# MTCT

**Daniele De Luca, MD, PhD**
AP-HP Université Paris Saclay, France

# No conflict of interest to disclose

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# Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Vertical Transmission in Neonates Born to Mothers With Coronavirus 2019 (COVID-19) Pneumonia

*Xiaolin Hu*, MD, *Jinzhi Gao*, MD, PhD, *Xiaoping Luo*, MD, PhD, *Ling Feng*, MD, PhD, *Weiyong Liu*, MD, *Juan Chen*, MD, PhD, *Alexandra Benachi*, MD, PhD, *Daniele De Luca*, MD, PhD, and *Ling Chen*, MD, PhD

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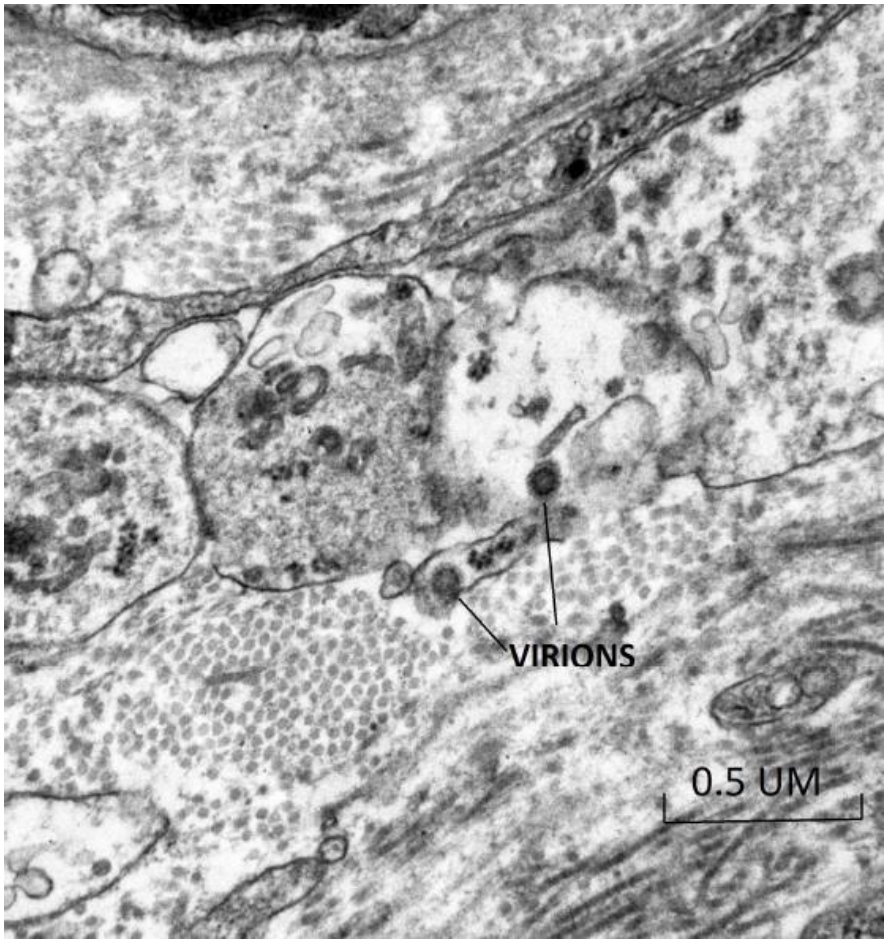
**Table 2. Clinical Characteristics of the Neonates**

| Characteristic | Case No. 1* | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|---|
| Sex | Male | Male | Female | Male | Male | Male | Male |
| Gestational age (wk) | 40 | 41 2/7 | 38 4/7 | 39 5/7 | 38 2/7 | 38 2/7 | 37 2/7 |
| Birth weight (g) | 3,250 | 3,470 | 3,250 | 3,670 | 3,180 | 3,200 | 3,300 |
| 1-min Apgar score | 8 | 8 | 8 | 8 | 7 | 8 | 8 |
| 5-min Apgar score | 9 | 9 | 9 | 9 | 8 | 9 | 9 |
| Fever | No | No | No | No | No | No | No |
| Transfusion of blood product | No | No | No | No | No | No | No |
| Weight loss (%) | 0 | 2.9 | 2.5 | 5.4 | 1.9 | 2.5 | 3 |
| Complications | No | No | No | No | No | No | No |
| Chest radiograph | Normal | Normal | Normal | Normal | Normal | Normal | Normal |
| RT-PCR for SARS-CoV-2 | Positive* | Negative | Negative | Negative | Negative | Negative | Negative |

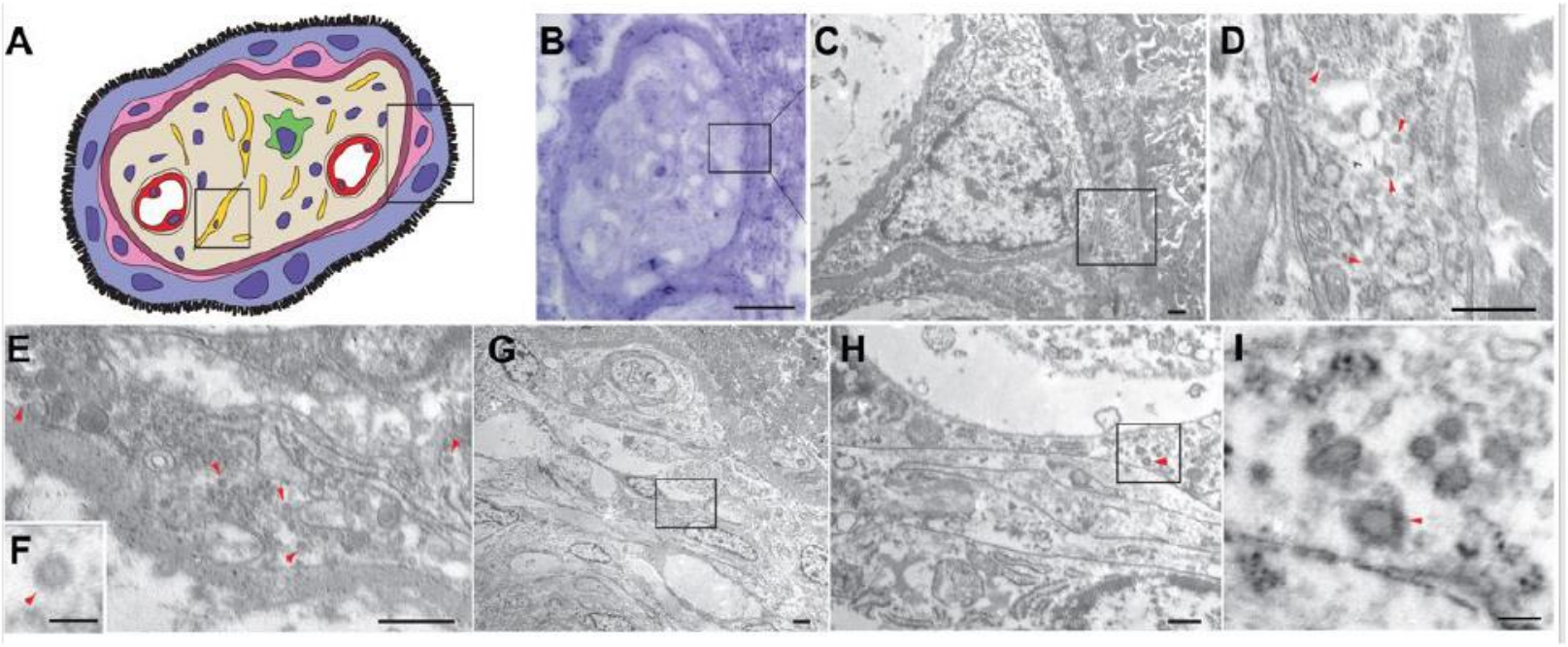
RT-PCR, reverse transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
* This neonate had throat swabs positive for SARS-CoV-2 at 36 hours of life. Subsequently, throat swabs as well as blood, urine, and feces were negative.

***Hu X. Obstet Gynecol 2020***



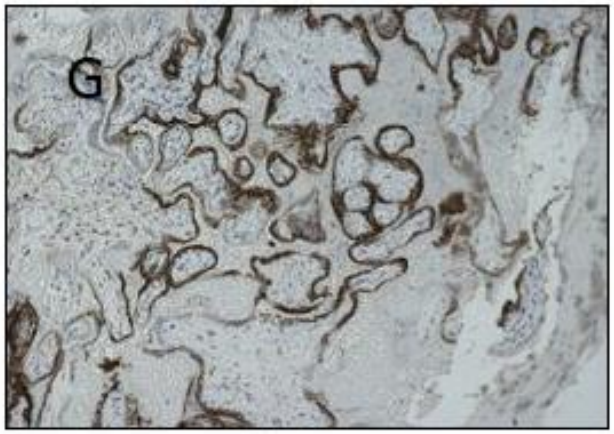

*Algarroba GN. Am J Obstet Gynecol 2020*
*Hosier H. J Clin Invest 2020*

# SARS-CoV-2 localized predominantly to syncytiotrophoblast cells at the fetal interface of the placenta.

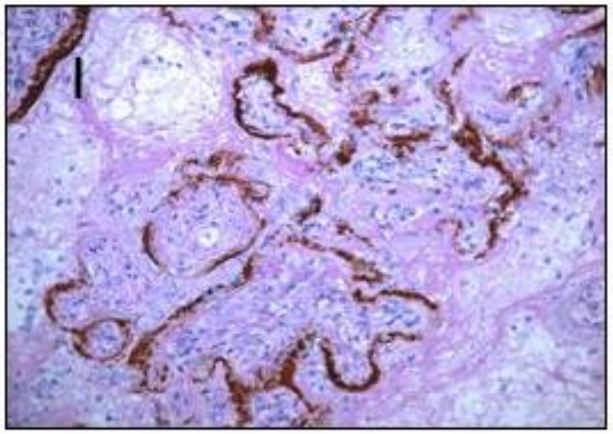


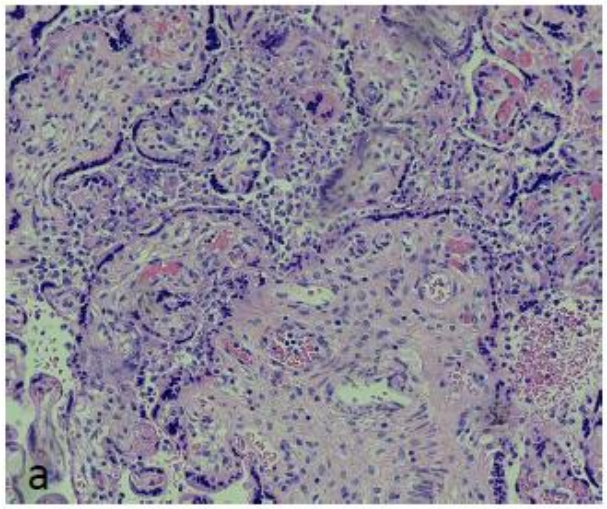

*Algarroba GN. Am J Obstet Gynecol 2020*
*Hosier H. J Clin Invest 2020*

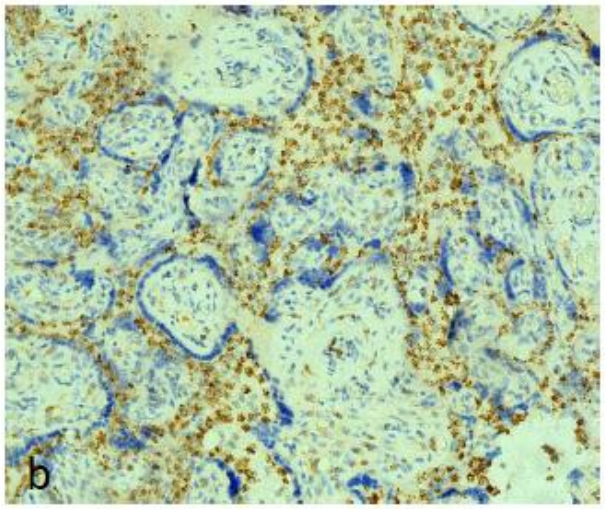
# SARS-CoV-2 causes placental inflammation!

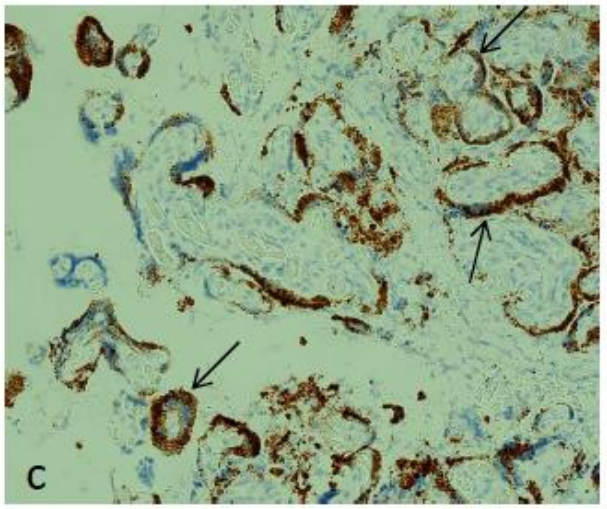







*Vivanti A. Nature Commun preprint 2020*
*Patané L. Am J Obstet Gynecol 2020*
*Hosier H. J Clin Invest 2020*

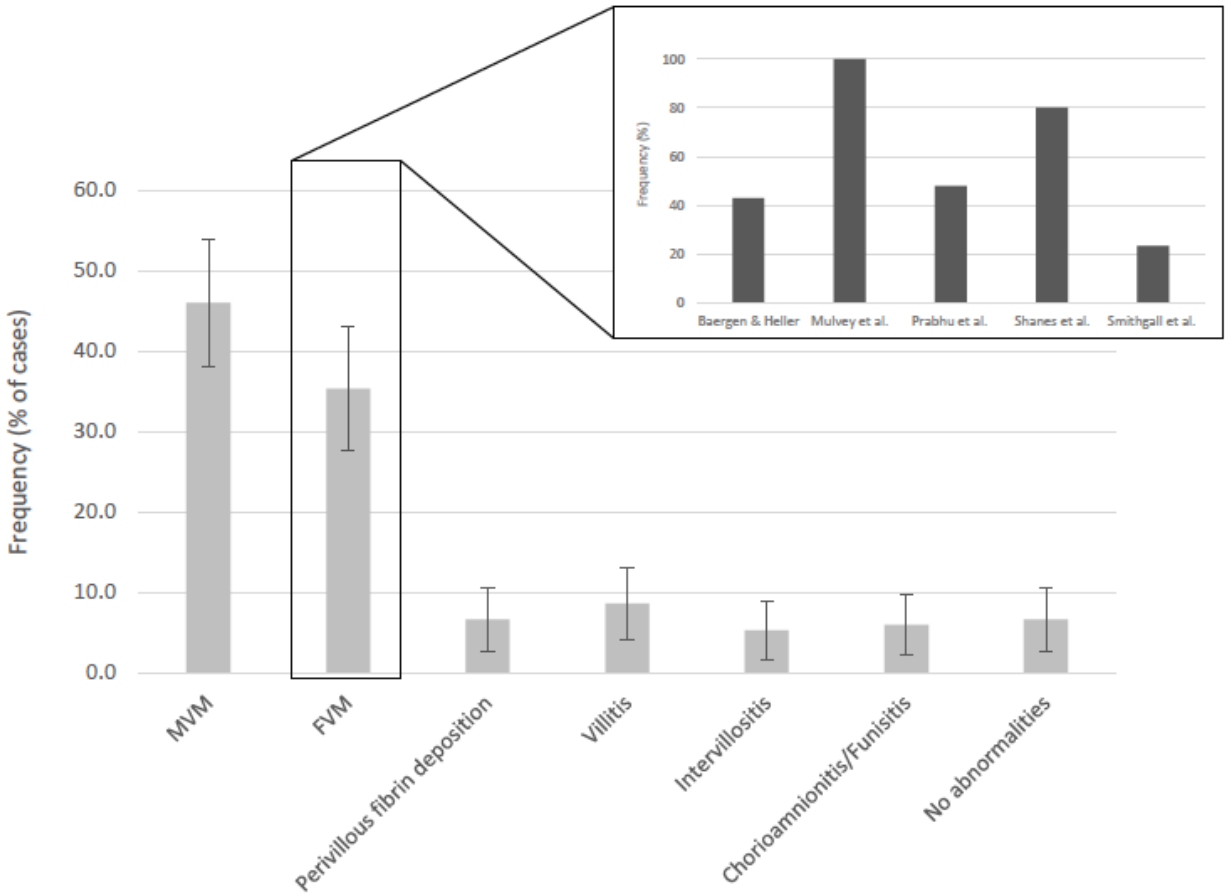
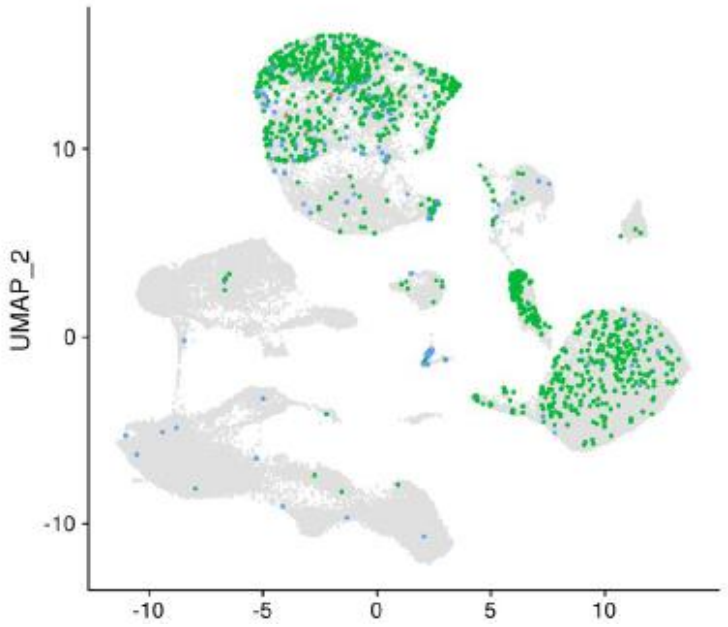
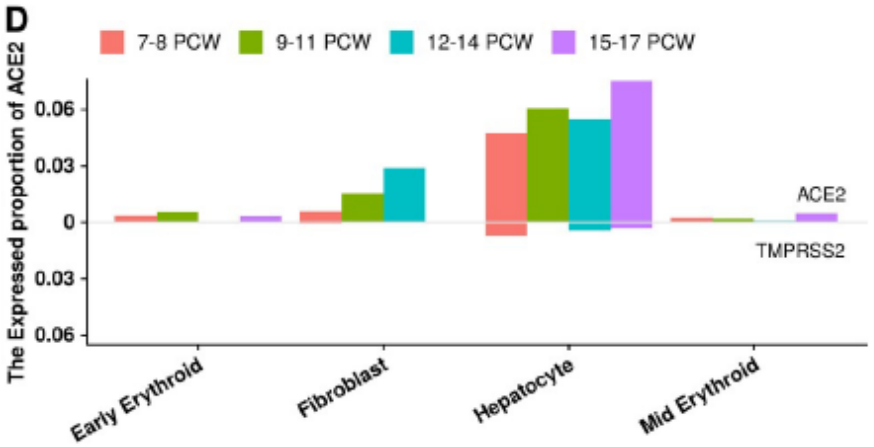



**Fig. 2. Proportion of third trimester cases with placental histopathological lesions or showing no abnormalities of placental pathology in women with SARS-CoV-2 infection.** Error bars show 95% confidence intervals. Inset shows that estimates of FVM by individual studies vary in frequency from 23.5 to 100%. MVM: maternal vascular malperfusion, FVM: fetal vascular malperfusion.

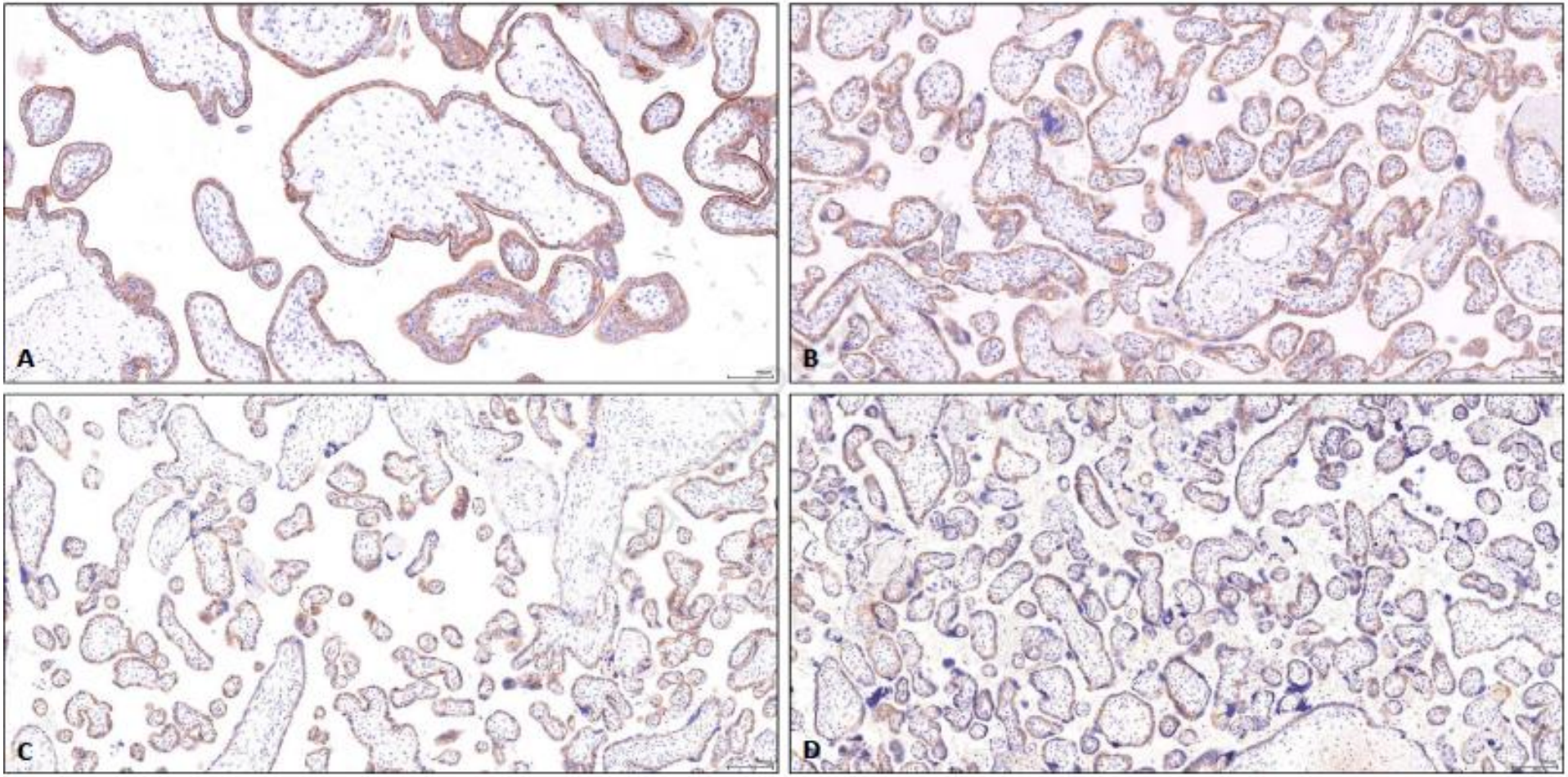
***Sharps MC. Placenta 2020***

# ACE-2 receptors expression peaks at the end of pregnancy in placenta and fetal tissues




*Li M. PloS One 2020*
*Vento-Tormo R. Nature 2018*

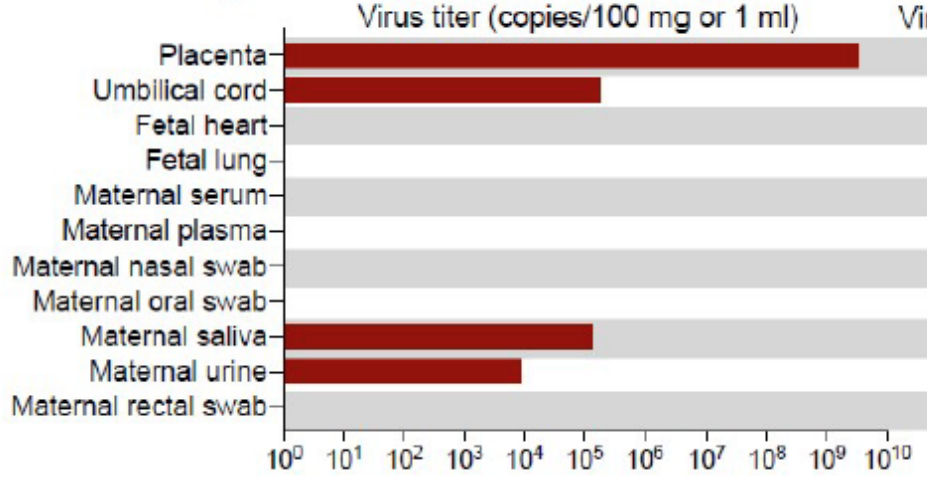



**Annex:** Diffuse membranous staining of villous cytotrophoblast cells with monoclonal Anti-ACE2 antibody (clone CL4035), dilution 1/1000, 10X at various gestational ages (16 (A), 22 (B), 31 (C) and 40 (D) weeks gestation) in control COVID-19 negative mothers.

***Gengler C. Clin Micriobiol Infect 2020***

# SARS-CoV-2 can reach the cord blood from the placenta

**A** SARS-CoV-2 qRT-PCR results post-operatively




| | Virus N1 Ct | Virus N2 Ct | Human RP Ct | Result |
|---|---|---|---|---|
| Placenta | 13.9 | 15.3 | 21.3 | Positive |
| Umbilical cord | 30.6 | 30.6 | 28.2 | Positive |
| Fetal heart | ND | ND | 29.9 | Negative |
| Fetal lung | ND | ND | 34.6 | Negative |
| Maternal serum | ND | ND | 28.5 | Negative |
| Maternal plasma | 38.5 | 38.6 | 28.0 | Negative |
| Maternal nasal swab | ND | ND | 33.4 | Negative |
| Maternal oral swab | ND | ND | 30.9 | Negative |
| Maternal saliva | 32.6 | 33.8 | 25.1 | Positive |
| Maternal urine | 36.2 | 36.7 | 36.4 | Positive |
| Maternal rectal swab | 38.5 | ND | 32.9 | Negative |

*Algarroba GN. Am J Obstet Gynecol 2020*
*Hosier H. J Clin Invest 2020*

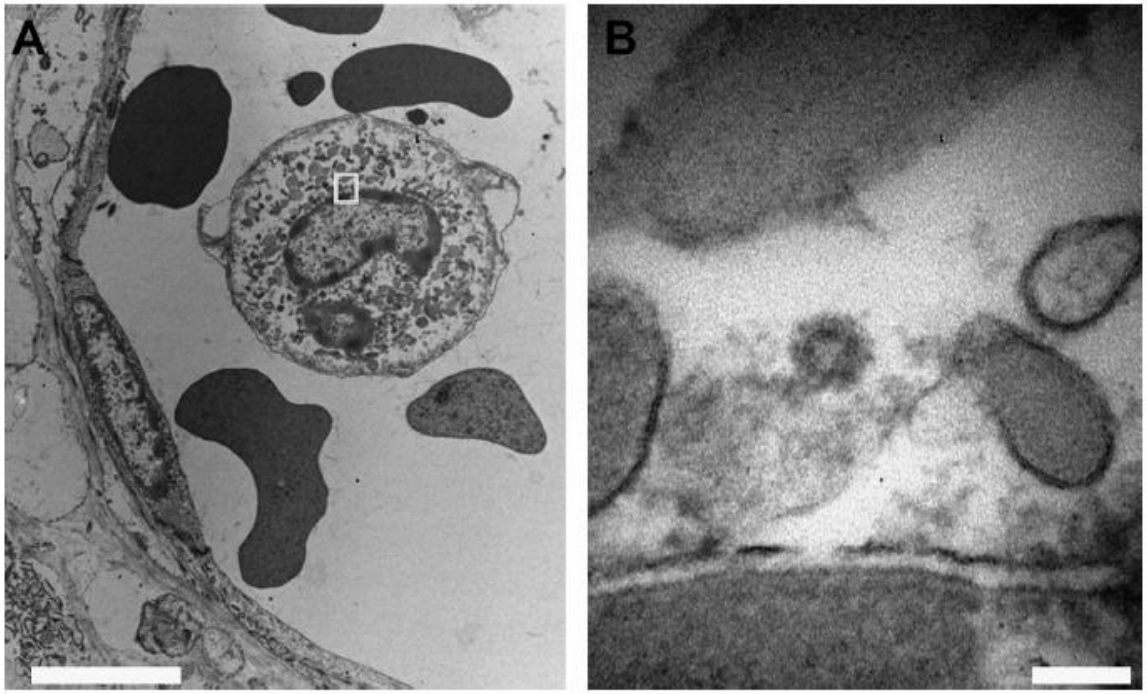
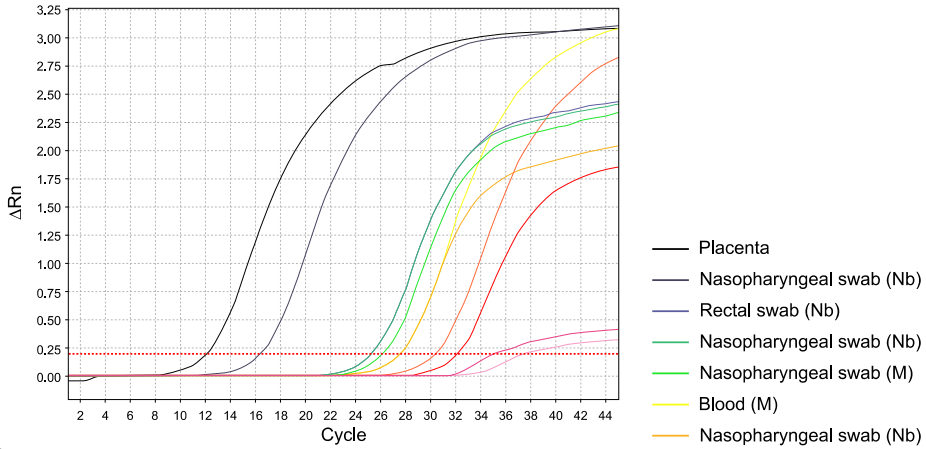


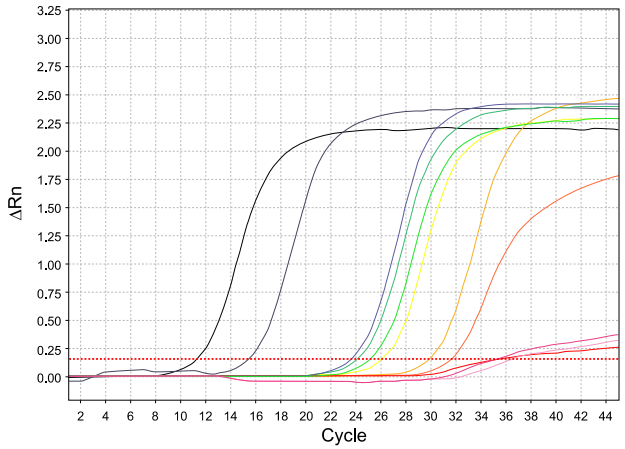

**Fig. 3.** Electron microscopy of SARS-CoV-2 viral particle within an intra-capillary monocyte.
(A, B) In the cytoplasm of an intra-capillary monocyte (A, bar 5 $\mu$m) a particle morphologically consistent with coronavirus is present (B, high magnification of the area shown in A, bar 100 nm).

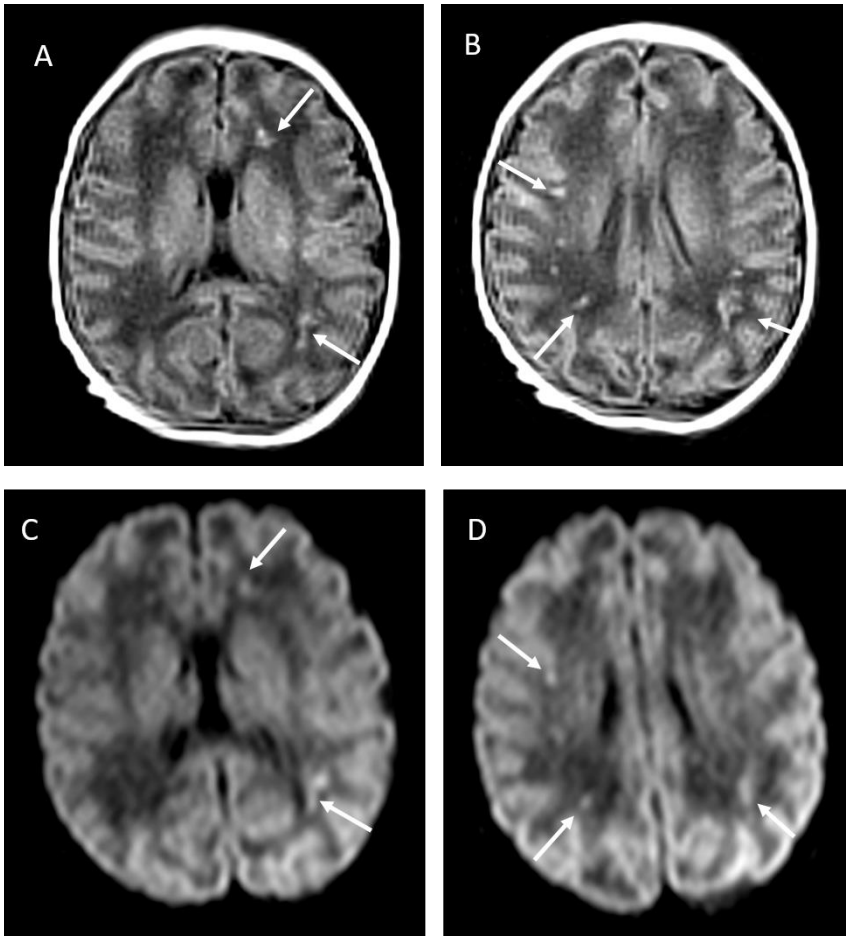
***Facchetti F. EBioMedicine 2020***

A




B




C

| Mother | | Neonate | |
|---|---|---|---|
| **Sample** | **Viral load (Log)** | **Sample** | **Viral load (Log)** |
| Nasopharyngeal swab | 4.22 | Blood | 1.15 |
| Vaginal swab | 0.63 | Nasopharyngeal swab (DOL1) | 2.21 |
| Placenta | 11.15 | Rectal swab | 4.71 |
| Amniotic fluid | 2.09 | Nasopharyngeal swab (DOL3) | 7.30 |
| Blood | 4.87 | Nasopharyngeal swab (DOL18) | 4.54 |

***Vivanti A. Nature Commun 2020***

| Patient | Category | Case Definition |
|---|---|---|
| Neonatal infection acquired intrapartum | | |
| Clinical features of infection in newborn and mother with SARS-CoV-2 infection | Confirmed | Detection of the virus by PCR in nasopharyngeal swab at birth (collected after cleaning the baby) AND at 24-48 hours of age AND alternate explanation for clinical features excluded |
| | Probable | Detection of the virus by PCR in nasopharyngeal swab at birth (collected after cleaning baby) but not at 24-48 hours of age AND alternate explanation for clinical features excluded |
| | Possible | No detection of the virus by PCR in nasopharyngeal swab at birth AND detection of the virus by PCR in any of maternal vaginal/placental/cord/skin swab at birth AND alternate explanation for clinical features excluded |
| | Unlikely | No detection of the virus by PCR in nasopharyngeal swab at birth (collected after cleaning baby) OR in any of maternal vaginal/placental/cord/neonatal nasopharyngeal/skin swab at birth AND alternate explanation for clinical features not identified |
| | Not infected | No detection of the virus by PCR in nasopharyngeal swab at birth (collected after cleaning baby) OR in any of maternal vaginal/placental/cord/neonatal nasopharyngeal/skin swab at birth AND alternate explanation for clinical features identified |
| No clinical features of infection in newborn and mother with SARS-CoV-2 infection | Confirmed | Detection of the virus by PCR in nasopharyngeal swab at birth (collected after cleaning the baby) AND at 24-48 hours of age |
| | Possible | Detection of the virus by PCR in nasopharyngeal swab at birth (collected after cleaning the baby) AND not at 24-48 hours |
| | Not infected | No detection of the virus by PCR in nasopharyngeal swab at birth AND no detection of the virus by PCR in any of vaginal swab in mother/placental swab/skin/cord swab at birth |
| Neonatal infection acquired postpartum | | |
| Clinical features of infection in newborn at ≥48 hours age (parent or caregiver may or may not have SARS-CoV-2 infection or were not tested) | Confirmed | Detection of the virus by PCR in nasopharyngeal/rectal swab at ≥48 hours of birth in a neonate whose respiratory sample tested negative by PCR at birth |
| | Probable | Detection of the virus by PCR in nasopharyngeal/rectal swab at ≥48 hours of birth in a neonate who was not tested at birth |
| | Not infected[a] | No detection of the virus by PCR in nasopharyngeal/rectal swab at ≥48 hours of birth and other cause identified |

***Shah O. Acta Obstet Gyencol 2020***

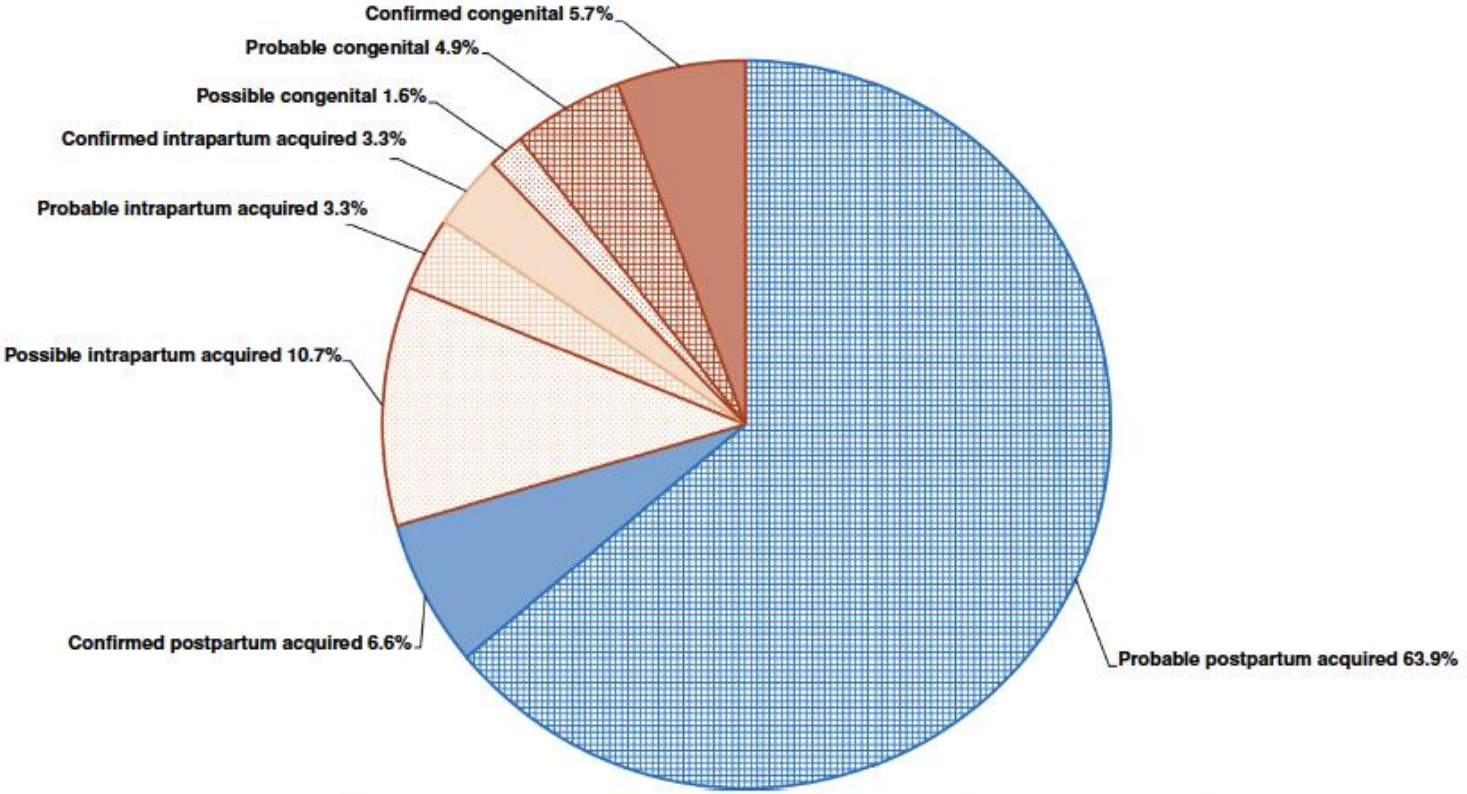



**Fig. 2 Classification of neonatal SARS-CoV-2 infections according to the definition of maternal, fetal, and neonatal SARS-CoV-2 infections.** Classification is based on a system including several virological tests (on placental tissues, amniotic fluid, cord and newborn blood or nasopharyngeal swabs), as well as the presence of clinical manifestations[16]. Cases are divided into: (1) congenital infections, (2) intrapartum acquired infections, or (3) postpartum acquired infections and into five mutually exclusive categories of the likelihood of infection: "confirmed", "probable", "possible", "unlikely", and "not infected". Classification was applied to 122 cases (for 54 neonates, data needed to classify the infection were missing despite repeated requests to the authors of the articles). Areas in blue depict the infections confirmed or supposed to be environmentally acquired (i.e.: postpartum), while areas in brown depict confirmed or supposed to be vertically (either intrapartum or congenitally) transmitted infections; numbers represent the %.



***Raschetti R. Nature Commun 2020***

**Table 2 Basic data of the reported neonates.**

| Neonates (176) | Summary statistics | Min-max range |
|---|---|---|
| Gestational age (weeks) | 36.9 (3.4) | 26–41 |
| Birth weight (grams) | 2782 (799) | 900–4500 |
| Birth weight *Z*-score | 0 [−0.8;0.8] | −2.41–2.41 |
| Male sex | 63 (62.4%)[a] | - |
| Caesarean section | 66 (37.5%) | - |
| 5′ Apgar score | 9 [8.5;10] | 2–10 |
| Postnatal age at the diagnosis (days) | 5 [2;15] | 0–30 |
| Symptomatic neonates | 97 (55.1%) | - |

Data are expressed as mean (standard deviation) or median [interquartile range], min-max or number (%), as appropriate.
[a]Male sex percentage is referred to 101 neonates, as gender data were missing for the others, despite repeated requests to the authors of the articles.

**Table 3 Distribution of clinical features in the subgroup of neonates presenting with signs or symptoms compatible with COVID-19.**

| Clinical features | Neonates (%) |
|---|---|
| Respiratory | 51 (52.5%) |
| Fever | 43 (44.3%) |
| Gastrointestinal | 35 (36%) |
| Neurological | 18 (18.6%) |
| Hemodynamic | 10 (10.3%) |
| Others | 9 (9.2%) |

Clinical features are listed in order of frequency; multiple features are possible in a patient; percentage is calculated for the group of symptomatic neonates ($n = 97$). More details in the text.

| Lab/Imaging features | Neonates (%) |
|---|---|
| Abnormal lung imaging | 62.5% |
| Lymphopenia | 14.6% |
| Inflammatory status | 14.6% |
| Raised liver enzymes | 6.2% |
| Abnormal brain imaging | 4.2% |

***Raschetti R. Nature Commun 2020***

# Neonatal ARDS due to COVID19



## The Montreux definition of neonatal ARDS: biological and clinical background behind the description of a new entity

Daniele De Luca, Anton H van Kaam, David G Tingay, Sherry E Courtney, Olivier Danhaive, Virgilio P Carnielli, Luc J Zimmermann, Martin C J Kneyber, Pierre Tissieres, Joe Brierley, Giorgio Conti, Jane J Pillow, Peter C Rimensberger

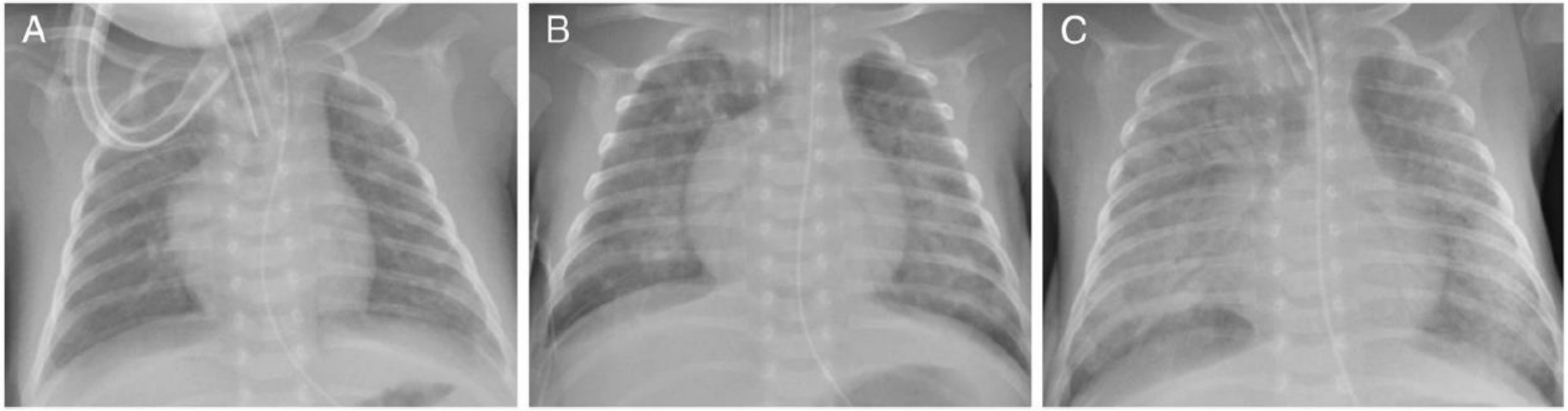
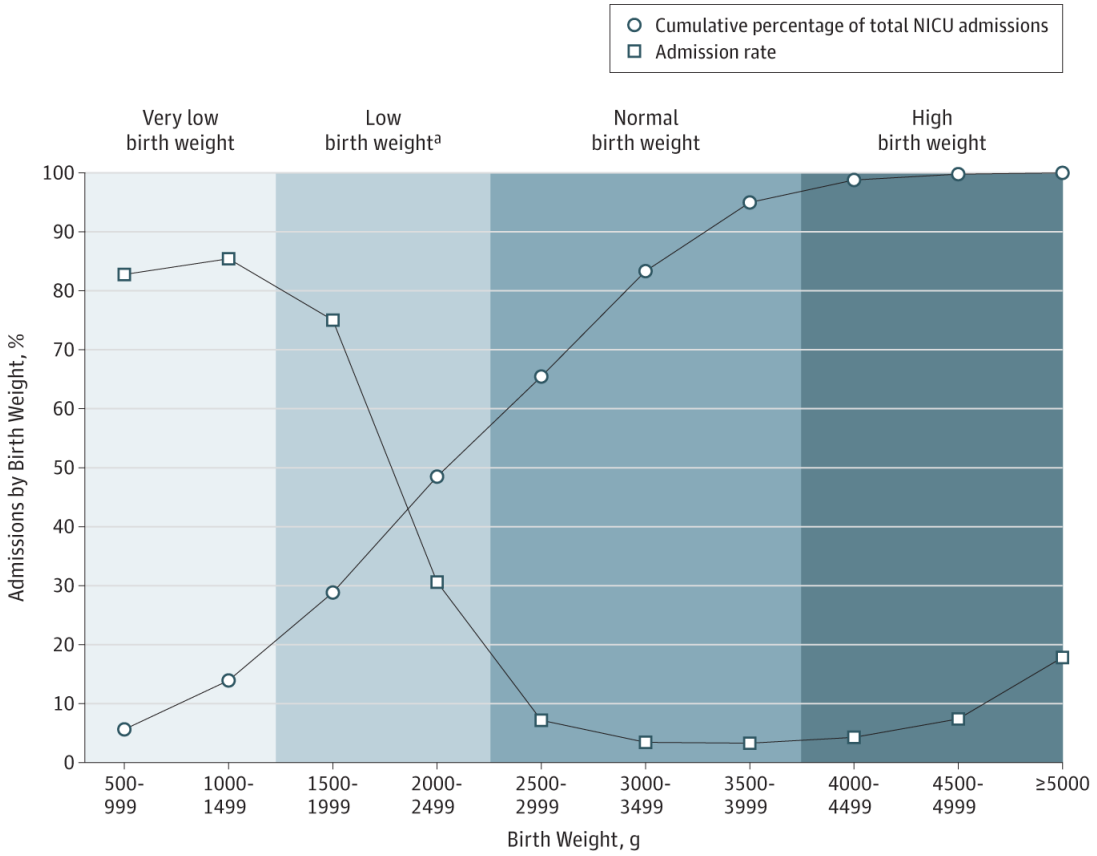



**FIGURE 2**
Chest radiographs performed. A, Performed on day 2. B, Performed on day 5. C, Performed on day 6. Initially, only mild bilateral ground-glass opacities were present. Subsequent radiologic worsening is noted with progressive airspace opacification (day 5) and bilateral consolidation with predominant peripheral distribution, lung overinflation, and right basal pneumothorax (day 6).

***Frauenfelder C. Pediatrics 2020***
***De Luca D. Lancet Resp Med 2017***

# 24% NICU admission

Median stay 11.5 [7-17]d




***De Luca D – under review***

***Harrison W. JAMA Pediatr 2015***

## Managing neonates with respiratory failure due to SARS-CoV-2

In their Comment in *The Lancet Child & Adolescent Health*, Jianhui Wang and colleagues[1] suggested a plan to handle neonates with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections and outbreaks in neonatal

and extracorporeal life support cannot be suggested for every patient, because no evidence-based data exist. Epidemiologically, the priority is to diagnose neonatal acute respiratory distress syndrome (ARDS) according to the age-specific definition (the so-called Montreux definition of neonatal ARDS[3]) and use it to classify clinical severity. This allows production of solid epidemiology data and


1 Wang J, Qi H, Bao L, Li F, Shi Y. A contingency plan for the management of the 2019 novel coronavirus outbreak in neonatal intensive care units. *Lancet Child Adolesc Health* 2020; published online Feb 7. https://doi.org/10.1016/S2352-4642(20)30040-7.

2 Nates JL, Nunnally M, Kleinpell R, et al. ICU admission, discharge, and triage guidelines: a framework to enhance clinical operations, development of institutional policies, and further research. *Crit Care Med* 2016; **44:** 1553–602.

3 De Luca D, van Kaam AH, Tingay DG, et al. The Montreux definition of neonatal ARDS: biological and clinical background behind the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https://doi.org/10.1016/
S2352-4642(20)30073-0

Second, neonates positive for SARS-CoV-2 must be isolated and clinically monitored, but this does not necessarily require NICU admission. It might be done in a single room, without full NICU capabilities, according to local settings. Admitting all neonates to NICU would be similar to admitting all positive adults to an ICU, whereas strict admission criteria and prioritisation are needed and not yet universally implemented.[2] A general ICU admission might lead to mistakes in epidemiological data and overestimation of the severity of the disease, and it is important to reserve NICU beds for patients who are in life-threatening situations.

Third, surfactant, inhaled nitric oxide, various ventilation methods, media seem to exclude it.

Finally, older children (aged >1 month) are not affected or present with mild symptoms, which could be due to a reduced inflammatory response and a relatively low viral cytotoxicity. Thus, these pathogenetic mechanisms could also apply to neonates and might lead to consideration of steroid therapy for refractory respiratory failure upon evaluation of the risk-benefit ratio.[5]

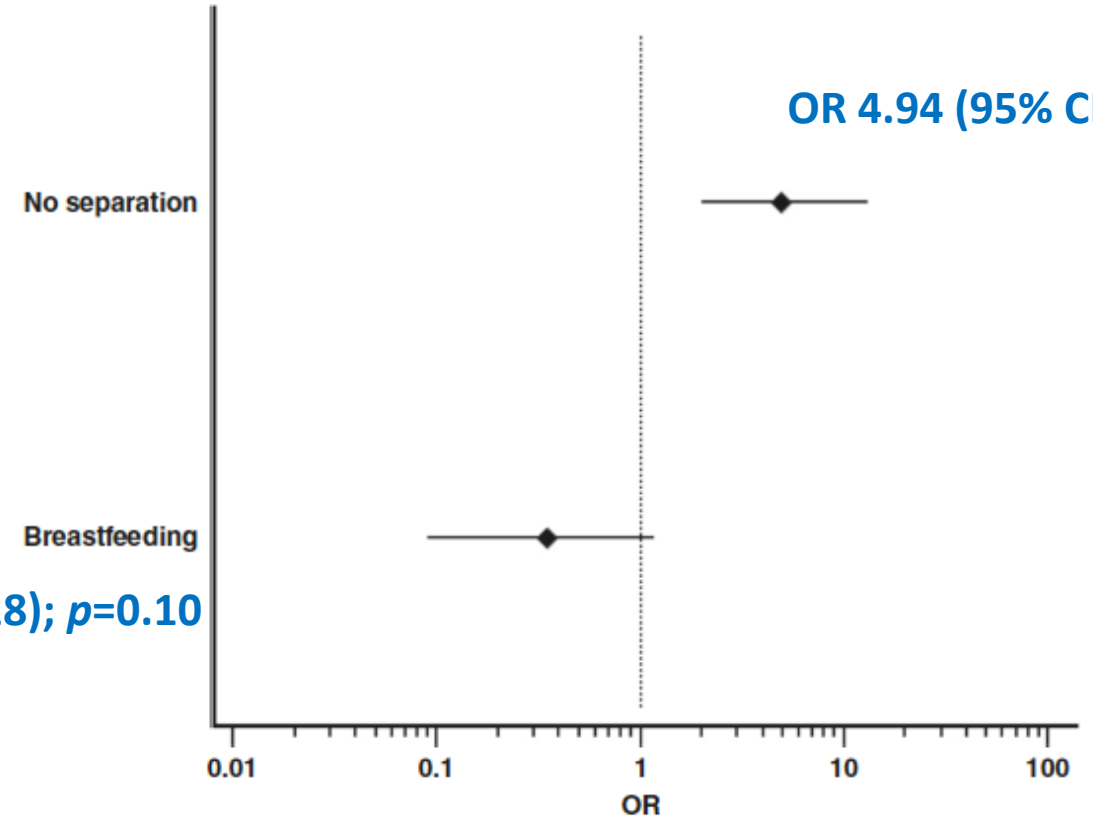
I declare no competing interests.

*Daniele De Luca*
**dm.deluca@icloud.com**

Division of Pediatrics and Neonatal Critical Care, "A Béclère" Medical Center, Paris Saclay University Hospitals, Assistance Publique-Hopitaux de Paris, Paris, France; and Therapeutic Innovation Unit, U999, Paris Saclay University, Paris, France

***De Luca D. Lancet Child Health 2020***

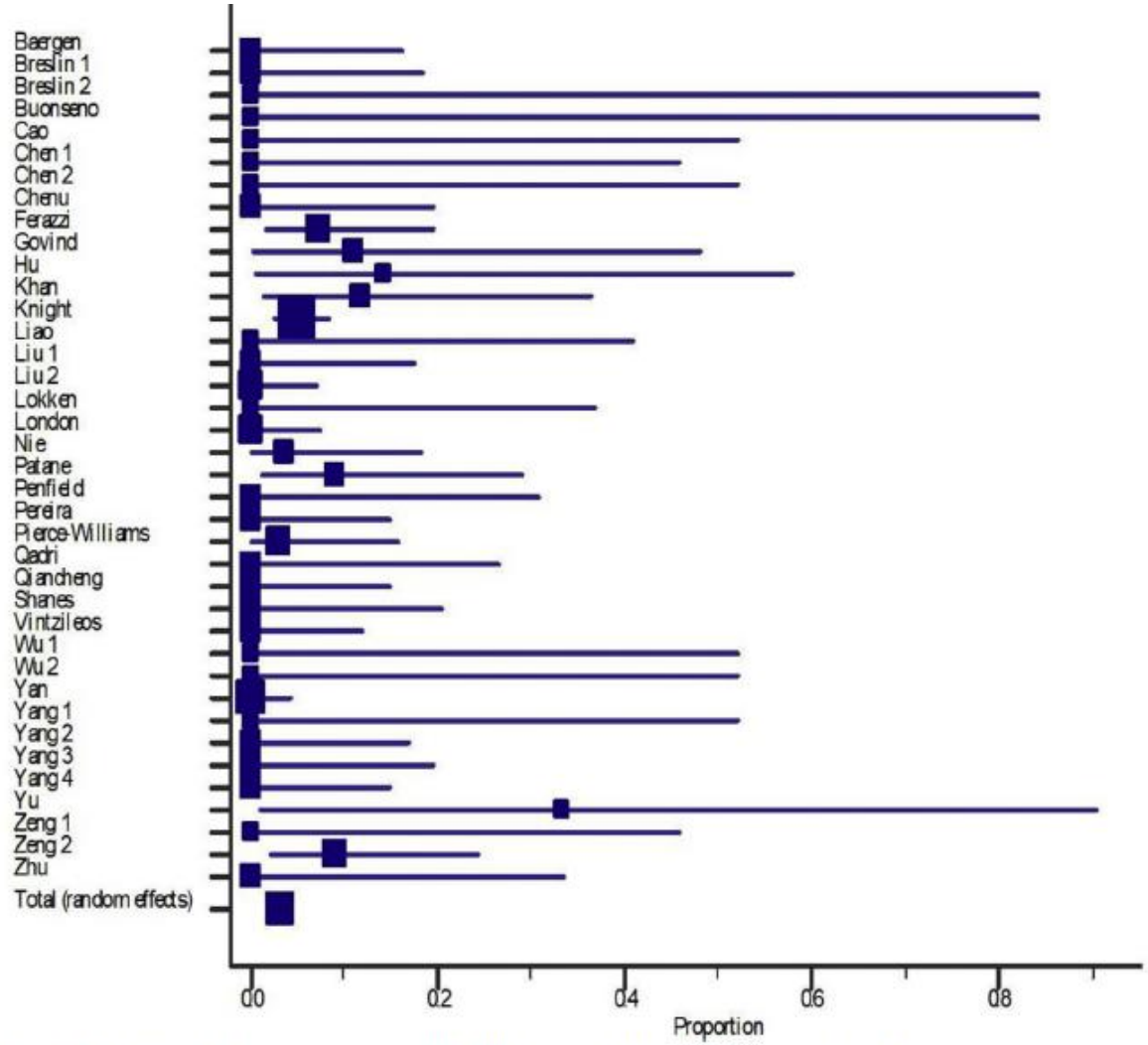
OR 4.94 (95% CI: 13); *p*=0.0002




OR 35 (95% CI: 18); *p*=0.10

**Fig. 3 Effect of mother-neonate separation and breastfeeding on the occurrence of late SARS-CoV-2 infections.** Late infections are defined as those diagnosed after the first 72 h of life. Diamonds and horizontal lines represent the odds ratio (OR) and its 95% confidence interval (CI), respectively. Horizontal axis is on a log scale for better visualization; vertical hatched line represents OR = 1. Analysis was performed for 133 neonates for whom infection could have been classified as early- or late-onset. Figure illustrates OR 4.94 (95% CI: 1.98–13.08), $p = 0.0002$, for lack of mother-neonate separation from birth and OR 0.35 (95% CI: 0.09–1.18), $p = 0.10$ for breastfeeding. Analyses were performed with two-sided Fisher exact test.

***Raschetti R. Nature Commun 2020***




| N | Proportion (%) | 95% CI | Weight (%) |
|---|---|---|---|
| 21 | 0.0 | 0.0 – 16.1 | 2.26 |
| 18 | 0.0 | 0.0 – 18.5 | 1.95 |
| 2 | 0.0 | 0.0 – 84.2 | 0.31 |
| 2 | 0.0 | 0.0 – 84.2 | 0.31 |
| 5 | 0.0 | 0.0 – 52.2 | 0.62 |
| 6 | 0.0 | 0.0 – 45.9 | 0.72 |
| 5 | 0.0 | 0.0 – 52.2 | 0.62 |
| 17 | 0.0 | 0.0 – 19.5 | 1.85 |
| 42 | 7.1 | 1.5 – 19.5 | 4.41 |
| 9 | 11.1 | 0.3 – 48.3 | 1.03 |
| 7 | 14.3 | 0.4 – 57.9 | 0.82 |
| 17 | 11.8 | 1.5 – 36.4 | 1.85 |
| 244 | 4.9 | 2.6 – 8.4 | 25.2 |
| 7 | 0.0 | 0.0 – 41.0 | 0.82 |
| 19 | 0.0 | 0.0 – 17.6 | 2.05 |
| 51 | 0.0 | 0.0 – 7.0 | 5.34 |
| 8 | 0.0 | 0.0 – 36.9 | 0.92 |
| 48 | 0.0 | 0.0 – 7.4 | 5.03 |
| 28 | 3.6 | 0.1 – 18.3 | 2.98 |
| 22 | 9.1 | 1.1 – 29.2 | 2.36 |
| 10 | 0.0 | 0.0 – 30.9 | 1.13 |
| 23 | 0.0 | 0.0 – 14.8 | 2.46 |
| 33 | 3.0 | 0.1 – 15.8 | 3.49 |
| 12 | 0.0 | 0.0 – 26.5 | 1.33 |
| 23 | 0.0 | 0.0 – 14.8 | 2.46 |
| 16 | 0.0 | 0.0 – 20.6 | 1.75 |
| 29 | 0.0 | 0.0 – 11.9 | 3.08 |
| 5 | 0.0 | 0.0 – 52.2 | 0.62 |
| 5 | 0.0 | 0.0 – 52.2 | 0.62 |
| 86 | 0.0 | 0.0 – 4.2 | 8.93 |
| 5 | 0.0 | 0.0 – 52.2 | 0.62 |
| 20 | 0.0 | 0.0 – 16.8 | 2.16 |
| 17 | 0.0 | 0.0 – 19.5 | 1.85 |
| 23 | 0.0 | 0.0 – 14.8 | 2.46 |
| 3 | 33.3 | 0.8 – 90.6 | 0.41 |
| 6 | 0.0 | 0.0 – 45.9 | 0.72 |
| 33 | 9.1 | 1.9 – 24.3 | 3.49 |
| 9 | 0.0 | 0.0 – 33.6 | 1.03 |
| 936 | 3.2 | 2.2 - 4.3 | 100.00 |

**Heterogeneity:** Cochran's Q: 36.20 df=37 p=0.506
$I^2$=0.00% 95% CI for $I^2$: 0.00 – 35.6%

*CI*, confidence interval; *df*, degrees of freedom; *SARS-CoV-2*, severe acute respiratory syndrome coronavirus 2.

*Kotlyar. Vertical transmission of COVID-19: a systematic review and meta-analysis. Am J Obstet Gynecol 2020.*

***Kotlyar M. Am J Obstet Gynecol 2020***


Thanks for listening
dm.deluca@icloud.com
epicentre@mcri.edu.au
De Luca D. Eur J Pediatr 2020