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Optimal Delivery Management for the Prevention of Early Neonatal SARS-CoV-2

Infection: Systematic review and Meta-analysis

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ABSTRACT AND KEY WORDS

Objective: Delivery management interventions (DMI) were recommended to prevent delivery-associated transmission of maternal SARS-CoV-2 to infants without evidence of effect on early neonatal SARS-CoV-2 infection (ENI) and neonatal death <28 days of life (ND). This systematic review describes different DMI combinations and the frequency of ENI and ND.

Study Design: Individual patient data were collected from articles published 1 January 2020 - 31 December 2021 from Cochrane review databases, Medline and Google Scholar. Article inclusion criteria were: Documented maternal SARS-CoV-2 PCR positive status 10 days before delivery or symptomatic at delivery with a positive test within 48 hours, known delivery method and known infant SARS-CoV-2 PCR result. Primary outcomes were ENI (positive PCR at 12 hours-10 days) and ND. All characteristics were pooled using DerSimonian-Laird inverse variance method. Primary outcome analyses were carried out using logit transformation and random effect. Pooled results were expressed as percentages (95% confidence intervals). Continuity correction was applied for all pooled results if any included study has 0 event.

Results: 11,075 publications were screened. 117 publications representing 244 infants and 230 mothers were included. All publications were case reports. ENI and ND were reported in 23.4% (18.2, 29.18) and 2.1% (0.67, 4.72) of cases respectively. Among cases with available information, DMIs were reported for physical environment (85-100%), delivery specific interventions (47-100%), and infant care practices (80-100%). No significant comparisons could be performed between different DMI combinations due to small sample size.

Conclusion: The evidence supporting any DMI in SARS-CoV-2 infected mothers to prevent ENI nor ND is extremely limited. Limitations of this meta-analysis include high risk of bias, small sample size and large confidence intervals. This identifies the need for multinational

database generation and specific studies designed to provide evidence of DMI guidelines best suited to prevent transmission from mother to neonate.

Key Words: COVID-19, SARS-CoV-2, neonates, pregnancy, delivery management

KEY POINTS

- In this review we analyzed 2 years of maternal SARS-CoV-2.
- We analyzed delivery management interventions (DMI).
- We assessed association of DMI with infant SARS-CoV-2 infection.
- We found no evidence supporting any DMI for that purpose.
- Large studies are needed to determine best practice.

BACKGROUND

The first case of coronavirus disease of 2019 (COVID-19) was reported from China in November 2019. It was later found to be caused by a novel virus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)^{1,2}. On 30 January 2020, the World Health Organization² declared the outbreak a Public Health Emergency of International Concern³. By 11 March 2020, COVID-19 was characterized as a global pandemic². The rapid progression of COVID-19/SARS-CoV-2 dramatically impacted healthcare, especially for pregnant women and infants at increased risk for maternal death, severe maternal morbidities, and neonatal morbidities⁴. With significant numbers of pregnant women infected with SARS-CoV-2⁴, lack of consistent vaccine availability in many countries⁵ and vaccine hesitancy especially for pregnant women⁶ evidence for practice recommendations designed to reduce transmission to infants remains a pressing concern.

The mode and significance of SARS-CoV-2 transmission from mother to fetus or infant remains unclear. Confirmation of diagnosis and source of transmission is challenging, given the subtle presentation of symptoms and clinical course in newborn infants and the possible close contact of multiple caregivers who may be infectious⁷. With available reports, it has been challenging to accurately determine exact timing or route of transmission as this would require extensive testing including immunocytochemistry, in situ hybridization and/or RT-PCR in all possible pregnancy and delivery material (placenta, amniotic fluid, vaginal secretions, colostrum, blood, stools, urine, nasopharyngeal secretions in the mother), and serially timed PCR sampling of the infant and sampling among all caregivers.

Infection control practices recommended by international, national, regional and hospital-specific guidelines designed to limit transmission to the newborn have had unintended consequences. For example, interventions intended to prevent maternal-neonatal transmission of virus have changed the routine practice of a planned normal birth. The decision for an unplanned caesarean section delivery, separation of infants right after birth, strict isolation and visitation policies have resulted in a variety of medical and psychosocial effects on the mother-infant dyad and family^{8,9}.

Different countries, international/national/regional organizations and hospitals have published recommendations on the management of a SARS-CoV-2-positive mother during labor, delivery, and for her infant (Figure 1). All recommendations were designed to balance alterations in delivery management to reduce SARS-CoV-2 transmission to the infant, with routine care recommendations that promote bonding and are beneficial to mother and infant. In the absence

of data, guidelines were created ad hoc and with significant variation in practice¹⁰. Several of these recommendations for delivery of mothers with active SARS-CoV-2 were based on other infectious diseases (e.g., influenza), with little knowledge about the incidence and clinical presentation of neonatal SARS-CoV-2 infection.

To date, there has been no systematic review or study comparing combinations of delivery management interventions (DMI) with routine care and the risk of early neonatal infection (ENI) or neonatal death before 28 days of life (ND). ENI may be evident between 12 hours of life and 15 days of life with the average incubation period of five days¹¹. Differing opinions from various expert consensus guidelines make the best choices for DMI challenging. Many suggest shared decision-making between healthcare providers and patients for management during the perinatal period¹². Recent reports also do not support an association of decreased ENI or ND with changes in delivery management; instead, neonates are overwhelmingly asymptomatic and neonatal symptomatology are often associated with maternal illness severity or with premature delivery because of maternal health concerns^{13,14}. With the ubiquitous burden of this disease, it remains important to assess DMI that could minimize ENI and ND while ensuring safety and optimal care to both mother and infant. This systematic review was designed to describe different DMI combinations and the frequency of ENI and ND when compared with routine delivery practice.

METHODS

SUBJECTS: For pragmatic purposes, this review focuses on ENI which may encompass both *in utero* infections and perinatal infections. ENI is defined as neonatal SARS-CoV-2 PCR-positive between 12 hours and 10 days of life. This may include *in utero* and perinatal infection. Beyond

this period, delivery management is less likely to affect whether an infant is SARS-CoV-2-positive.

MEASUREMENTS

DMI were categorized into three broad categories: 1) physical environment, 2) delivery-specific, and 3) infant-care practices (Figure 1). Within each category there are individual interventions intended for infection prevention at various times during delivery. In different countries and birth centers, these interventions were applied in different combinations because of unique circumstances dictating resource allocation, disease burden, and local practice. Each DMI was described with reference to several country-specific guidelines that were available at the inception of this review (see Appendix 1).

FACTORS NOT ADDRESSED

Enteral feeding practices and post-partum behaviors also likely impact ENI and ND. As these are detailed and nuanced decisions often made independent of the DMI, enteral feeding is beyond the scope of this review.

It was also difficult to completely remove the risk of a SARS-CoV-2 positive healthcare worker or family member for ENI and ND. For many countries, the possibility of a healthcare worker contributing to early infection is a highly litigious aspect of infant care and will not be reported in case reports or databases. For pragmatic reasons, this review did not address transmission of SARS-CoV-2 from family members or healthcare workers to the neonate.

PROTOCOL

The protocol for this review was submitted to PROSPERO ID CRD42021267892. Articles published 1 January 2020 - 31 December 2021 from Cochrane review databases, Medline and Google Scholar were searched. Primary screening was conducted by 2 reviewers (CSC and JYK) using specific search criteria (Appendix 2).

We included the following studies (listed in the order of the strength of evidence):

1. Randomized controlled trials
2. Quasi-randomized trials
3. Cohort studies
4. Case-control studies
5. Cross-sectional studies
6. Case series/case reports

Specific inclusion criteria included:

1. mothers with SARS-CoV-2 PCR positive status within 10 days before delivery or symptomatic at delivery with a positive test within 48h after delivery
2. delivery method described
3. infant SARS-CoV-2 PCR result known

Types of DMI (Figure 1)

- A. Physical environment (aerosolization and droplet management):
 1. Negative pressure in delivery area
 2. Separate room from delivery room

3. Distance of ≥ 6 feet from mother during resuscitation
 4. Maternal masking during delivery compared to no maternal masking during delivery
- B. Delivery-specific interventions (minimization of contact during delivery with maternal fluids):
1. Caesarean section for infection prevention
 2. Early cord clamping compared to delayed cord clamping
- C. Infant care practices (minimizing infant skin contact):
1. Infant cleaning/decontamination as soon as possible after resuscitation compared to routine skin care
 2. Prevention of skin-to-skin contact after stabilization compared to skin-to-skin contact after stabilization

Primary outcomes

1. Confirmation of early neonatal SARS-CoV-2 infection by a positive PCR on any neonatal samples taken at 12 hours and up to 10 days of life.
2. Neonatal death occurring before 28 days of life.

Secondary outcomes were selected by their potential relationship with SARS-CoV-2 infection:

1. Maternal characteristics:
 - a. Age
 - b. maternal symptom severity (Appendix 4)
 - i. Asymptomatic

- ii. Mild
 - iii. Moderate
 - iv. Severe
 - v. Critical
2. Delivery metrics:
- a. Gestational age
 - b. Infant sex
 - c. Birth weight
 - d. Apgar scores at one minute and five minutes
3. Clinical status in SARS-CoV-2 positive infants (Appendix 4)
- a. Asymptomatic
 - b. Mild
 - c. Moderate
 - d. Severe
 - e. Critical

DATA COLLECTION AND ANALYSIS

Cochrane search was used for the initial search (initial strategy). A combination of Medline and Google Search (updated strategy) was used by two review authors for later search and screening (JMH, LPB). Comparison of the initial and updated strategies found 96.5% overlap of the two strategies for publication identification and inclusion. Two review authors (CSC, JYK) independently screened all titles, abstracts and full-text reports for eligibility. Any differences in decision between authors was resolved by discussion leading to consensus. The selection process

was recorded in sufficient detail to complete a PRISMA flow diagram (Figure 2). Data extraction was accomplished using a pilot-tested Microsoft Excel spreadsheet. A comprehensive list of included articles can be found in Appendix 5.

Primary outcomes were ENI and ND. Both outcomes were treated as binary variables. All analyses were carried out using individual patient level data. All maternal and infant characteristics were pooled using DerSimonian-Laird inverse variance method. Pooled results were expressed as percentages with 95% confidence interval (95% CI) for categorical variables and as mean (95% CI) or median (95% CI), whichever appropriate, for continuous variables. Primary outcome analyses were carried out using logit transformation and random effect. Continuity correction was applied for all pooled results if any included study has 0 event. The heterogeneity of included studies was evaluated with I^2 statistics, considering a value less than 25% as low heterogeneity, 50-75% as medium heterogeneity and greater than 75% were considered as high heterogeneity. All the analyses were carried out using SAS version 9.4 (SAS Institute; Cary, NC, USA) and R ('meta' library).

A post-hoc sensitivity analysis was conducted to compare the frequency of ENI among all patients who had DMI involving any component of category A with that among all those who did not have any component of category A. Similar comparisons were done for category B and for category C. These analyses were done using chi-square analysis or Fisher's exact test.

RESULTS

Of 11,075 publications initially screened, 117 articles were selected for inclusion (Figure 2).

Data used for this analysis from the 117 publications included 244 infants and 230 mothers. Case reports and case series comprised all the included reports as cohort and cross-sectional studies lacked the granularity of information required to meet the preset inclusion criteria. Randomized controlled trials, quasi-randomized trials and case-control studies are currently not available.

Clinical characteristics are described in Table 1. The mean maternal age was 31.2 years. The majority, 31.3% [29.97, 32.49], of these women infected with SARS-CoV-2 showed moderate illness severity. Delivery was by cesarean-section in 79% [69.2, 88.9] of women. The mean gestational age was 35.6 [34.2, 37.1] weeks, mean birthweight was 2550 grams [2300, 2790] and 58% [44.6, 72.2] of these cases were male infants. Median Apgar scores were 8 [8, 8] at 1 minute, and 9 [9, 10] at 5 minutes. ENI was described in 23.4% [18.2, 29.18] of cases. ND was reported in 2.1% [0.67, 4.72] of cases.

Total cases of each DMI are depicted in Table 2. A total of 67 cases reported on the physical environment designed to minimize aerosolization and droplets from the infected mother. Among 25 cases with information on the use of negative pressure in the delivery room, this DMI was used in 21 (85.5% [73.15, 97.79]). Among 34 cases with information on the use of a separate room for infant resuscitation or a distance of > 6 feet from the mother during the resuscitation, this DMI was used in 32 (94.3% [84.23, 100]). Among 38 cases with information on maternal masking during delivery, all reported use of this DMI (100% [90.39, 100]).

Among 59 cases with information on delivery-specific interventions designed to minimize contact during delivery with maternal secretions, use of cesarean section for infection prevention purposes was reported in 58; 41 reported use of this DMI (47.3% [28.72, 65.83]). Among 18 cases with information on early cord clamping, all reported use of this DMI (100% [86.03, 100]).

Among 79 cases with information on infant care practices designed to minimize infant skin contact with infected secretions, 5 cases reported on infant cleaning or decontamination right after the resuscitation: 4 reported use of this DMI (80% [40.8, 100]). Among 79 cases with information on preventing skin-to-skin with the mother after infant stabilization, all reported use of this DMI (100% [93.88, 100]).

Primary outcomes are described in Table 3. Combination A describes physical environmental changes, combination B describes delivery-specific interventions and combination C describes infant care interventions. Combination 1) A only, 2) B only, 3) C only, 4) A plus B plus C, 5) A plus B without C, 6) B plus C without A, and 7) A plus C without B were evaluated for incidence of the primary outcomes ENI and ND compared to routine care. Pooled frequencies of ENI and ND were reported as random effect with all DMI alone and DMI combinations (7 total comparisons). No routine care was described in these publications so the primary comparison of DMI combinations to routine care was not possible. Sample size for each combination was too small to conduct any valid comparison of the 6 different DMI combinations.

Subgroup analyses of maternal illness severity and gestational age effects on ENI and ND are described in Table 4. Neither maternal illness severity nor gestational age had statistically significant effects on ENI or ND.

The sensitivity analysis showed no significant difference in ENI among those with DMI involving category A (29/68, 42.6%) versus those without A (3/10, 30%) ($P = 0.45$), among those with category B (42/186, 22.6%) versus those without category B (16/57, 28.1%) ($P = 0.40$), and among those with category C (31/80, 38.8%) versus those without category C (8/12, 66.7%) ($P = 0.12$). However, sample size for all these comparisons was much less than needed to reach a power of 0.8. Observed power was, respectively, 0.11, 0.13 and 0.46.

DISCUSSION:

This is the first systematic review of published cases describing specific interventions in delivery management that were recommended during the pandemic to reduce the possibility of ENI and ND before 28 days of life. Review of all available published data over 2 years of the pandemic revealed no randomized trials and no high-quality prospective cohorts. No cases were reported that describe ENI or ND in the setting of routine delivery practices. No DMI combination was strong enough to show superiority over any other DMI combination or lack of that DMI. We are uncertain about these results because of high risk of bias, small sample size and large confidence intervals. The evidence supporting any DMI to prevent ENI nor ND remains limited.

While the pandemic has changed with the introduction of several vaccines and the exposure of most worldwide populations to SARS-CoV-2, the question of how best to protect infants from an

airborne infection remains relevant. Recommendations (accessed in 2023) continue to suggest DMI and other infection prevention measures that may result in added separation measures between an infected mother and her newborn^{15,16}. DMI that encourage cesarean section with its known risks to mothers, separate the delivery environment from the infant resuscitation environment, decrease mother-infant bonding by preventing skin-to-skin, and disrupt known benefits of delayed bathing in infants continue to be practiced without clear evidence of their effectiveness in preventing ENI and ND¹⁷. Sunuwar, et al described a small retrospective review of 104 women who were SARS-CoV-2 positive during any trimester of pregnancy and delivered by vaginal delivery or cesarean section and followed their neonatal outcomes¹⁸. They found that in their infants 51% were born with low Apgar scores, 18% were born prematurely, 19% had low birth weight, 7% required NICU admission, 3% experienced neonatal asphyxia, 2% died and none were SARS-CoV-2 positive. However, there was no significant difference in neonatal outcomes between the group delivered by vaginal delivery and the group delivered by cesarean section¹⁸. This correlates with the findings of this systematic review and suggests that DMI proposed early in the pandemic should be specifically reviewed and guidelines for delivery adjusted accordingly.

In the current review limited to mothers with SARS-CoV-2 PCR positive status within 10 days before delivery or symptomatic at delivery with a positive test within 48h after delivery, ENI was documented by PCR in 23.4% (95% CI 18.2%, 29.2%). In contrast, in a large prospective multinational cohort in 2020, among 416 neonates born to women with COVID-19 diagnosis (98% by PCR), 54 (13.0%, 95% CI 9.9% 16.6%) neonates tested positive within 48 hours. In a large prospective cohort in the US ENI was documented in 144 among 6486 tested infants

(2.2%, 95%CI 1.9%. 2.6%) born to mothers who tested SARS-CoV-2 positive between 14 days before and 10 days after delivery¹⁹. The high frequency of ENI in the current review compared with that in cohort studies raises concern about selection bias in case reports included in the analysis.

Current reviews continue to combine discussions of DMI along with antepartum and postpartum care without evidence to direct DMI^{17,20}. It is difficult to distinguish the risks of SARS-CoV-2 transmission attributable to antepartum care compared to postnatal delivery management.

Between 1% and 15% of adults with COVID-19 have RNAemia and pregnant women are more susceptible to COVID-19 than the general population^{1,21}. Physiologic mechanisms for *in utero* infections include angiotensin-converting enzyme 2 (ACE2), the receptor of SARS-CoV-2 as an integral component of human-to-human transmission that is²² expressed in maternal-fetal interface cells²³, placenta^{24,25} as well as several fetal organ cells^{23,26}. Detection of SARS-CoV-2 RNA in pharyngeal or stool specimens of infants born to mothers with a remote history of SARS-CoV-2 infection during pregnancy, suggests possible congenital infection as persistence of the virus is expected for up to five weeks after onset of symptoms²⁷. *In-utero* infection with SARS-CoV-2 has been suggested via the amniotic fluid²⁸ as well as placenta²⁹. The detection of IgM in infants shortly after birth despite failure to isolate viral RNA also suggests the transmission of infection prior to delivery³⁰⁻³³.

This systematic review attempted to address perinatal factors in transmission of SARS-CoV-2 as guidelines for delivery management were designed to address postnatal exposure. In the immediate postnatal period, direct exposure of infants to infected maternal stool, blood or

amniotic fluid can increase transmission risk to the infant³⁴. There was also theoretical risk of airborne transmission from mothers who have experienced a recent aerosol-generating procedure such as intubation or electrocautery of surgical wound³⁵. There was also concern that the second stage of labor, while not typically described as an aerosol-generating event, is a period when mothers may be breathing heavily, shouting, coughing, or vomiting - all activities that increase risk of aerosol exposure³⁴. This systematic review pragmatically used ENI as a proxy for perinatal transmission, but in utero transmission may have contributed significantly.

Limitations of this review include significant publication biases inherent during the active phases of the pandemic including preferential publication of deliveries where management was altered without similar descriptions of outcomes for deliveries conducted in routine fashion. Preferential publication of cases involving ENI and ND and publication of multiple reports that did not include specific information regarding routine delivery management practices was also observed. Other limitations of this review include lack of randomized trials and high-quality cohorts, lack of any study comparing DMI with routine care, and small sample size in all publications included in the analyses, which most often required continuity correction and had large confidence intervals. All these limitations contribute to the ongoing inability to provide evidence for best practice delivery management modifications for reducing ENI and ND.

Given these findings, it is uncertain what contribution DMI carried out to reduce SARS-CoV-2 transmission may have on neonatal outcomes. Instead, ENI and ND may be influenced by maternal illness severity prior to delivery, viral load soon before or after delivery, and post-partum practices where mild to moderately symptomatic mothers could cohort with their infants.

While more data is needed to accurately assess the effect of these DMI on ENI and ND, from a pragmatic point of view this may not be possible. Since the frequency of ENI in prospective cohorts is much smaller than that suggested by the current systematic review of case reports, it is also very likely, even if accomplished, that no specific DMI or combination of DMIs would have a clinically significant impact even with further data collection given the low transmission rate of SARS-CoV-2 to newborn infants. This study highlights the need to invest in large, multinational, prospective database creation with specific attention to DMI to more systematically address the question of optimal delivery management for prevention of airborne transmission from mother to infant.

DATA AVAILABILITY STATEMENT: The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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CONFLICT OF INTEREST

JYK has no conflicts of interest to declare.

CSC has no conflicts of interest to declare.

RS has no conflicts of interest to declare.

VM has no conflicts of interest to declare.

KLB has no conflicts of interest to declare.

KM has no conflicts of interest to declare.

EHA has no conflicts of interest to declare.

KTY has no conflicts of interest to declare.

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33. Zeng H, Xu C, Fan J, et al. Antibodies in Infants Born to Mothers With COVID-19 Pneumonia. *JAMA* 2020 (In eng). DOI: 10.1001/jama.2020.4861.
34. Palatnik A, McIntosh JJ. Protecting Labor and Delivery Personnel from COVID-19 during the Second Stage of Labor. *Am J Perinatol* 2020. DOI: 10.1055/s-0040-1709689.
35. Mick P, Murphy R. Aerosol-generating otolaryngology procedures and the need for enhanced PPE during the COVID-19 pandemic: a literature review. *J Otolaryngol Head Neck Surg* 2020;49(1):29. DOI: 10.1186/s40463-020-00424-7.

Figure 1. Depiction of delivery management interventions (DMI). At minimum a single intervention from category A – Physical Environment, category B – Delivery-Specific, or category C – Infant Care in combination or alone are evaluated for the primary outcomes and are compared to routine care. The different categories of interventions are 1) Combo A alone, 2) Combo B alone, 3) Combo C alone, 4) Combo A + B + C, 5) Combo A + B not C, 6) Combo B + C not A, and 7) Combo A + C not B.

Figure 2. PRISMA Flow Diagram of included studies. Search strategies included Cochrane search 1 January 2020 to 22 July 2020, PubMed and Google Scholar Search 22 July 2020 to 31 December 2020, and PubMed and Google Scholar Search 1 January 2021 to 31 December 2021.

Table 1. Clinical characteristics of maternal-infant pairs affected by perinatal COVID-19

Characteristics	Summary
Maternal age at delivery (years) [*] (n = 222)	31.23 [29.97, 32.49]
Maternal illness severity [□] (n = 228)	
Asymptomatic	10.01 [0.00, 20.65]
Mild	28.83 [14.40, 43.26]

Moderate	31.26 [17.00, 45.52]
Severe	10.56 [3.50, 17.62]
Critical	8.30 [1.58, 15.03]
Delivery mode [□] (n = 231)	
Cesarean section	79.04 [69.19, 88.89]
Vaginal delivery	20.96 [11.11, 30.81]
Gestational age (weeks) [*] (n = 235)	35.64 [34.20, 37.08]
Male sex [□] (n = 128)	58.41 [44.62, 72.20]
Birthweight (kg) [*] (n = 183)	2.55 [2.30, 2.79]
Apgar score at 1 min [□] (n = 225)	8 [8, 8]
Apgar score at 5 min [□] (n = 225)	9 [9, 10]
Early neonatal infection [□]	23.36 [18.20, 29.18]
Early neonatal death <28 days [□]	2.05 [0.67, 4.72]

Notes: [□] Summary is expressed as median [95%CI]. ^{*} Summary is expressed as mean [95%CI]. [□] Summary is expressed as percentage [95%CI]. CI represents confidence interval.

Table 2. Totals of infants and mothers with described delivery management interventions.

Delivery Management Intervention	Number of infants or mothers	Percentages (95%CI)
A: Physical environment (aerosolization and droplet management)	67	
Negative pressure in delivery room	21/25	85.47 [73.15, 97.79]
Separate room for resuscitation of infant or Distance of ≥ 6 feet from mother during resuscitation	32/34	94.33 [84.23, 100.00]
Maternal masking during delivery	38/38	100.00 [90.39, 100.00]
B: Delivery-specific interventions (minimization of contact during delivery with maternal fluids)	59	
Caesarean section for infection prevention purpose	41/58	47.27 [28.72, 65.83]
Early cord clamping	18/18	100.00 [86.03, 100.00]

C: Infant care practices (minimization of infant skin contact)	79	
Infant cleaning or decontamination right after resuscitation	4/5	80.00 [40.80, 100.00]
Prevent skin-to-skin after stabilization	79/79	100.00 [93.88, 100.00]
Notes:		
<ul style="list-style-type: none"> • Denominator represents # of participants with reported (yes/no) particular exposures while numerator represents number of mothers /children had that particular exposure. Participants were not included in the analysis, if there was any missing exposure. • DerSimonian-Laird inverse variance estimator were used to pool the results. Simple approximation with continuity correction of 0.5 in studies with zero cell frequencies was applied. Variables were expressed as percentages (95%CI). CI represents confidence interval. 		

Table 3. Primary outcomes of early neonatal infection and neonatal death by delivery management interventions *individually by category and in combinations of different categories.*

Combinations	Early neonatal SARS-CoV-2 infection			Neonatal death occurring before 28 days of life		
	n/N	Percentage (95% confidence interval)	I ² (%)	n/N	Percentage (95% confidence interval)	I ² (%)
Combo A only	7/23	37.29 [21.36; 56.57]	0	1/22	23.98 [12.56; 40.92]	0
Combo B only	1/24	13.38 [3.97; 36.60]	5	0/24	9.62 [2.77; 28.45]	0
Combo C only	8/22	43.45 [25.50; 63.30]	0	0/22	20.86 [10.51; 37.17]	0
Combo A + B + C	9/18	49.64 [29.77; 69.62]	0	0/18	22.34 [11.01; 40.07]	0
Combo A + B NOT C	1/2	50.00 [9.42; 90.58]	0	0/2	25.00 [3.35; 76.22]	0
Combo B + C NOT A	2/15	30.83 [8.10; 69.27]	26	0/15	15.92 [4.55; 42.93]	0
Combo A + C NOT B	11/24	47.18 [31.46; 63.48]	0	1/24	25.91 [15.06; 40.81]	0
Routine Care	0/0	-		0/0	-	-

Note: Combination A describes physical environmental changes. Combination B describes delivery specific interventions. Combination C describes infant care interventions. Logit transformation and random effects were used. Continuity correction was applied to all if any one study had 0

event. I² represent heterogeneity between studies.

Table 4: Subgroup analysis of maternal illness severity and gestational age. This lists frequencies of primary outcomes for cases describing maternal illness severity and infant gestational age described in large categories <34 weeks gestational age (GA) or ≥34 weeks GA.

Subgroup analysis	n/N	Early Neonatal Infection, % [95% confidence interval]	n/N	Neonatal Death, % [95% confidence interval]
Maternal Illness Severity: n/total (%)				
Asymptomatic	5/29	30.66 [6.87; 54.45]	0/29	0.00 [0.00; 8.72]
Mild	28/84	42.39 [28.53; 56.24]	2/84	1.50 [0.00; 7.30]
Moderate	6/68	8.74 [0.00; 17.50]	1/67	0.60 [0.00; 6.94]
Severe	8/24	33.33 [12.60; 54.07]	1/24	4.15 [0.00; 16.38]
Critical	7/33	22.82 [7.36; 38.29]	1/32	3.04 [0.00; 13.50]
Gestational Age: n/total (%)				
Moderate or very preterm (<34 weeks GA)	19/53	33.70 [18.92; 48.48]	4/52	6.82 [0; 15.10]
Term/late preterm (≥34 weeks GA)	33/183	27.41 [18.40; 36.42]	1/182	0.22 [0; 3.94]

SUPPLEMENTAL MATERIAL

Appendix 1. Country specific guidelines for reducing SARS-CoV2 exposure.

Delivery management alterations described by guidelines. This is not a comprehensive review of all guidelines regarding obstetric and neonatal practice. This is a pragmatic review for select recommendations for or against practices that have been described in case reports regarding management of SARS-CoV-2-positive mothers and their infants designed to reduce transmission to the newborn.

Delivery Management Alternation	Guidelines Recommending Practice	Guidelines Recommending Against Practice
Negative pressure in delivery room or resuscitation room	AAP 2020; China 2020a; China 2020b; China 2020c; China 2020g; France 2020a; France 2020b; France 2020c; SOAP SMGM 2020;	
Separate room from delivery room for neonatal resuscitation or distance from mother during resuscitation of six feet or	AAP 2020; China 2020d; China 2020f;	

<p>more</p>	<p>China 2020g; CPS 2020; France 2020a; France 2020c; India 2020; Saudi 2020;</p>	
<p>Mother masked during labor/delivery</p>	<p>AAP 2020; China 2020d; France 2020a; France 2020c; RCOG 2020; SOGC 2020; Spain 2020;</p>	
<p>Cesarean delivery for infection prevention purposes</p>		<p>AAP 2020; ACOG 2020; CDC 2020; China 2020i; France 2020a; France 2020c; India 2020; RCOG 2020; Saudi 2020;</p>

		SOGC 2020;
Early cord clamping	China 2020a; China 2020b; China 2020c; China 2020d; China 2020f; China 2020g; Saudi 2020; Spain 2020	AAP 2020; ACOG 2020; CDC 2020; CPS 2020; India 2020; RCOG 2020; SOGC 2020;
Infant cleaning or decontamination as soon as possible after resuscitation	None documented	None documented
Avoidance of skin-to-skin contact	None documented	None documented

1. AAP 2020: American Academy of Pediatrics. Management of infants born to mothers with COVID-19. downloads.aap.org/AAP/PDF/COVID%2019%20Initial%20Newborn%20Guidance.pdf (accessed prior to 2 April 2020).
2. ACOG 2020: The American College of Obstetricians and Gynecologists. COVID-19 FAQs for obstetricians-gynecologists, obstetrics. www.acog.org/clinical-information/physician-faqs/covid-19-faqs-for-ob-gyns-obstetrics (accessed 23 March 2020).
3. China 2020a: Kaixu W, Yu H, Fang L, Yuan S, Children's Hospital of Chongqing Medical University, National Clinical Research Center for Child Health and Disorders,

7. China 2020e: Zhou WH, Working Group for the Prevention and Control of Neonatal 2019-nCoV Infection in the Perinatal Period of the Editorial Committee of Chinese Journal of Contemporary Pediatrics. Perinatal and neonatal management plan for prevention and control of 2019 novel coronavirus infection (1st edition) [新新新新新新新新新新新新新新新新新新新新新新新新新新新新新新新新新新]. www.zgddk.com/EN/abstract/abstract14940.shtml (accessed 30 January 2020).
8. China 2020f: Yue Shao Jie (corresponding author) Hunan Neonatal Medical Quality Control Center. The programme for prevention and control of SARS-CoV-2 infection in neonates in Hunan Province [新新新新新新新新新新新新新新新新新新新新新新新新新新新新新新新新新新]. China Journal of Modern Medicine 2020;30(4):65-71. [DOI: 10.3969/j.issn.1005-8982.2020.04.012]
9. China 2020g: Chen M-Y, Lu X, Qian X, School of Public Health, Fudan University. An overview of official measures for COVID-19 prevention and control in maternal and neonatal population in China [新新新新新新新新新新新新新新新新新新新新新新新新新新新新新新新新新新]. Shanghai Journal of Preventive Medicine 2020. [DOI:10.19428/j.cnki.sjpm.2020.20249] [kns.cnki.net/kcms/detail/31.1635.r.20200525.1929.003.html]
10. China 2020h: Li Yu Hong, Chen Qian et al (新新新新新新新新新新新新新新新新新新新新新新新新新新新新新新新新新新), Shandong Province Maternal and Child Health Centre (新新新新新新新新新新新新新新新新新新新新新新新新新新新新新新新新新新). Shandong Medicine 2020;60(10):110-113. [DOI: 10.3969 /j.issn.1002-266X.2020.10.029]
11. China 2020i: Fong Ling (新新) (corresponding author), Wuhan Tongji Hospital (Tongji Medical College of Huazhong University of Science and Technology). Guidelines for management of pregnant women and neonates with novel coronavirus infection in Wuhan Tongji Hospital during the epidemic period [新新新新新新-新新新新新新新新新新新新新新新新新新新新新新新新新新新新新新新新新新].

新新新新新新新新新(新新新)]. China Journal of Obstetrics Emergency 2020;9(1):1-4. [DOI: 10.3877/cmaj.issn.2095-3259.2020.01.001]

12. CPS 2020: Canadian Paediatric Society. Delivery room considerations for infants born to mothers with suspected or proven COVID-19.
www.cps.ca/en/documents/position/delivery-room-considerations-infants-born-to-mothers-with-suspected-or-proven-covid-19 (accessed 6 May 2020).
13. France 2020a: Collège National des Gynécologues et Obstétriciens Français (CNGOF). Prise en charge aux urgences maternité d'une Patiente enceinte suspectée ou infectée par le coronavirus (COVID 19) (Management of a pregnant patient suspected or infected with coronavirus (COVID 19)). www.cngof.fr/coronavirus-go-cngof (accessed 17 March 2020).
14. France 2020b: Société Française d'Hygiène Hospitalière. Avis relatif aux mesures d'hygiène pour la prise en charge d'un patient considéré comme cas suspect, possible ou confirmé d'infection à 2019-nCoV. www.sf2h.net/wp-content/uploads/2020/01/Avis-prise-en-charge-2019-nCoV-28-01-2020.pdf (accessed 28 January 2020).
15. France 2020c: Académie Nationale de Médecine. Covid-19, pregnancy and childbirth. www.academie-medecine.fr/wp-content/uploads/2020/03/20.3.30-Communiqu%C3%A9-Covid19-et-grossesse-ENG.pdf (accessed 30 March 2020).
16. India 2020: Federation of Obstetric & Gynaecological Societies of India National Neonatology Forum, India Indian Academy of Pediatrics. Perinatal-neonatal management of COVID-19.
www.nnfi.org/assets/upload/announcement-pdf/Summary_FOGSI_NNF_IAP_Perinatal_Covid19-ver2May11merged.pdf (accessed prior to 10 July 2020).

17. RCOG 2020: Department of Health and Social Care (DHSC), Public Health Wales (PHW), Public Health Agency (PHA) Northern Ireland, Health Protection Scotland (HPS), Public Health Scotland, Public Health England and NHS England (official guidance). COVID-19: infection prevention and control guidance.
www.rcog.org.uk/en/guidelines-research-services/guidelines/coronavirus-pregnancy/ (accessed 27 April 2020).
18. Saudi 2020: Saudi MOH Guideline for neonate born to mothers with suspected or confirmed COVID-19 infection.
www.moh.gov.sa/Ministry/MediaCenter/Publications/Documents/Guideline-for-Neonate-born-to-COVID-19-Mother.pdf (accessed prior to 10 July 2020).
19. SOAP SMGM 2020: Society for Obstetric Anesthesia and Perinatology (SOAP), Society for Maternal-Fetal Medicine (SMFM). Labor and delivery COVID-19 considerations.
soap.org/education/provider-education/expert-summaries/interim-considerations-for-obstetric-anesthesia-care-related-to-covid19/ (accessed prior to 14 April 2020).
20. SOGC 2020: Society of Obstetricians and Gynaecologists of Canada (SOGC). Updated SOGC committee opinion – COVID-19 in pregnancy.
www.sogc.org/en/content/featured-news/Updated-SOGC-Committee-Opinion_COVID-19-in-Pregnancy.aspx (accessed 13 March 2020).
21. Spain 2020: Spanish Society of Neonatology. Recommendations for management of newborns for SARS-CoV-2 infection.
www.seneo.es/images/site/noticias/home/Recomendaciones_SENeo_COVID-19_v6_eng.pdf (accessed prior to 10 July 2020).

Appendix 2. Search strategies

We accepted peer-reviewed published studies, both in full article and abstract forms as long as the minimum inclusion criteria are met: maternal SARS-CoV-2 PCR status known positive within 10 days of delivery or if symptomatic and status is known positive within 48h of delivery, delivery method, and infant SARS-CoV-2 PCR status known. We did not apply language restrictions. If non-English records were identified, we obtained a translation of the full-text report of the record to assess eligibility or had an author reviewer fluent in that language evaluate for eligibility.

Initial Search Strategy

We used the standard search strategy of Cochrane Neonatal to search Cochrane Central Register of Controlled Trials (CENTRAL 2020, Issue 7) in the Cochrane Library; Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R); Cochrane COVID-19 Study Register; CINAHL; World Health Organization (WHO) COVID-19 Global literature on coronavirus disease; and the Centers for Disease Control and Prevention COVID-19 Research Articles Database on 23 July 2020. We also searched clinical trials databases and reference lists of retrieved articles for randomized controlled trials and quasi-randomized trials.

We conducted a comprehensive search on 23 July 2020 including:

1. Cochrane Central Register of Controlled Trials (CENTRAL 2020, Issue 7) in the Cochrane Library;
2. Cochrane COVID-19 Study Register, via CRS Web;
3. Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) (2019 to current);
4. CINAHL (2019 to current);
5. World Health Organization (WHO) COVID- 19 Global Research Database;
6. Centers for Disease Control and Prevention COVID- 19 Research Article Database;
7. International Standard Randomized Controlled Trial Number Registry (www.isrctn.com).

The neonatal filters were created and tested by the Cochrane Neonatal Information Specialist.

The terms for COVID-19 were adapted from the PubMed search used for the Cochrane COVID-19 Study Register (<https://community.cochrane.org/about-covid-19-study-register>).

CENTRAL via CRS Web:

Date searched: 23 July 2020

Terms:

1 ("2019 nCoV" OR 2019nCoV OR "2019 novel coronavirus" OR "2019-novel CoV" OR ((coronavirus OR "corona virus") AND (Huanan OR Hubei OR Wuhan)) OR "coronavirus-19" OR "coronavirus disease-19" OR "coronavirus disease-2019" OR ((coronavirus OR "corona virus") ADJ3 2019) OR "COVID 19" OR COVID19 OR "COVID 2019" OR "nCov 2019" OR ncov19 OR "ncov 19" OR "new coronavirus" OR "new coronaviruses" OR "novel coronavirus" OR "novel coronaviruses" OR "novel coronavirus" OR "novel corona viruses" OR "SARS-

CoV2" OR "SARS CoV-2" OR SARSCoV2 OR "SARSCoV-2" OR "SARS-coronavirus-2" OR "SARS-like coronavirus" OR "Severe Acute Respiratory Syndrome Coronavirus-2" OR "severe acute respiratory syndrome coronavirus 2" OR ("spike protein" ADJ3 SARS-CoV-2)) AND CENTRAL:TARGET

2 MESH DESCRIPTOR Infant, Newborn EXPLODE ALL AND CENTRAL:TARGET

3 infant or infants or infant's or "infant s" or infantile or infancy or newborn* or "new born" or "new borns" or "newly born" or neonat* or baby* or babies or premature or prematures or prematurity or preterm or preterms or "pre term" or premies or "low birth weight" or "low birthweight" or VLBW or LBW or ELBW or NICU AND CENTRAL:TARGET

4 MESH DESCRIPTOR Mothers EXPLODE ALL AND CENTRAL:TARGET

5 mother* AND CENTRAL:TARGET

6 maternal AND CENTRAL:TARGET

7 MESH DESCRIPTOR Cesarean Section EXPLODE ALL AND CENTRAL:TARGET

8 (caesarean ADJ3 (section* or deliver*)) AND CENTRAL:TARGET

9 (cesarean ADJ3 (section* or deliver*)) AND CENTRAL:TARGET

10 C-section* AND CENTRAL:TARGET

11 (vaginal* adj3 (birth* or deliver*)) AND CENTRAL:TARGET

12 MESH DESCRIPTOR Delivery, Obstetric EXPLODE ALL AND CENTRAL:TARGET

13 MESH DESCRIPTOR Delivery Rooms EXPLODE ALL AND CENTRAL:TARGET

14 delivery room* AND CENTRAL:TARGET

15 birth suite* AND CENTRAL:TARGET

16 MESH DESCRIPTOR Umbilical Cord EXPLODE ALL AND CENTRAL:TARGET

17 ((umbilicus or umbilical or cord or navel-string) adj2 clamp*) AND CENTRAL:TARGET

18 #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR
#14 OR #15 OR #16 OR #17 AND

CENTRAL:TARGET

19 #1 AND #18 AND CENTRAL:TARGET

MEDLINE via Ovid:

Date ranges: 01 January 2019 to 23 July 2020

Terms:

1. 2019 nCoV.ti,ab.
2. 2019nCoV.ti,ab.
3. 2019 novel coronavirus.ti,ab.
4. 2019-novel CoV.ti,ab.
5. ((coronavirus or "corona virus") and (Huanan or Hubei or Wuhan)).ti,ab.
6. coronavirus-19.ti,ab.
7. coronavirus disease-19.ti,ab.
8. coronavirus disease-2019.ti,ab.
9. ((coronavirus or "corona virus") adj3 "2019").ti,ab.
10. COVID 19.ti,ab.
11. COVID19.ti,ab.
12. COVID 2019.ti,ab.
13. nCov 2019.ti,ab.
14. ncov19.ti,ab.
15. ncov-19.ti,ab.
16. new coronavirus.ti,ab.

17. new coronaviruses.ti,ab.
18. novel coronavirus.ti,ab.
19. novel coronaviruses.ti,ab.
20. novel corona virus.ti,ab.
21. SARS-CoV2.ti,ab.
22. SARS CoV-2.ti,ab.
23. SARSCoV2.ti,ab.
24. SARSCoV-2.ti,ab.
25. SARS-coronavirus-2.ti,ab.
26. SARS-like coronavirus.ti,ab.
27. Severe Acute Respiratory Syndrome Coronavirus-2.ti,ab.
28. COVID-19.rs.
29. COVID-19.rx.
30. COVID-19.kw.
31. COVID-19.kf.
32. coronavirus disease 2019.kw.
33. coronavirus disease 2019.kf.
34. coronavirus disease 19.kw.
35. coronavirus disease 19.kf.
36. corona virus disease 2019.kw.
37. corona virus disease 2019.kf.
38. severe acute respiratory syndrome coronavirus 2.os,ox.
39. severe acute respiratory syndrome coronavirus 2.kw.

40. severe acute respiratory syndrome coronavirus 2.kf.
41. SARS-CoV-2.kw.
42. SARS-CoV-2.kf.
43. COVID-19 drug treatment.ps.
44. COVID-19 drug treatment.px.
45. spike protein, SARS-CoV-2.nm.
46. spike protein, SARS-CoV-2.rn.
47. or/1-46
48. exp infant, newborn/
49. (newborn* or new born or new borns or newly born or baby* or babies or premature or prematurity or preterm or pre term or low birth weight or low birthweight or VLBW or LBW or infant or infants or 'infant s' or infant's or infantile or infancy or neonat*).ti,ab.
50. exp Mothers/
51. mother*.mp.
52. maternal.mp.
53. exp Cesarean Section/
54. (caesarean adj3 (section* or deliver*)).mp.
55. (cesarean adj3 (section* or deliver*)).mp.
56. C-section*.mp.
57. (vaginal* adj3 (birth* or deliver*)).mp.
58. exp delivery, obstetric/
59. exp Delivery Rooms/

60. delivery room*.mp.
61. birth suite*.mp.
62. exp Umbilical Cord/
63. ((umbilicus or umbilical or cord or navel-string) adj2 clamp*).mp.
64. or/48-63
65. 47 and 64
66. exp Animals/
67. exp Humans/
68. 66 not 67
69. (editorial or comment or letter or newspaper article).pt.
70. 68 or 69
71. 65 not 70
72. limit 71 to yr="2019 -Current"

Cochrane COVID- 19 Study Register via CRS Web:

Date searched: 23 July 2020

Terms:

1 MESH DESCRIPTOR Infant, Newborn EXPLODE ALL AND INREGISTER

2 infant or infants or infant's or "infant s" or infantile or infancy or newborn* or "new born" or "new borns" or "newly born" or neonat*

or baby* or babies or premature or prematures or prematurity or preterm or preterms or "pre term" or premies or "low birth weight"

or "low birthweight" or VLBW or LBW or ELBW or NICU AND INREGISTER

3 MESH DESCRIPTOR Mothers EXPLODE ALL AND INREGISTER
4 mother* AND INREGISTER
5 maternal AND INREGISTER
6 MESH DESCRIPTOR Cesarean Section EXPLODE ALL AND INREGISTER
7 (caesarean adj3 (section* or deliver*)) AND INREGISTER
8 (cesarean adj3 (section* or deliver*)) AND INREGISTER
9 (C-section or C-sections) AND INREGISTER
10 (vaginal* adj3 (birth* or deliver*)) AND INREGISTER
11 MESH DESCRIPTOR Delivery, Obstetric EXPLODE ALL AND INREGISTER
12 MESH DESCRIPTOR Delivery Rooms EXPLODE ALL AND INREGISTER
13 delivery room* AND INREGISTER
14 birth suite* AND INREGISTER
15 MESH DESCRIPTOR Umbilical Cord EXPLODE ALL AND INREGISTER
16 ((umbilicus or umbilical or cord or navel-string) adj2 clamp*) AND INREGISTER
17 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13
OR #14 OR #15 OR #16

CINAHL via EBSCOhost:

Date ranges: 01 January 2019 to 23 July 2020

Terms:

("2019 nCoV" OR 2019nCoV OR "2019 novel coronavirus" OR "2019-novel CoV" OR

((coronavirus OR "corona virus") AND

(Huanan OR Hubei OR Wuhan)) OR "coronavirus-19" OR "coronavirus disease-19" OR "coronavirus disease-2019" OR ((coronavirus or "corona virus") N3 2019) OR "COVID 19" OR COVID19 OR "COVID 2019" OR "nCov 2019" OR ncov19 OR "ncov 19" OR "new coronavirus" OR "new coronaviruses" OR "novel coronavirus" OR "novel coronaviruses" OR "novel corona virus" OR "novel corona viruses" OR "SARS-CoV2" OR "SARS CoV-2" OR SARSCoV2 OR "SARSCoV-2" OR "SARS-coronavirus-2" OR "SARS-like coronavirus" OR "Severe Acute Respiratory Syndrome Coronavirus-2" OR "severe acute respiratory syndrome coronavirus 2" OR ("spike protein" N3 SARS-CoV-2)) AND (infant or infants or infant's or infantile or infancy or newborn* or "new born" or "new borns" or "newly born" or neonat* or baby* or babies or premature or prematures or prematurity or preterm or preterms or "pre term" or premies or "low birth weight" or "low birthweight" or VLBW or LBW or mother* or maternal or (caesarean N3 (section* or deliver*)) or (cesarean N3 (section* or deliver*)) or C-section* or (vaginal* N3 (birth* or deliver*)) or delivery room* or birth suite* or ((umbilicus or umbilical or cord or navel-string) N2 clamp*))

Limiters - Published Date: 20190101-20201231

World Health Organization (WHO) COVID-19 Global literature on

coronavirus disease:

(<https://search.bvsalud.org/global-literature-on-novel-coronavirus-2019-ncov>)

Date searched: 23 July 2020

Terms:

infant or infants or infant's or infantile or infancy or newborn* or "new born" or "new borns" or "newly born" or neonat* or baby* or

babies or prematures or prematurity or preterm or preterms or "pre term" or premies or "low birth weight" or "low birthweight" or

VLBW or LBW or mother* or maternal or caesarean or cesarean or "vaginal birth" or "vaginal delivery" or "vaginal deliveries" or

"delivery room" or "delivery rooms" or "birth suite" or "birth suites" or "umbilical cord clamping" or "cord clamping"

Centers for Disease Control and Prevention COVID-19 Research

Articles Database via EndNote database:

(<https://www.cdc.gov/library/researchguides/2019novelcoronavirus/researcharticles.html>)

Date searched: 23 July 2020

Terms:

infant*

Baby

babies

neonat*

Newborns

Preterm

mother*

Maternal

caesarean

cesarean

C-section

C-sections

vaginal birth

vaginal delivery

vaginal deliveries

delivery room

delivery rooms

birth suite

birth suites

Umbilical cord clamping

cord clamping

ISRCTN:

Date searched: 24 July 2020

Terms:

covid-19 AND (Participant age range: Neonate)

covid-19 AND infant*

covid-19 AND newborns

covid-19 AND neonat*

covid-19 AND preterm*

covid-19 AND "delivery room*"

covid-19 AND vaginal delivery

covid-19 AND vaginal birth

covid-19 AND caesarean

covid-19 AND cesarean

covid-19 AND mother*

covid-19 AND maternal

covid-19 AND cord clamping

Updated Search Strategy

Comparison of the initial search strategy and an updated search strategy using PubMed and Google Scholar showed that 96.5% of total searched articles were captured using the PubMed and Google updated search approach. Two author reviewers conducted this updated search strategy (LPB, JMH). Updates through PubMed and Google Scholar were subsequently conducted July 23, 2020 until end date December 31, 2021.

PubMed key word search strategy: (*year published) (covid-19 OR SARS-cov-2 OR coronavirus) AND (neonatal OR newborn OR neonates OR infants OR pregnancy OR (vertical transmission))*

Google Scholar key word search strategy: ((covid-19 OR SARS-cov-2 OR coronavirus) AND (neonatal OR newborn OR neonates OR infants OR pregnancy OR (vertical transmission))) AND (("2021"[Date - Publication] : "2021"[Date - Publication])) NOT (Cohort OR Cohorts) NOT (Commentary OR Commentaries) NOT (Editorial OR Editorials) NOT (analysis OR meta-analysis) NOT (Review OR Reviews) NOT (Vaccine OR Vaccines OR Immunization) NOT (Test OR testing)

Appendix 3: Detailed Description of Delivery Management Interventions.

Category A: Physical environment - aerosolization and droplet management

1. Presence of negative pressure in delivery room

Negative pressure refers to the pressure differential creating air flow into a patient room whenever the door is opened. This is recommended to prevent aerosolized particles generated in the patient room from contaminating areas outside the patient environment¹. Given the concern that SARS-CoV-2 may transmit through aerosol and contact surfaces, negative pressure delivery rooms have been recommended for any laboring mother who is SARS-CoV-2-positive^{2,3}. As of January 2022, it remains unclear whether a negative pressure room reduces the risk of early neonatal infection.

2. Location for neonatal resuscitation

There is currently limited knowledge on the optimal location for neonatal resuscitation, especially when advanced resuscitation requiring a larger resuscitation team is anticipated due to a preterm birth or complicated perinatal course. Immediate separation from an infected mother could potentially minimize the risk of exposure to the neonate. However, providing infant resuscitation at a mother's bedside has been shown to have beneficial effects on infant transition because of the ability to do immediate skin-to-skin contact and delayed cord clamping⁴. Mother-infant bonding is also promoted by having the baby nearby during the transition period. In situations where resuscitation is required, family presence has been shown to improve family understanding during cardiopulmonary resuscitation⁵. Separation by room or distance decreases family-centered care and may increase anxiety, decrease bonding, and create distrust of the medical team.

3. Maternal masking during labor

Maternal masking has been suggested as a method for reducing the aerosolized respiratory droplets that may be formed especially during the second and third stages of labor⁶. Maintaining this mask is difficult especially in situations where a mother may require additional oxygen for the progression of labor. The risks and benefits of such practice as it pertains to early neonatal infection remains hypothetical.

Category B: Delivery specific interventions - minimization of contact during delivery with maternal fluids

1. Mode of delivery

Caesarean delivery has been suggested as a mode to minimize or avoid neonatal exposure to maternal vaginal secretions, urine, or stool where SARS-CoV-2 viral load is presumably higher based on extrapolations from HIV prevention measures⁷. If high viral load is present, vertical transmission risk might theoretically decrease with caesarean section done after shorter duration of ruptured membranes. This potential benefit may be negligible, especially if low/undetectable viremia was associated with lower risk of vertical transmission, as seen with HIV. Importantly, caesarean delivery may increase the risk of droplet or airborne spread in the case of endotracheal intubation for maternal anesthesia, high-flow oxygen or electrocautery of the surgical wound⁸.

Caesarean delivery for infection prevention will also increase the medical morbidity to the mother, as well as the cost and complexity of this and future pregnancies⁹. It is also well known that caesarean birth is associated with high risk for neonatal respiratory complications secondary to the delayed transition of fetal to newborn adaptation¹⁰.

2. Timing of cord clamping

Delayed cord clamping, as defined by 30 seconds or more, has been demonstrated to have beneficial effects for both preterm and term infants¹¹⁻¹⁴ and is currently recommended for all infants who do not need resuscitation at birth¹⁵. However, it may have the unintended effect of increasing transplacental viral passage and prolonged infant exposure to maternal secretions because of positioning the neonate within close proximity of the mother.

Conversely, early cord clamping as defined by less than 30 seconds from delivery of infant to cord clamping, may reduce viral transmission and avoid prolonged exposure of infant to infected maternal secretions or stool. With delayed cord clamping being the current standard of care (in most countries and hospitals), early cord clamping may potentially deprive the preterm neonate of the benefits of risk reduction in necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH), or even death¹³.

Category C: Infant care practices - minimizing infant skin contact

1. Skin-to-skin contact

Immediate mother-to-infant skin-to-skin contact after delivery has been shown to provide benefits to the mother and infant dyad. For the postpartum mother, there is evidence that it can accelerate the third stage of labor and in turn prevent postpartum hemorrhage¹⁶.

Skin-to-skin contact right after birth can also improve newborn vital signs including temperature stability, promote bonding, and improve breastfeeding success¹⁷. With concerns of infectious risk from a SARS-CoV-2 infected mother to her infant, several countries have recommended against skin-to-skin care in order to minimize direct neonatal exposure to droplets¹⁸.

2. Decontamination of neonate after delivery

Cleaning the infant immediately after birth may theoretically reduce the risk of transmission especially when mother is viremic and the exposed infant has direct contact with maternal bodily fluids like blood and amniotic fluid infected with SARS-CoV-2.

However, immediate cleaning will decrease the availability of vernix which has many beneficial effects for newborn infant skin health including a barrier to prevent water loss, temperature regulation, innate immunity and even promotion of healthy intestinal development^{19,20}. In addition, cleaning extremely low gestational age infants might increase the risk of hypothermia and skin breakdown, especially when antiseptic solutions are used²¹.

Appendix 4. Clinical Status Classifications for SARS-CoV-2 Positive Patients

Pediatric Patients: Dong, et al. describes the clinical characteristics of more than 2000 pediatric patients and divides their clinical status into asymptomatic, mild, moderate, severe and critical²²:

1. Asymptomatic: without clinical signs and symptoms and chest imaging is normal.
2. Mild: symptoms of acute upper respiratory tract infection, including fever, fatigue, myalgia, cough, sore throat, runny nose, and sneezing. Physical examination shows congestion of the pharynx without auscultatory abnormalities. Some may present with digestive symptoms such as nausea, vomiting, abdominal pain, and diarrhea.
3. Moderate: diagnosed with pneumonia, with fever and cough, wheezing, and upper respiratory congestion without hypoxemia. Some cases may be asymptomatic but will have chest CT or X-ray showing subclinical lung lesions.
4. Severe: hypoxia with other previously described symptoms with or without imaging findings.
5. Critical: Multi-organ dysfunction with respiratory failure, shock, encephalopathy, myocardial impairment, coagulation dysfunction or kidney injury.

Maternal Patients: Severity of maternal COVID-19 symptoms have been described in levels from asymptomatic to critical based on the Berlin Definition for Acute Respiratory Distress Syndrome²³.

1. Asymptomatic;
2. Mild: any signs and symptoms (e.g. fever, cough, sore throat, malaise, headache, muscle pain) without shortness of breath, dyspnea, or abnormal chest imaging);
3. Moderate: lower respiratory disease by clinical assessment or imaging and a saturation of oxygen > 93% on room air;
4. Severe: respiratory frequency > 30 breaths per minute, SaO₂ ≤ 93% on room air, ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO₂ /FiO₂) < 300, or lung infiltrates > 50%;
5. Critical: respiratory failure, septic shock, and/or multiple organ dysfunction.

Appendix 5: List of articles included by year for final analysis.

2020 Articles Included: Total 93

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PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page 2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 6-9
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 9
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 9-10
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 10 and Appendix 2
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Appendix 2
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 13
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 13
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 11-12
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 11-13
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 13
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 13-14
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Page 13
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 13
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 13
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 13-14
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Page 16 and Appendix 6
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	n/a
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	n/a
Certainty	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	n/a



PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
assessment			
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 13, Figure 2
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Figure 2
Study characteristics	17	Cite each included study and present its characteristics.	Figure 2, Appendix 2
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	n/a
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	n/a
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	n/a
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Page 13-14
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	n/a
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	n/a
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	n/a
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	n/a
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 16
	23b	Discuss any limitations of the evidence included in the review.	Page 16
	23c	Discuss any limitations of the review processes used.	Page 16
	23d	Discuss implications of the results for practice, policy, and future research.	Page 17
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 10, PROSPERO CRD42021267 892
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page 10
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Page 10
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 18
Competing interests	26	Declare any competing interests of review authors.	Page 18
Availability of data, code and	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	n/a

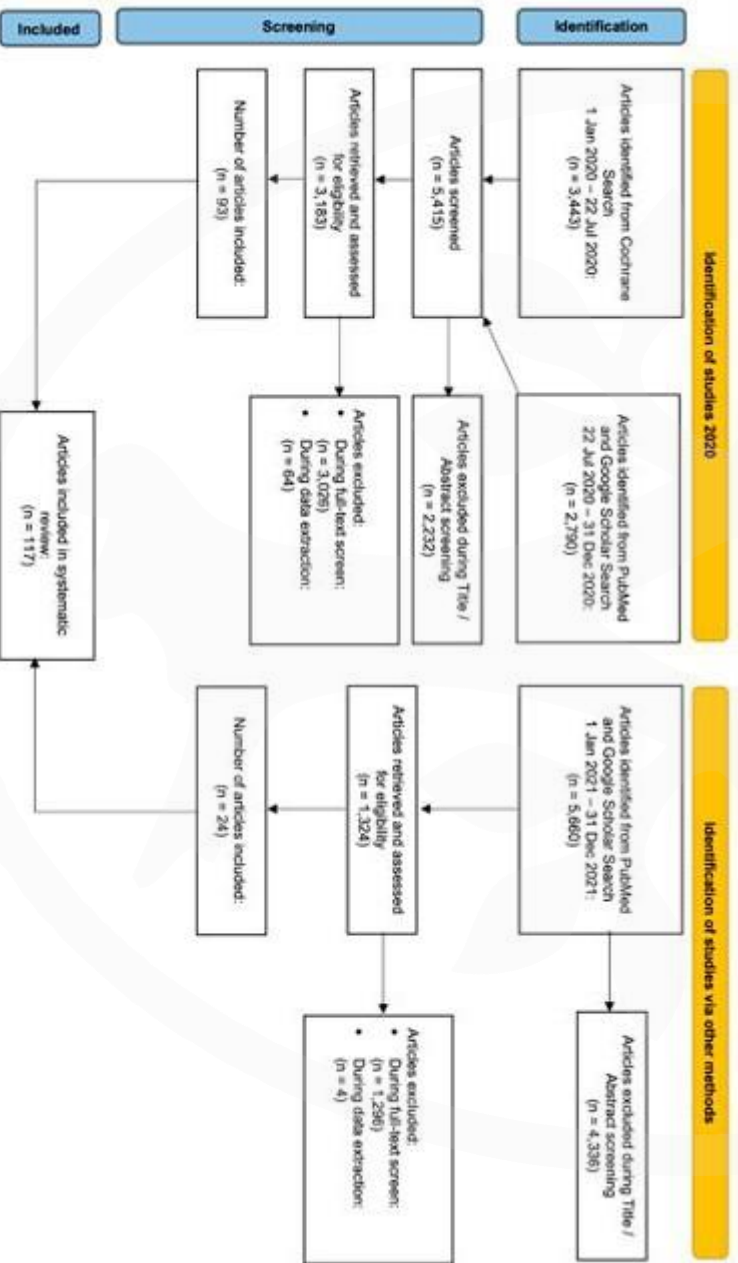
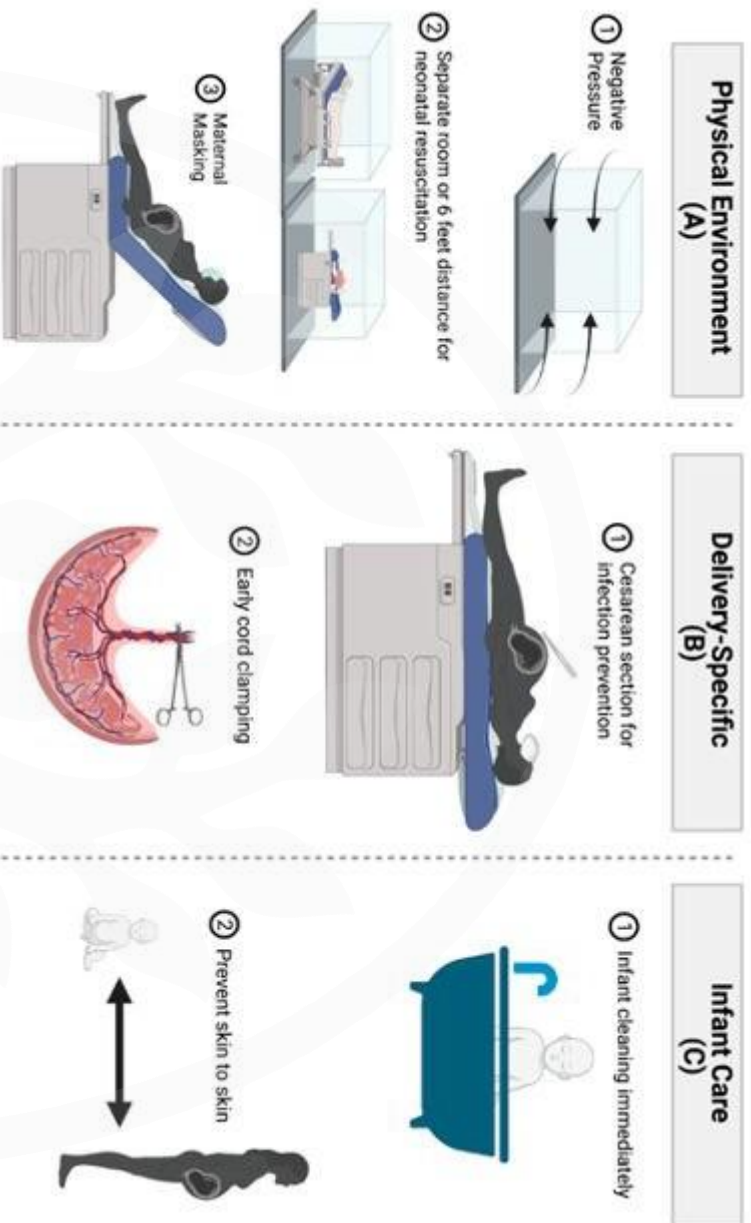


PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
other materials			

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: <http://www.prisma-statement.org/>



From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: <http://www.dripsna-statement.org/>