

Neonatal SARS-CoV-2 infections: systematic review, synthesis and meta-analysis of reported cases

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Abstract

It is unclear if COVID-19 affects neonates. Some cases of neonatal SARS-CoV-2 infections have been reported but not systematically analysed. We aim to clarify the main transmission route, clinical features and outcomes of neonatal SARS-CoV-2 infections and we performed an individual patient data meta-analysis, following PRISMA guidelines, of neonates infected by SARS-CoV-2 (demonstrated by: at least one positive nasopharyngeal swab and/or the presence of specific IgM). We analysed 117 infected neonates. 68% and 32% of infections were due to environmental and vertical transmission, respectively. Approximately 55% of infected neonates developed clinically evident COVID-19. Commonest clinical features were fever (50%), gastrointestinal (43.7%), respiratory (42.2%) and neurological manifestations (20.3%). Lung imaging was abnormal in 59.4%. The lack of mother-neonate separation from birth was associated with the incidence of late SARS-CoV-2 infection (OR 5.1 (95% CI: 1.6-18); $p=0.003$), while breastfeeding was not (OR 0.49 (95% CI: 0.12-1.94); $p=0.35$).

Introduction

Since December 2019, the outbreak of a novel beta-coronavirus (SARS-CoV-2) infection has spread worldwide and caused a potentially lethal disease (COVID-19). The World Health Organization (WHO) on March 11, 2020¹ declared COVID-19 a public health emergency of international concern and, since then, approximately 13,000,000 cases and 600,000 deaths have occurred worldwide.²

Clinically, COVID-19 appears with influenza-like symptoms, eventually progressing towards pneumonia and acute respiratory distress syndrome (ARDS); cardiovascular, renal, neurological and gastrointestinal symptoms and signs have also been reported. The pathophysiology of COVID-19 includes the direct viral cytopathic effect, but also an exaggerated inflammatory response (the so-called “cytokine storm”), with impairment of coagulation and tissue damage. COVID-19 is more frequent and tends to be more severe with increasing age and in patients with certain risk factors, some of which are represented by comorbidities typical of older adults (such as, hypertension or other cardiovascular disorders).³ Moreover, children might be less prone to develop the chaotic inflammatory host response that contributes to the clinical picture of COVID-19.⁴ Therefore, children affected by COVID-19 seem to have a milder clinical course than adults.⁵

Because of these characteristics, and the uncertainty regarding the maternal-fetal transmission of SARS-CoV-2, it was unclear if COVID-19 would affect neonates. However, with the pandemic spreading around the world, some cases of SARS-CoV-2 infection in the first month of life have been reported in the literature or in the mass media,⁴ and it has been hypothesized that neonatal COVID-19 might occasionally become clinically apparent. SARS-CoV-2 has been isolated in placental tissues^{6,7} and, in a few cases, maternal-fetal transmission was suspected.⁸ However, guidance criteria for the diagnosis of perinatal and neonatal SARS-CoV-2 infections have been released only recently and the cases published so far were not systematically analyzed according to these criteria.⁹

Compared with adult medicine, neonatology suffers from a clear knowledge gap about the SARS-CoV-2 infection, since: 1) the main transmission route is unknown, as neonates can be infected antenatally (through the placenta), during the delivery, or postnatally (through environmental exposure); 2) the clinical features of neonatal SARS-CoV-2 infections are unclear; 3) outcomes of neonatal SARS-CoV-2 infections are unknown. We aimed to fill this knowledge gap by performing a systematic review and synthesis of reported cases of neonatal SARS-CoV-2 infections.

Methods

Protocol

Prior to commencing the search, a detailed protocol was agreed to determine the databases to be searched, search modalities, eligibility criteria and all methodological details. Several virtual meetings between the authors were organized and a dedicated online archive was created to share the data of the reviewed manuscripts. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed throughout the project.¹⁰ The French Ethical Committee for the Research in Obstetrics and Gynecology reviewed the work and confirmed that the institutional review board approval was unnecessary. The case study was performed in agreement with principles of the Declaration of Helsinki and all analyzed data were anonymous and respecting to local and European privacy regulations.

Eligibility criteria

We looked for cohort, cross-sectional and case-control studies, as well as case series or case reports published as articles or letters to the editors describing neonates (i.e. infants within the first month of life) infected by SARS-CoV-2, as demonstrated by: 1) at least one positive real-time reverse transcription polymerase chain reaction (RT-PCR) on nasopharyngeal swabs, and/or 2) positive serology with detection of specific IgM. These laboratory tests had to be performed according to World Health Organization technical guidance principles or appropriate national guidelines.¹¹ Moreover, articles had to be published between December 1, 2019, and July 14, 2020. No language restriction was applied: non-English publications were translated personally by the investigators or using the Google translation service.

Information sources and search strategy

We conducted an extensive search of the following databases: PubMed, The Cochrane Library, Web of Science, as well as BioXRiv and MedXRiv preprint archives. We used the following keywords or MeSH terms: "Coronavirus", "COVID-19", "SARS-CoV-2", "newborn", "preterm" and "neonates". We also hand-searched references cited in the eligible manuscripts or in review articles on the subject and the authors' personal archives. We used the following Boolean string: (COVID-19 AND neonates) OR (coronavirus AND newborn)) OR (coronavirus AND preterm)) OR (coronavirus AND neonates)) OR (SARS-CoV-2 AND newborn)) OR (SARS-CoV-2 AND preterm)) OR (SARS-CoV-2 AND neonates)) OR (COVID-19 AND

preterm)) OR (COVID-19 AND newborn)) AND (("2019/12/01"[Date - Create] : "2020/07/14"[Date - Create])).

Study selection

Articles were assessed by two independent researchers (RR and AJV), as recommended by the quality standards issued by the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) Group.¹² Investigators reviewed abstracts and (where necessary) the full text of each article, excluding those not meeting the eligibility criteria and removing duplicates. If an article was eligible but reported data on neonates mixed with those of older children (beyond the first month of life), neonatal data were directly extracted or the authors were contacted to provide the data needed. Authors were also contacted when more information was needed and at least two emails were sent to the corresponding author, one week apart, asking for additional data. If discrepancies or uncertainties persisted, they were resolved by discussion between the two independent researchers and, if no agreement was reached, with a third researcher (DDL). All articles finally deemed eligible were collected using Zotero (5.0.87, Roy Rosenzweig Centre for History and New Media, Fairfax, VI – USA) and used for the review.

Data collection process

We developed a dedicated online data extraction sheet (Excel 7.0; Microsoft Corporation, Redmond, WA-USA), pilot-tested it on three randomly selected manuscripts, and refined it accordingly. Data from included records were extracted independently by two investigators (RR and AJV) using the data extraction sheet and then cross-verified. If some data were lacking, at least two emails were sent to the corresponding authors one week apart to ask them for the missing data. If discrepancies or uncertainties persisted, they were resolved by discussion between the two independent researchers and, if no agreement was reached, with a third researcher (DDL).

Data items

Data collected included study details, number of enrolled patients and their basic characteristics, as mean gestational age, birth weight, sex, mode of delivery, Apgar score, postnatal age at the diagnosis and comorbidities. According to postnatal age at the diagnosis, the SARS-CoV-2 infection was classified as early- or late-onset (i.e. occurring ≤ 72 or > 72 hours of life, respectively), as commonly done for neonatal sepsis. We recorded any RT-PCR result in placental tissue, amniotic fluid, cord or newborn blood and swabs. We also recorded the presence of SARS-CoV-2-IgM, and classified the cases according to the classification system defining maternal, fetal and neonatal SARS-CoV-2 infections.⁹ In detail, cases were divided into: 1) congenital infections, 2) intrapartum acquired infections, or 3) postpartum acquired (i.e. environmentally acquired) infections and into five mutually exclusive categories of the likelihood of infection: (a) confirmed, (b) probable, (c) possible, (d) unlikely, and (e) not infected.⁹

Finally, clinical signs/symptoms, imaging and laboratory findings, use of antiviral therapy, isolation and feeding policies, need for neonatal intensive care unit (NICU) admission and outcomes were also

recorded.

Assessment of risk of bias

Since we expected the majority of analyzed articles to be case reports or case series, we decided to evaluate their methodological quality according to four domains (selection, ascertainment, causality and reporting). To perform this evaluation, we used the Mayo Evidence-Based Practice Centre tool.¹³ Two investigators (RR and AJV) independently summarized the results of this evaluation by aggregating the eight binary responses into a 0–8 score. Evaluation results were also qualitatively summarized, as recommended.¹³ If discrepancies or uncertainties persisted, they were resolved by discussion between two researchers (RR and AJV) and, if no agreement was reached, with a third researcher (DDL).

Summary measures

Estimates of event rates (frequency) were reported as a percentage. Continuous data were described as mean (standard deviation) or median [interquartile range], as appropriate; minimum and maximum values were also reported. Event rates were compared with Fisher's exact test and association between variables was expressed by means of the odds ratio (OR) and 95% confidence interval (CI). Calculations and statistics were performed with Excel 7 (Microsoft Corporation, Redmond, WA-USA) and MedCalc 13.3 (MedCalc, Ostend, Belgium). *p*-values < 0.05 were considered statistically significant.

Results

Figure 1 illustrates the project flow chart with included and excluded records (and the reasons for their exclusions). Finally, 58 articles were considered, consisting of 29 case series, 28 case reports, and one retrospective cohort study.^{14–71} The manuscript characteristics are reported in Table 1. The methodological quality of case reports and series was estimated as intermediate-to-good (median score 5 [3;6]).

Table 1: Characteristics of articles included in the systematic review. For articles reporting both infected and non-infected neonates, only those with proven infection (defined as at least one positive nasopharyngeal swab, and/or the presence of specific IgM) were included in the review. The methodological quality of case reports and case series was evaluated using the Mayo Evidence-Based Practice Center tool¹³ summarized both as a 0-8 score and as overall qualitative evaluation. The tool was not applied to the single retrospective cohort study⁴⁰ included in the review. n.a.: not applicable.

First ***** / reference No.	***** type	Country	Quality score	Overall quality	No. neonates
Aghdam [14]	**** report	Iran	4	Intermediate	1
***** Diaz [15]	Case report	Spain	5	Intermediate	1
Alzamora [16]	**** report	Peru	3	Intermediate	1
**** [17]	Case series	Kuait	1	Low	2
***** [18]	Case series	Italy	4	Intermediate	1
***** [19]	Case report	Italy	4	Intermediate	1
Chacon-Aguilar [20]	Case report	Spain	5	Intermediate	1
Coronado Munoz [21]	**** report	USA	4	Intermediate	1
Demirjian [22]	Case report	UK	4	Intermediate	1
Dong [23]	Case report	China	6	Good	1
**** [24]	Case report	USA	6	Good	1
Feng [25]	Case series	China	3	Intermediate	4
Fenzia [26]	Case series	Italy	5	Intermediate	2
***** [27]	Case series	Italy	1	Low	3
***** [28]	Case series	Italy	2	Low	15
Gonzales ***** [29]	**** report	Spain	3	Intermediate	1
Gordon [30]	Case report	UK	2	Low	1
Gregorio-Hernandez [31]	Case series	Spain	5	Intermediate	3
Groß [32]	Case series	Germany	5	Intermediate	1
Han [33]	Case report	South Korea	6	Good	1
Hantoushzadeh [34]	Case series	Iran	6	Good	1
Hu [35]	Case series	China	6	Good	1
Ibarra Rios [36]	**** report	Mexico	5	Intermediate	1
Kanburoglu [37]	**** report	Turkey	1	Low	1
Kayem [38]	Case series	France	1	Low	1
Kirtsman [39]	Case report	Canada	6	Good	1
Knight [40]	***** cohort study	UK	n.a.	n.a.	12
L'***** [41]	Case series	Switzerland	1	Low	1
***** [42]	Case report	Germany	6	Good	1
Martinez-Peres [43]	Case series	Spain	1	Low	4
Meredith [44]	Case series	UK	1	Low	1
Meslin [45]	Case series	France	6	Good	4
Mithal [46]	Case series	USA	3	Intermediate	4
Ng [47]	**** series	UK	6	Good	1
Paret [48]	Case series	USA	3	Intermediate	1
Patanè [49]	Case series	Italy	6	Good	2
Pierce-Williams [50]	Case series	USA	5	Intermediate	1
Piersigilli [51]	Case report	Belgium	6	Good	1
Precit [52]	Case report	USA	5	Intermediate	1
**** [53]	Case report	USA	1	Low	1
Salvatori [54]	Case series	Italy	6	Good	2
Savasi [55]	Case series	Italy	1	Low	4
***** [56]	**** report	UK	3	Intermediate	1
Sinelli [57]	**** report	Italy	6	Good	1
Sisman [58]	Case report	USA	6	Good	1
Sun [59]	Case series	China	6	Good	1

***** [60]	Case report	France	6	Good	1
**** [61]	Case report	China	6	Good	1
Wang S [62]	Case report	China	6	Good	1
Wardell [63]	Case series	USA	6	Good	4
White [64]	**** series	USA	6	Good	3
Xia [65]	Case series	China	4	Intermediate	3
Yu [66]	**** report	China	4	Intermediate	1
Zamaniyan [67]	Case report	Iran	6	Good	1
**** L [68]	Case series	China	6	Good	3
Zeng LK [69]	Case report	China	6	Good	1
Zeng H [70]	Case series	China	2	Low	2
Zhang [71]	Case series	China	5	Intermediate	2
Total					117

These articles described 117 neonates infected by SARS-CoV-2, whose general characteristics are reported in Table 2. Seven (5.9%) neonates required delivery room resuscitation and 36 (30.8%) needed to be admitted to the NICU; the median NICU stay was 7.3 [4.3;17] days (min 2; max 26 days).

Table 2: Basic data of the reported neonates. Data are expressed as mean (standard deviation) or median [interquartile range], min - max or number (%), as appropriate. * Male sex % is referred to 59 neonates, as gender data were missing for the others, despite repeated requests to the authors of the articles.

Neonates (117)	Summary statistics	Min-max range
Gestational age (weeks)	37.5 (3.3)	26 - 41
Birth weight (grams)	2924 (761)	960 - 4440
Birth weight Z-score	0 [-0.8;0.8]	-2.41 - 2.41
**** sex	38 (64.4%)*	--
Caesarean section	39 (33.3%)	--
5' Apgar score	9 [9;10]	2 - 10
Postnatal age ** the ***** (days)	7 [1;18]	0 - 30
Symptomatic neonates	64 (54.7%)	--

SARS-CoV-2 infection was classified as shown in **Figure 2**: the majority of infections were likely transmitted postpartum, that is, were due to environmental exposure, although approximately 32% of cases were likely due to vertical transmission, either intrapartum or congenitally. Of these, only about 11% of cases were confirmed vertical infections (4.9% for intrapartum and 6.2% for congenitally transmitted infections, respectively).

Sixty-four neonates presented with clinical features related to COVID-19 and their distribution is shown in Table 3. Respiratory manifestations mainly consisted of tachypnoea, intercostal retractions and rhinitis; neonatal ARDS was not diagnosed in any case. Gastrointestinal manifestations were primarily represented by feeding difficulties, diarrhea and vomiting, while neurological ones consisted of hypertonia and irritability, but also hypotonia and lethargy, as well as apnea. Cardiovascular features were tachycardia and hypotension. Other manifestations included conjunctivitis, hypothermia and cutaneous rash. Laboratory abnormalities were evident in a minority of cases: ten (15.6%) and four (6.3%) out of 64 neonates presented with lymphopenia and raised liver enzymes, respectively. Inflammatory markers (C-reactive protein and procalcitonin) were increased in 11 (17.2%) neonates. Lung imaging was abnormal in 38 (59.4%) neonates and consisted of an interstitial-alveolar pattern at lung ultrasound or chest X-ray

and ground-glass opacities at CT-scan. One neonate presenting with neurological manifestations also showed bilateral gliosis of the deep white periventricular and subcortical matter, together with signs of cerebral vasculitis, which was not totally remitted at the hospital discharge. Three neonates were treated with oral hydroxychloroquine and/or azithromycin, one with intravenous remdesivir, one intranasal interferon- α 1b, while all the others received supportive care; all neonates survived and were eventually discharged.

Table 3: Distribution of clinical features in the subgroup of neonates presenting with signs or symptoms compatible with COVID-19. Clinical features are listed in order of frequency; multiple features are possible in a patient; % is calculated for the group of symptomatic neonates (n=64). More details in the text.

Clinical features	Neonates (%)
Fever	32 (50%)
Gastrointestinal	28 (43.7%)
Respiratory	27 (42.2%)
Neurological	13 (20.3%)
Hemodynamic	7 (10.9%)
Others	9 (14%)

The lack of mother-neonate separation from birth was significantly associated with the incidence of late (i.e. occurring after the first 72 hours of life) SARS-CoV-2 infection (OR 5.1 (95% CI: 1.6–18); $p = 0.003$), while breastfeeding was not (OR 0.49 (95% CI: 0.12–1.94); $p = 0.35$; Fig. 3).

Discussion

Several cases of neonates infected by SARS-CoV-2 are reported in the literature and here we have systematically analyzed and synthesized them. Our findings confirm that SARS-CoV-2 can infect neonates and that the majority of these infections occur postnatally, although vertical transmission may be possible in about one third of cases. Neonatal SARS-CoV-2 become clinically evident in half of the patients as they developed features of COVID-19. The clinical appearance of neonatal COVID-19 seems similar to those reported in older patients, both in terms of symptoms and laboratory or imaging abnormalities, and the outcome was generally favorable. Neonates who were not transiently separated from their mothers seem to have a higher incidence of SARS-CoV-2 infections occurring after the first 72 hours of life.

These findings are important as they formally describe neonatal SARS-CoV-2 infection and partially fill our aforementioned knowledge gap. There are some interesting points to be highlighted. First, transplacental transmission of SARS-CoV-2 is indeed possible and this is corroborated by a consistent background of laboratory findings, since angiotensin-converting enzyme receptors are expressed in placental tissues, with the expression reaching a peak at the end of gestation,⁷² and SARS-CoV-2 may invade the placenta^{6,7} potentially causing miscarriage.⁷³ Second, neonatal COVID-19 manifestations seem similar to those observed in adults, while fever seems to be more frequent in COVID-19 than in common neonatal infections⁷⁴ and no cases of neonatal ARDS were evident.⁷⁵ Third, the choice between rooming-in or mother-infant separation is an important one and the synthesis of available cases shows

that the avoidance of separation may be associated with a higher risk of late onset neonatal SARS-CoV-2 infections. This is potentially important since neonatal SARS-CoV-2 infections are more commonly postnatal, through environmental exposure. There are wide differences on this matter between the clinical guidelines issued by scientific societies and authorities worldwide.^{76–78} Thus, we believe that correct and complete counselling should be given to families in order to allow a well-informed choice. This should factor in the benefits of mother-neonate bonding, the risk of neonatal infection and the higher maternal contagiousness during the symptomatic period.⁷⁹ If rooming-in is chosen appropriate hygiene advices should be given to reduce the transmission risk. Breastfeeding does not seem to be associated with SARS-CoV-2 infections and this suggests that viral transmission through the milk, if any, should be rare. These findings seem to support the safety of expressed breast milk even during mother-neonate separation. However, since few studies have investigated this matter and have yielded conflicting results,^{32,80} larger studies are needed to clarify this issue.⁸

The results of this synthesis of neonatal SARS-CoV-2 infections are also consistent with a review performed in older children and adolescents from Asia: SARS-CoV-2 infection usually seems mild in pediatric patients presenting with same clinical features or laboratory and imaging abnormalities.⁵ The analyzed neonates had a quite more frequent need for NICU hospitalization compared to neonates of similar gestational age⁸¹ and to older children.⁵ However, this may be influenced by many factors such as local setting, logistics and isolation policy, since the NICU could represent the only area to isolate infected babies; this should be avoided if NICU care is not actually needed, in order to avoid the shortage of NICU beds during the pandemic.⁸²

Since a significant proportion of infections are asymptomatic, it has so far been hard to ascertain the disease burden on neonates and the possibility of transmission to healthcare providers. We shed some light on this, although our findings may change as soon as the pandemic progresses and new experience is accumulated. Meanwhile, it is suggested that evidence derived from case reports and case series is the best available and should be used to inform decision making until higher level of evidence is available.¹³

This work has limitations. Although the quality of the reviewed reports is intermediate-to-good, we should remember that uncontrolled case descriptions and their synthesis are at the bottom of the evidence pyramid.¹³ As this is a meta-analysis of mainly case series, the rating of the quality of evidence is 4, according to the JAMA-modified Oxford Centre for Evidence-based Medicine classification.^[71] However, the Grading of Recommendations, Assessment, Development and Evaluation guidelines admit the decision-making process based on low-quality evidence in some particular circumstances and the pandemic surely represents an extraordinary situation. ^{[83][82][83][82][81][80][72]} The classification system for diagnosing maternal, fetal and neonatal SARS-CoV-2 infections may be cumbersome, as it requires consideration of clinical data and of the results of several virological tests: the relatively low number of confirmed infections may be due to the difficulty in obtaining the virological tests in various samples (placenta, amniotic fluid, blood, swabs).⁹ However, this represents so far the best tool available to correctly identify these infections for epidemiological and clinical purposes and it should be promoted.

Furthermore, the classification may be adjusted, and a case can be re-classified, if its likelihood of infection changes, as more information becomes available. Similarly, the availability of new diagnostic tests may lead to changes in the diagnostic criteria. We cannot exclude that some of the clinical features presented by the analyzed cases were due to other concomitant disorders, as this level of detail is not attainable with a synthesis of published reports; however, the analyzed data are coherent and consistent with those from older COVID-19 patients. Finally, we have almost no information on neonatal COVID-19 therapies, as these will require more experience and it is unclear if the neonatal SARS-CoV-2 infection may have long-term consequences, as no follow-up studies have been performed so far.

In conclusion, the synthesis of uncontrolled cases of neonatal SARS-CoV-2 infection shows that infections mainly occur postnatally through environmental exposure, although nearly 30% of infections may be acquired vertically. Approximately half of infected neonates develop clinically apparent COVID-19, which is often characterized by febrile status and favorable outcome. Mother-neonate rooming-in is associated with a higher incidence of SARS-CoV-2 infections occurring after the first 72 hours of life.

Declarations

COMPETING INTERESTS STATEMENT

Authors have no conflict of interest to disclose

AUTHORS' CONTRIBUTION

Acquisition, analysis, or interpretation of data: Raschetti, Vivanti, Benachi, Vaulop-Fellous and Loi;

Drafting of the manuscript: Raschetti; Statistical analysis: Vivanti; Administrative, technical, or material support: Benachi, Vaulop-Fellous and Loi; Study concept, design and supervision: De Luca

Critical revision of the manuscript for important intellectual content: All authors

Raschetti and Vivanti contributed equally and should be considered co-first authors.

All authors take full responsibility for the content of the manuscript.

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DATA AVAILABILITY STATEMENT

All data generated during this study are included in this published article. Raw data used for the analyses are presented in the original manuscripts or available upon request.

Drafting of the manuscript: Raschetti; Statistical analysis: Vivanti; Administrative, technical, or material support: Benachi, Vauloup-Fellous and Loi; Study concept, design and supervision: De Luca

Critical revision of the manuscript for important intellectual content: All authors

Raschetti and Vivanti contributed equally and should be considered co-first authors.

All authors take full responsibility for the content of the manuscript.

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Figures

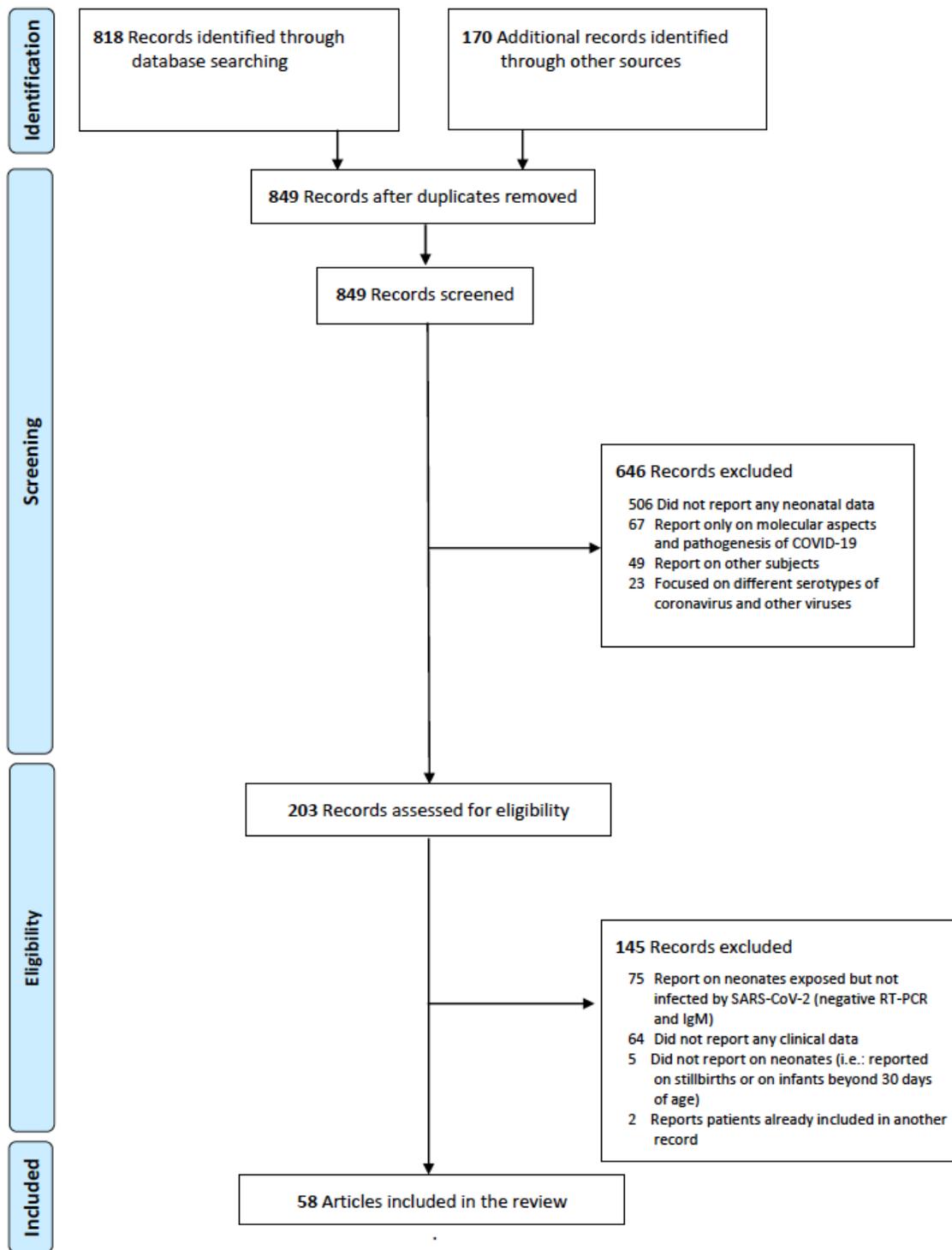


Figure 1

Study flow chart

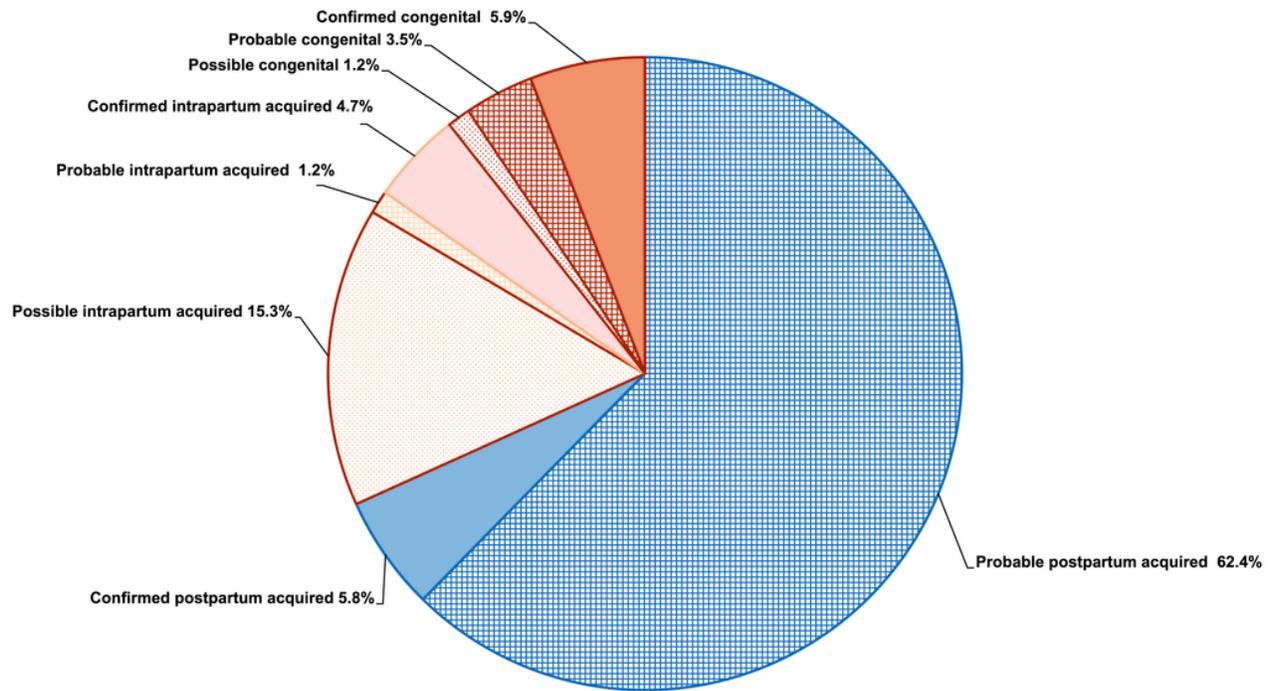


Figure 2

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.[9] 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: (a) confirmed, (b) probable, (c) possible, (d) unlikely, and (e) not infected. Classification was applied to 85 cases (for 32 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 %.

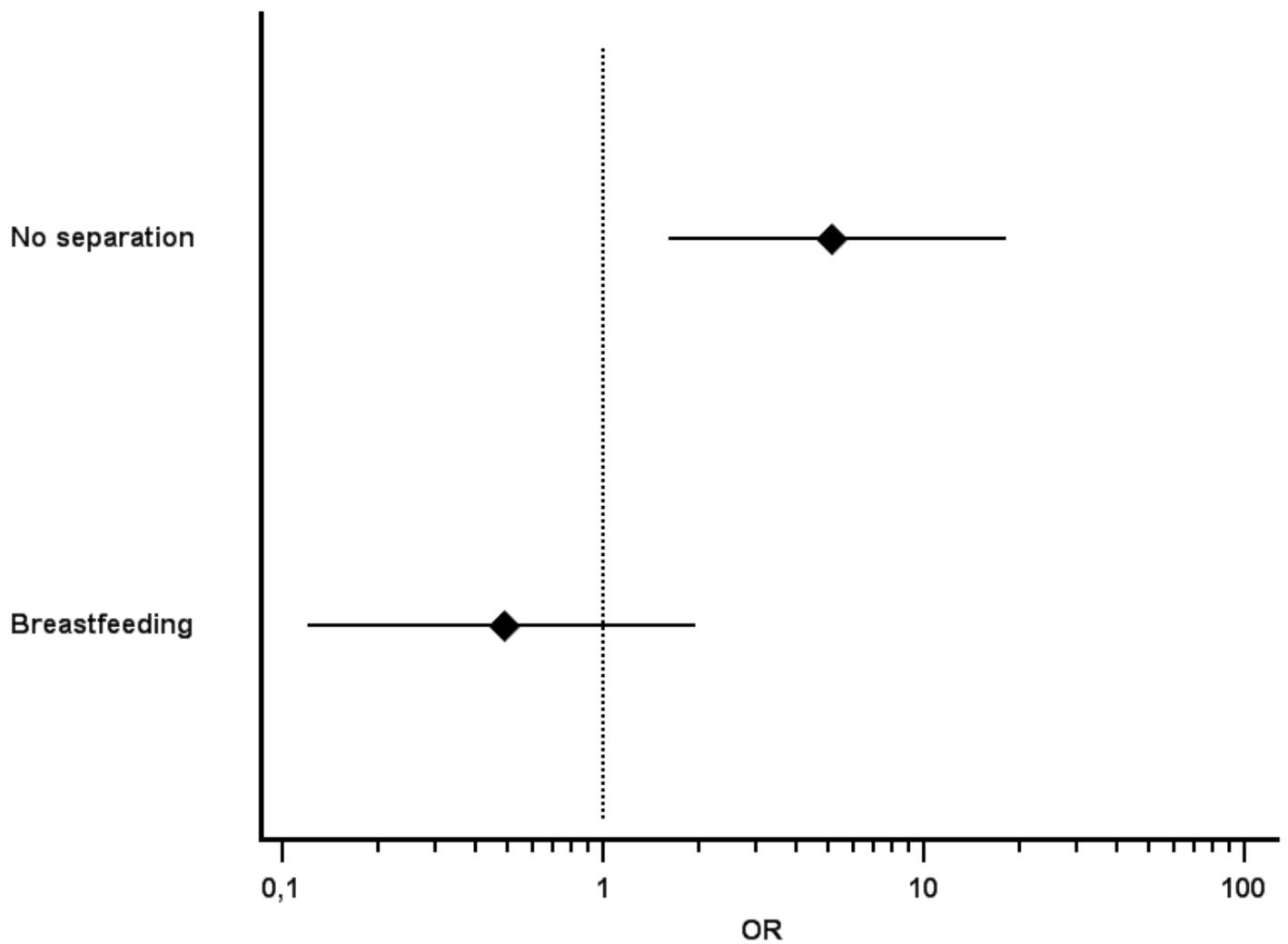


Figure 3

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 hours of life. Diamonds and horizontal lines represent the odds ratio (OR) and its 95% confidence interval (CI), respectively. Horizontal axis is in a log scale for better visualization. More details in the text.