptomatic patients or those who have been in contact with an individual testing positive for COVID-19
		Thermostat-controlled crib
	Health care providers	Weekly nasopharyngeal swabs
		Repetition in the event contact with an individual testing positive for COVID-19 or showing symptoms
		Surgical masks and gloves
		Protective clothing, gloves, and N95 masks for COVID-19 positive or suspected newborn
		Avoidance of close contact with other colleagues and parents
		Supportive psychological service available
	Parents	Triage
		Nasopharyngeal swabs on admission and weekly thereafter
		Restricted access
		Avoidance of close contact with parents
		Standardized procedures for hand cleaning and wearing protective clothing before accessing the NICU
		Supportive psychological service available

Cavicchiolo ME, et al. *Pediatr Pulmono*. 2020;1–3.

Summary of Current Treatment Options and Management for Adults and Children

	Type of treatment	Drugs used
Anti-inflammatory, immunodulatory treatment	Symptomatic	Vitamin D Chloroquine Tocilizumab Steroids (??)
Anti-viral treatment	Untargeted	Lopinavir-Ritonavir Remdesivir
Prevention of coagulopathy and thrombo-embolic complications secondary to inflammation storm	Symptomatic	Heparin NAO
Respiratory management	Supportive-symptomatic	Oxygen ECMO
Inhibitors of viral entry into the cells	(Un)targeted	Chloroquine ACE2 inhibitors

NO COVID-19-SPECIFIC TREATMENT CURRENTLY EXISTS

Waiting for a vaccine: Are there any potentially innovative/alternative treatments?

- Resveratrol
- Lactoferrin
- L-asparaginase
- Hyperimmune plasma from donor

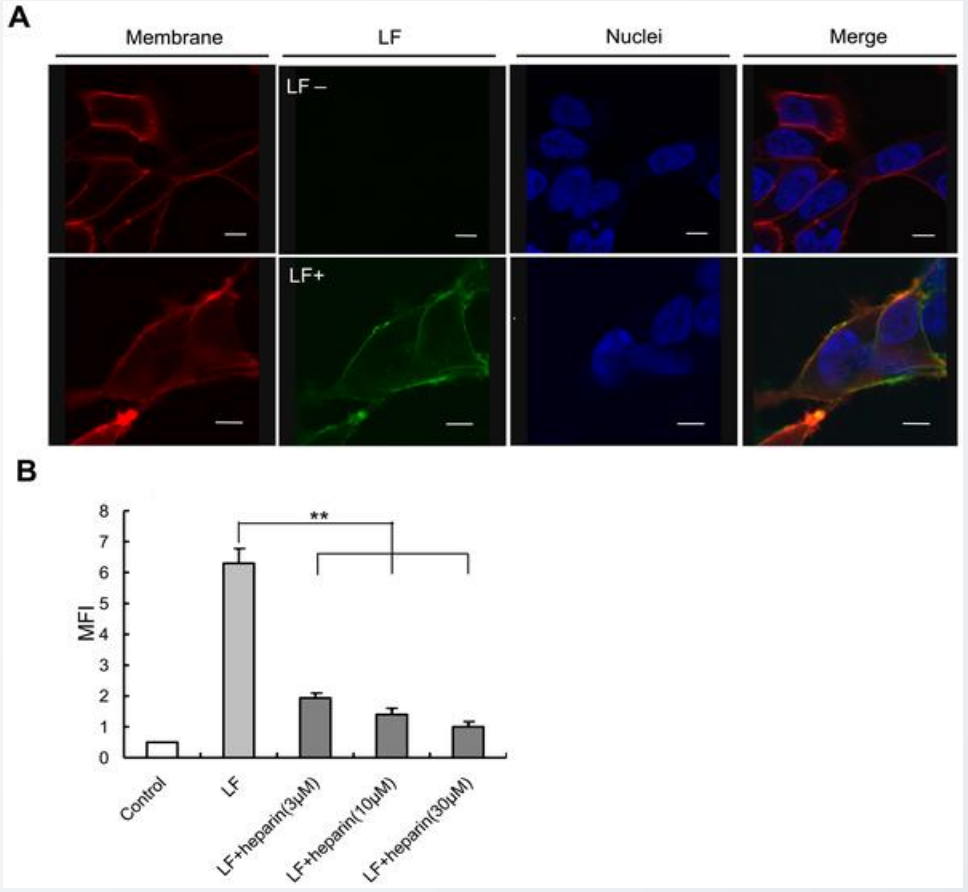
RESVERATROL

Resveratrol *in vitro* significantly inhibits MERS-CoV infection by 3 main pathways:

1. Upregulation of the ACE2 gene expression
2. Decreasing the expression of nucleocapsid (N) protein essential for MERS-CoV replication
3. Down-regulating the apoptosis induced by MERS-CoV

LACTOFERRIN

Lactoferrin *in vitro* localizes to the cell membrane by targeting and inhibiting Heparan Sulfate Proteoglycans (HSPGs), a cell entry protein that is critical for cell entry by the SARS Pseudovirus



L-ASPARAGINASE

Background and Rationale →

- COVID-19 links with the sites of ACE2, using this cellular receptor to enter the cells of the lung, digestive system and the genitourinary tract of man.
- Most of the attack sites of ACE2 are glycosylation areas where sugar molecules bind to a cell membrane protein.
- The last amino acid of the cell membrane protein is almost always asparagine.
- By using the enzyme L-asparaginase, we can eliminate the amino acid asparagine, thus preventing the binding of the virus to its specific cellular receptor.
- Once asparagine has been eliminated, COVID no longer has any point of attack.

Suggested Combination Treatment
(currently patented in USA by Italian researchers; RCTs ongoing):
L-asparaginase
+
Chloroquine
+
Heparin

PLASMA TRANSFUSION from Convalescent Donor

Background and Rationale →

- COVID-19 formerly positive patients may become donors of hyperimmune plasma once they have recovered and returned negative
- The potential for this treatment has been tested in previous coronavirus epidemics (specifically, SARS and MERS) in Asia
- Preliminary experiences in China, Italy and Spain in the last weeks look promising
- COVID+ ICU patients are described to recover much faster after receiving hyperimmune plasma
- Some 22 patients have been treated so far in Mantua Hospital (Lombardy) with good results and no adverse effects (personal communication)
- RCTs ongoing in the Lombardy ICU Network

SARS, severe acute respiratory syndrome; MERS, Middle East respiratory syndrome.

Bloch, EM, et al. *J Clin Invest*. 2020. [published online ahead of print April 7, 2020]

Key Takeaways

- The COVID-19 epidemic is an unprecedented challenge for all health care systems worldwide.
- Pediatricians need to know that children MAY be affected, but usually with less severity.
- Children MAY be carriers of the virus.
- Gastrointestinal symptoms and fecal-oral transmission are frequent in children.
- No vertical transmission demonstrated to date.
- Neonates can occasionally experience mild-to-moderate forms of the disease.
- No specific treatment, nor vaccine exists to date.