



EDITORIAL

Neonates in the COVID-19 pandemic

Pediatric Research _#####_; <https://doi.org/10.1038/s41390-020-1096-y>

The coronavirus disease 2019 (COVID-19) pandemic has predominantly affected adults of higher age groups, and the effect of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on infants and neonates appears to be small. While we are gathering emerging evidence on the exact SARS-CoV-2 disease process, intrauterine or perinatal transmission of SARS-CoV-2 remains ambiguous,¹ and vertical transmission has yet to be proven although viral RNA by reverse transcription polymerase chain reaction has been found in placental membranes and breast milk.^{2–5} In contrast, breast milk of mothers who contracted COVID-19 can provide antibodies against SARS-CoV-2.^{6,7} There are rare case reports of infected infants, the majority of whom were asymptomatic, and symptomatic late-onset viral sepsis has so far only been reported in a 3-week-old infant and a 26-week preterm infant.^{8–12} However, longer-term effects of perinatal exposure or sequelae from apparent or occult neonatal COVID-19 are yet unknown and warrant careful monitoring. In response to the sudden pandemic, a wide variation in recommendations for the management of infants born to mothers who are SARS-CoV-2 positive can be found in the literature. For example, the recommendations (1) for careful assessment of the need for personal protective equipment during newborn stabilisation,^{13,14} (2) for isolation of 2 weeks of an infant born to an affected mother, and (3) for the allowance of breastfeeding with precautions all vary widely.^{15–17}

We recently published an international comparison of guidelines on COVID 19 in neonates to inform the community of neonatologists about differences in management, which could possibly improve outcomes for newborns and their families.¹⁸ This collaboration encompassed 20 countries from 6 continents and compared national and local guidelines on the management of neonates in the early COVID pandemic. We highlighted that no clear-cut guidance on immediate delivery room management was given and that most recommendations suggested asymptomatic infants be not separated from their mother and could be breastfed with hygiene precautions. Important differences emerged that were not explained by the phase of the pandemic at the time of the survey. There were distinct differences in viral testing, advice for personal protective equipment use and family visits. The report highlights how, in the face of a pandemic like COVID-19, rapidly available, consensus-based international, real-time information exchange could better inform local guideline formation and implementation.

However, while few infants suffer relevantly from COVID-19, the “para-COVID” effects are felt prominently in many neonatal intensive care units (NICUs) and have significant collateral effects on the quality of care for neonates. The resources (financial, physical space, healthcare workers, ventilators) diverted to face the COVID-19 epidemic in the adult services strained perinatal and other NICU services. The restriction to parent visiting has potentially significant impact on parental attachment and well-being with secondary effects on infant physical and mental

health.¹⁹ Healthcare workers globally (n = 714) reported a 90% increase in stress related to the pandemic.²⁰ Sufficient resources to support the psychological impacts are required to protect families and healthcare workers. This pandemic has also highlighted major social disadvantages and inequalities in healthcare resources. Global concerns about maternal and neonatal health in countries with limited resources^{21,22} due to further shrinking of resources and illness in healthcare providers have been highlighted.

Positive side effects of the pandemic include the rapid development of virtual communication in many NICUs for parents to ensure families are supported and to allow social distancing. Virtual communication can improve extended family involvement in the early NICU period and may reduce the financial burden of illness for families. In addition, international collaborations and interactive conferences have flourished in the past few months.²³ The value of registries and longitudinal follow-up have been recognised and rapidly established at national and international levels²⁴: ROI COVID-19 National Register: PAN-COVID Pregnancy and Neonatal outcomes registry (UK); UKOSS COVID-19 in Pregnancy Study (UK); COVI-PREG Registry (Switzerland), OTIS/MotherToBaby Study (USA); Pregnancy Coronavirus Outcomes (PRIORITY) Registry (USA); National Perinatal COVID-19 (NPC-19) registry, American Academy of Pediatrics; CHOPAN Registry (Coronavirus Health Outcomes in Pregnancy and Neonates) – Australian Outcomes Registry; INNSIN Covid-19 (Italian Neonatal Network of Italian Society of Neonatology - Covid-19); EPICENTRE (ESPNIC Covid pEdiatric Neonatal Registry); Spanish Neonatal Society Registro Covid SENEo. The UKOSS initiative has already published their findings showing the relatively low rate of positive tests (5%) in neonates born to women who were SARS-CoV-2 positive.²⁵

Reasons for the disparity in serious disease between newborn, children and older adults are not fully understood, although differences in immune function have been described.^{26–28} Decreased angiotensin-converting enzyme 2 levels in the nasopharyngeal epithelium and less vigorous interleukin-6 responses during SAR-CoV-2 infection may contribute to the clinical picture.²⁹ In contrast to the relatively naive neonatal immune system, older adults have an altered response to inflammatory stimuli termed “inflammaging” and thymic involution.³⁰ However, older children are not immune to the effects of SAR-CoV-2 and may present with Multi-system Inflammatory Syndrome (MIS-C), a condition typically occurring 4–6 weeks post-acute SAR-CoV-2 infection with a spectrum of illness similar to Kawasaki’s disease or Toxic Shock syndrome, in some cases leading to shock and multiorgan failure.³¹

Among the many lessons in the management of adults with COVID-19, like using prone positioning for ventilation, the targeted use of surfactant, immune modulation to reduce organ injury by use of dexamethasone and virtual visiting, there are major similarities with neonatal intensive care. As a major positive, the example of the UK-wide RECOVERY trial might be highlighted ([recoverytrial.net](https://www.recoverytrial.net)). This national mega-trial, a collaborative effort between physicians from a wide range of specialities, was set up in ground-breaking speed of only 9 days from concept to first patient inclusion (ISRCTN50189673). It is already the largest ever multi-centre, randomised controlled trial, including 176 centres and patients of all ages, including especially vulnerable populations such as

Received: 15 July 2020 Accepted: 16 July 2020

Published online: 03 August 2020

pregnant women and children (<https://www.recoverytrial.net/news/first-patient-a-child-receives-convalescent-plasma-through-recovery-the-dedicated-covid-19-treatment-trial>). The hope is that with the International Neonatal COVID-19 Consortium such trials can be rapidly developed and extend globally.

Looking ahead, future interdisciplinary learning and collaboration between critical care groups from adults, paediatric and neonatal intensive care may have significant benefits for patients of all age groups. Thus far, the speed of national and international collaboration has been dramatic and it needs to continue to ensure a rapid response, especially as the next pandemic or disaster may disproportionately affect neonates. There is a dire need for supporting a Neonatal International Collaborative Group to promote information exchange for informed local implementation of all aspects of neonatal care. Our aspiration is to develop and maintain an international neonatal collaborative working group on neonatal disaster preparedness. The Collaboration started by Lavizzari and colleagues has already expanded from the initially included 20 countries from 6 continents to >90 collaborating countries worldwide. With such an engaged workforce, our aim is to develop early warning and rapid, evidence-based response systems for future regional and/or global disasters and to develop a multisite registry database.

Neonatal Registries:

- ROI COVID-19 National Register (<https://www.ucc.ie/en/npec/roicovid-19study/>);
- PAN-COVID Pregnancy and Neonatal outcomes registry (UK) (<https://pan-covid.org/>);
- UKOSS COVID-19 in Pregnancy Study (UK) (<https://www.npeu.ox.ac.uk/ukoss/current-surveillance/covid-19-in-pregnancy/>);
- COVI-PREG Registry (Switzerland) (<https://www.chuv.ch/fr/dfme/dfme-home/recherche/femme-mere/materno-fetal-and-obstetrics-research-unit-prof-baud/covi-preg/>);
- OTIS/ MotherToBaby Study (USA) (<https://mothertobaby.org/ongoing-study/coronavirus-covid-19/>);
- Pregnancy Coronavirus Outcomes (PRIORITY) Registry (USA) (<https://priority.ucsf.edu/>);
- National Perinatal COVID-19 (NPC-19) registry, American Academy of Pediatrics (<https://services.aap.org/en/community/aap-sections/sonpm/in-the-spotlight/>);
- CHOPAN Registry (Coronavirus Health Outcomes in Pregnancy and Neonates) – Australian Outcomes Registry (<https://www.neonatalcovid19study.com/>);
- INNSIN Covid-19 (Italian Neonatal Network of Italian Society of Neonatology - Covid-19) (<https://www.sin-neonatologia.it/>);
- EPICENTRE (ESPNIC Covid pEdiatric Neonatal Registry) (Eur J Pediatr. 2020 May 22;1–8); Spanish Neonatal Society Registro Covid SENEo (<https://www.se-neonatal.es/~josepr23/sociedades/SENEOV1/index.php/registro-covid-seneo>).

AUTHOR CONTRIBUTIONS

E.J.M., together with C.K., J.P., J.A.F.Z., A.L., F.M., C.F.B. and C.C.R., produced the first draft of the manuscript. All collaborators were included on the completion of the manuscript.

ADDITIONAL INFORMATION

Competing interests: The authors declare no competing interests.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Eleanor J. Molloy^{1,2,3,4}, Anna Lavizzari⁵, Claus Klingenberg^{6,7}, Jochen Profit^{8,9}, John A. F. Zupancic^{10,11}, Alexis S. Davis⁸, Fabio Mosca^{5,12}, Cynthia F. Bearer^{13,14},

Charles C. Roehr^{15,16} and The International Neonatal COVID-19 Consortium

¹Paediatrics, Academic Centre, Children's Hospital Ireland (CHI) at Tallaght, Trinity College, the University of Dublin, Dublin, Ireland; ²Trinity Translational Medicine Institute (TTMI) & Trinity Research in Childhood Centre (TRICC), Dublin, Ireland; ³Neonatology, Coombe Women and Infants' University Hospital, Dublin, Ireland; ⁴Neonatology, CHI at Crumlin, Dublin, Ireland; ⁵Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, NICU, Milan, Italy; ⁶Department of Paediatric and Adolescent Medicine, University Hospital of North Norway, Tromsø, Norway; ⁷Paediatric Research Group, Department of Clinical Medicine, UiT- The Arctic University of Norway, Tromsø, Norway; ⁸Division of Neonatal and Developmental Medicine, Department of Pediatrics, Stanford University School of Medicine, Palo Alto, CA, USA; ⁹California Perinatal Quality Care Collaborative, Palo Alto, CA, USA; ¹⁰Department of Neonatology, Beth Israel Deaconess Medical Center, Boston, MA, USA; ¹¹Division of Newborn Medicine, Harvard Medical School, Boston, MA, USA; ¹²Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy; ¹³Division of Neonatology, Department of Pediatrics, Rainbow Babies & Children's Hospital, University Hospitals of Cleveland, Cleveland, OH, USA; ¹⁴Department of Pediatrics, Case Western Reserve University, Cleveland, OH, USA; ¹⁵Newborn Services, John Radcliffe Hospital, Oxford University Hospitals NHS Foundation Trust, Oxford, UK and ¹⁶National Perinatal Epidemiology Unit, Nuffield Department of Population Health, University of Oxford, Oxford, UK; A list of International Neonatal COVID-19 Consortium members and their affiliations appears at the end of the paper. Correspondence: Eleanor J. Molloy (eleanor.molloy@tcd.ie)

REFERENCES

1. Lopes de Sousa, Á. F. et al. Effects of COVID-19 infection during pregnancy and neonatal prognosis: what is the evidence? *Int. J. Environ. Res. Public Health* **17**, E4176 (2020).
2. Penfield, C. A. et al. Detection of SARS-CoV-2 in placental and fetal membrane samples. *Am. J. Obstet. Gynecol. MFM* <https://doi.org/10.1016/j.ajogmf.2020.100133> (2020).
3. Groß, R. et al. Detection of SARS-CoV-2 in human breastmilk. *Lancet* **395**, 1757–1758 (2020).
4. Wu, Y. et al. Coronavirus disease 2019 among pregnant Chinese women: case series data on the safety of vaginal birth and breastfeeding. *BJOG* <https://doi.org/10.1111/1471-0528.16276> (2020).
5. Tam, P. C. K. et al. Detectable severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in human breast milk of a mildly symptomatic patient with coronavirus disease 2019 (COVID-19). *Clin. Infect. Dis.* <https://doi.org/10.1093/cid/ciaa673> (2020).
6. Preßler, J. et al. Postnatal SARS-CoV-2 infection and immunological reaction: a prospective family cohort study. *Pediatr. Allergy Immunol.* <https://doi.org/10.1111/pai.13302> (2020).
7. Dong, Y. et al. Antibodies in the breast milk of a maternal woman with COVID-19. *Emerg. Microbes Infect.* **9**, 1467–1469 (2020).
8. Kirtsman, M. et al. Probable congenital SARS-CoV-2 infection in a neonate born to a woman with active SARS-CoV-2 infection. *CMAJ* **192**, E647–E650 (2020).
9. Piersigilli, F. et al. COVID-19 in a 26-week preterm neonate. *Lancet Child Adolesc. Health* **4**, 476–478 (2020).
10. Sun, M. et al. Evidence of mother-to-newborn infection with COVID-19. *Br. J. Anaesth.* **125**, e245–e247 (2020).
11. Shalish, W., Lakshminrusimha, S., Manzoni, P., Keszler, M. & Sant'Anna, G. M. COVID-19 and neonatal respiratory care: current evidence and practical approach. *Am. J. Perinatol.* **37**, 780–791 (2020).
12. Coronado Munoz, A. et al. Late-onset neonatal sepsis in a patient with Covid-19. *N. Engl. J. Med.* **382**, e49 (2020).
13. Nolan, J. P. et al. European Resuscitation Council COVID-19 Guidelines Executive Summary. *Resuscitation* **153**, 45–55 (2020).
14. Trevisanuto, D. et al. Neonatal resuscitation where the mother has a suspected or confirmed novel coronavirus (SARS-CoV-2) infection: suggestion for a pragmatic action plan. *Neonatology* **117**, 133–140 (2020).
15. Shahbazi Sighaldehy, S. & Ebrahimi Kalan, M. Care of newborns born to mothers with COVID-19 infection; a review of existing evidence. *J. Matern. Fetal Neonatal Med.* <https://doi.org/10.1080/14767058.2020.1777969> (2020).

16. Thi Tran, H. et al. Appropriate care for neonates born to mothers with COVID-19 disease. *Acta Paediatr.* <https://doi.org/10.1111/apa.15413> (2020).
17. Ezenwa, B. N. et al. Management of covid-19: a practical guideline for maternal and newborn health care providers in Sub-Saharan Africa. *J. Matern. Fetal Neonatal Med.* <https://doi.org/10.1080/14767058.2020.1763948> (2020).
18. Lavizzari, A. et al. International comparison of guidelines for managing neonates at the early phase of the SARS-CoV-2 pandemic. *Pediatr. Res.* <https://doi.org/10.1038/s41390-020-0976-5> (2020).
19. Tscherning, C., Sizun, J. & Kuhn, P. Promoting attachment between parents and neonates despite the COVID-19 pandemic. *Acta Paediatr.* <https://doi.org/10.1111/apa.15455> (2020).
20. Semaan, A. et al. Voices from the frontline: findings from a thematic analysis of a rapid online global survey of maternal and newborn health professionals facing the COVID-19 pandemic. *BMJ Glob. Health* **5**, e002967 (2020).
21. Abdul-Mumin, A., Agbozo, F., Abubakari, A. & Jahn, A. Maintaining quality newborn care in Ghana amid the COVID-19 pandemic. *Pan Afr. Med. J.* **35**(Suppl 2), 6 (2020).
22. Truelove, S. et al. The potential impact of COVID-19 in refugee camps in Bangladesh and beyond: a modeling study. *PLoS Med.* **17**, e1003144 (2020).
23. Cavicchiolo, M. E., Lolli, E., Trevisanuto, D. & Baraldi, E. Managing a tertiary-level NICU in the time of COVID-19: lessons learned from a high-risk zone. *Pediatr. Pulmonol.* **55**, 1308–1310 (2020).
24. Gale, C. et al. National active surveillance to understand and inform neonatal care in COVID-19. *Arch. Dis. Child. Fetal Neonatal Ed.* **105**, 346–347 (2020).
25. Knight, M. et al. Characteristics and outcomes of pregnant women admitted to hospital with confirmed SARS-CoV-2 infection in UK: national population based cohort study. *BMJ* **369**, m2107 (2020).
26. Kloc, M., Ghobrial, R. M., Kuchar, E., Lewicki, S. & Kubiak, J. Z. Development of child immunity in the context of COVID-19 pandemic. *Clin. Immunol.* **217**, 108510 (2020).
27. Molloy, E. J. & Bearer, C. F. COVID-19 in children and altered inflammatory responses. *Pediatr. Res.* <https://doi.org/10.1038/s41390-020-0881-y> (2020).
28. Walker, K. F. et al. Maternal transmission of SARS-CoV-2 to the neonate, and possible routes for such transmission: a systematic review and critical analysis. *BJOG* <https://doi.org/10.1111/1471-0528.16362> (2020).
29. Soraya, G. V. & Ulhaq, Z. S. Interleukin-6 levels in children developing SARS-CoV-2. *Infect. Pediatr. Neonatol.* **61**, 253–254 (2020).
30. Scarpa, R., Costa, L., Del Puente, A. & Caso, F. Role of thymopoiesis and inflammaging in COVID-19 phenotype. *Pediatr. Neonatol.* **61**, 364–365 (2020).
31. Whittaker, E. et al. Clinical characteristics of 58 children with a pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2. *JAMA* <https://doi.org/10.1001/jama.2020.10369> (2020).

THE INTERNATIONAL NEONATAL COVID-19 CONSORTIUM

Dirk Bassler¹⁷, John Burn-Murdoch¹⁸, Olivier Danhaive¹⁹, Jonathan Davis²⁰, Walusa Assad Gonçalves Ferri²¹, Hans Fuchs²², Haiyan Ge²³, Amit Gupta²⁴, Munish Gupta²⁵, Anton van Kaam²⁶, Victor Javier Lara Díaz²⁷, Rodolfo Treviño-Pérez²⁷, Gonzalo Luis Mariani²⁸, Lars Naver²⁹, Atul Patel³⁰, Prakeshkumar Shah³¹, Tomasz Szczapa³², Maximo Vento³³, Sven Wellman³⁴ and Shmuel Zangen³⁵

¹⁷Zurich, Switzerland. ¹⁸The Financial Times, London, UK. ¹⁹Brussels, Belgium. ²⁰Perth, Australia. ²¹Sao Paulo, Brazil. ²²Freiburg i. B., Germany. ²³Shijiazhuang, China. ²⁴Oxford, UK. ²⁵Boston, USA. ²⁶Amsterdam, The Netherlands. ²⁷Monterrey, Mexico. ²⁸Buenos Aires, Argentina. ²⁹Stockholm, Sweden. ³⁰Nairobi, Kenya. ³¹Toronto, Canada. ³²Poznan, Poland. ³³Valencia, Spain. ³⁴Regensburg, Germany. ³⁵Ashkelon, Israel.