

A systematic review about the possibility of transmission of the SARS-CoV-2 antibody during breastfeeding

Uma revisão sistemática sobre a possibilidade de transmissão do anticorpo do SARS-CoV-2 durante a amamentação

Una revisión sistemática sobre la posibilidad de transmisión del anticuerpo SARS-CoV-2 durante la lactancia

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Abstract

Breastfeeding by COVID-19 positive mothers still deserves attention and care regarding the consequences for the baby. To date, studies demonstrate no risk. In view of this, there is a need to perform a systematic review and collect studies that have shown the presence of SARS-CoV-2 in human milk, by measuring IgM, IgG and IgA in biological material. After searching PubMed, Web of Science, Scopus, Google Scholar databases, 147 studies were identified, of which 37 at some point addressed breastfeeding and COVID-19, and 14 of which addressed antibody dosages in breast milk. Of these, one used the ELISA test for IgA detection. In the other studies, the methodology used was RT-PCR to detect the SARS-CoV-2 virus in breast milk, where the presence of the virus was detected in a few samples. These studies confirmed that SARS-CoV-2 can be identified in breast milk, but could not elucidate about the validation of the method and its sensitivity. In addition, there was no description if the viral load present in the milk would be sufficient to infect the baby. Furthermore, no completed research involving serological tests for the detection of antibodies in human colostrum has been found. Thus, more serological studies on COVID-19 positive breastfeeding mothers are mandatory.

Keywords: Breastfeeding; Colostrum; COVID-19; SARS-CoV-2; Serology; Systematic review.

Resumo

A amamentação por mães positivas para COVID-19 ainda merece atenção e cuidado quanto às consequências para o bebê. Até o momento, os estudos não demonstram nenhum risco. Diante disso, há necessidade de realizar uma revisão sistemática e coletar estudos que tenham demonstrado a presença de SARS-CoV-2 no leite humano, por meio da dosagem de IgM, IgG e IgA em material biológico. Depois de pesquisar as bases de dados PubMed, Web of Science, Scopus, Google Scholar, foram identificados 147 estudos, dos quais 37 em algum momento abordaram amamentação e COVID-19, e 14 dos quais abordaram dosagens de anticorpos no leite materno. Destes, um utilizou o teste ELISA para detecção de IgA. Nos demais estudos, a metodologia utilizada foi a RT-PCR para detectar o vírus SARS-CoV-2 no leite materno, onde foi detectada a presença do vírus em algumas amostras. Esses estudos confirmaram que o SARS-CoV-2 pode ser identificado no leite materno, mas não puderam elucidar sobre a validação do método e sua sensibilidade. Não havia descrição se a carga viral presente no leite seria suficiente para infectar o bebê. Além disso, não foram encontradas pesquisas concluídas envolvendo testes sorológicos para detecção de anticorpos no colostro humano. Assim, mais estudos sorológicos em mães que amamentam positivo para COVID-19 são obrigatórios.

Palavras-chave: Amamentação; Colostrum; COVID 19; SARS-CoV-2; Sorologia; Revisão sistemática.

Resumen

La lactancia materna de madres positivas para COVID-19 aún merece atención y cuidado en cuanto a las consecuencias para el bebé. Hasta el momento, los estudios no han mostrado ningún riesgo. Ante esto, surge la necesidad de realizar una revisión sistemática y recolectar estudios que hayan demostrado la presencia de SARS-CoV-2 en leche humana, a través de la medición de IgM, IgG e IgA en material biológico. Después de buscar en las bases de datos de PubMed, Web of Science, Scopus, Google Scholar, se identificaron 147 estudios, de los cuales 37 en algún momento abordaron la lactancia materna y el COVID-19, y 14 de los cuales abordaron las dosis de anticuerpos en la leche materna. De estos, uno utilizó la prueba ELISA para la detección de IgA. En otros estudios la metodología utilizada fue RT-PCR para la detección del virus SARS-CoV-2 en leche materna, donde se detectó la presencia del virus en algunas muestras. Estos estudios confirmaron que el SARS-CoV-2 puede identificarse en la leche materna, pero no pudieron dilucidar la validación del método y su sensibilidad. No se describió si la carga viral presente en la leche sería suficiente para infectar al bebé. Además, no se encontraron estudios completos que involucren pruebas serológicas para la detección de anticuerpos en calostro humano. Por lo tanto, es obligatorio realizar más estudios serológicos en madres lactantes positivas para COVID-19.

Palabras clave: Amamantamiento; Calostro; COVID-19; SARS-CoV-2; Serología; Revisión sistemática.

1. Introduction

The race to produce vaccines at the height of the COVID-19 pandemic involved questions about the production of immunological memory antibodies through contact with the virus or body fluids and secretions from infected people (Kutti-Sridharan, et al., 2020). Until 2020, there were no robust studies that have evidenced, through serological research of IgG, IgM and IgA antibodies, the presence of SARS-CoV-2 in human milk (Hand & Noble, 2020). According to the guidelines of the World Health Organization (WHO) and the Brazilian Ministry of Health, as there is no evidence of harm to the health of infants, it is not advisable to interrupt breastfeeding even in the face of the new coronavirus pandemic (WHO, 2019; Ministry of Health, 2020).

Serologic tests have great potential in helping diagnose COVID-19 since they detect recent or previous exposure to the

SARS-CoV-2 virus (Bohn, et al., 2020). The existing data on the antibody response (IgM, IgG and IgA) to the new coronavirus infection are still insufficient and the efficiency of the tests for this diagnostic method should be evaluated taking into consideration factors such as sensitivity and specificity of the test (Bryant, et al., 2020).

Breast milk has in its composition several immunoglobulins and other protective constituents transmitted and acquired throughout the mother's life and act as stimulators for the development of the baby's immune system (Passanha, et al., 2010). Thus, it is possible to consider the presence of antibodies to SARS-CoV-2 in breast milk from mothers who have been diagnosed with this virus (Vassilopoulou, et al., 2021).

Fox et al. (2020) demonstrated in preliminary studies that of 15 breast milk samples obtained from donors previously infected with SARS-CoV-2, 80% showed IgA reactivity. This study suggests that there may be a strong sIgA-dominant immune response to SARS-CoV-2 in human milk after infection in most individuals and that a comprehensive study of this response is highly needed.

Therefore, this systematic review aimed to gather articles on the dosing methodology for the detection of SARS-CoV-2 virus antibodies in human milk.

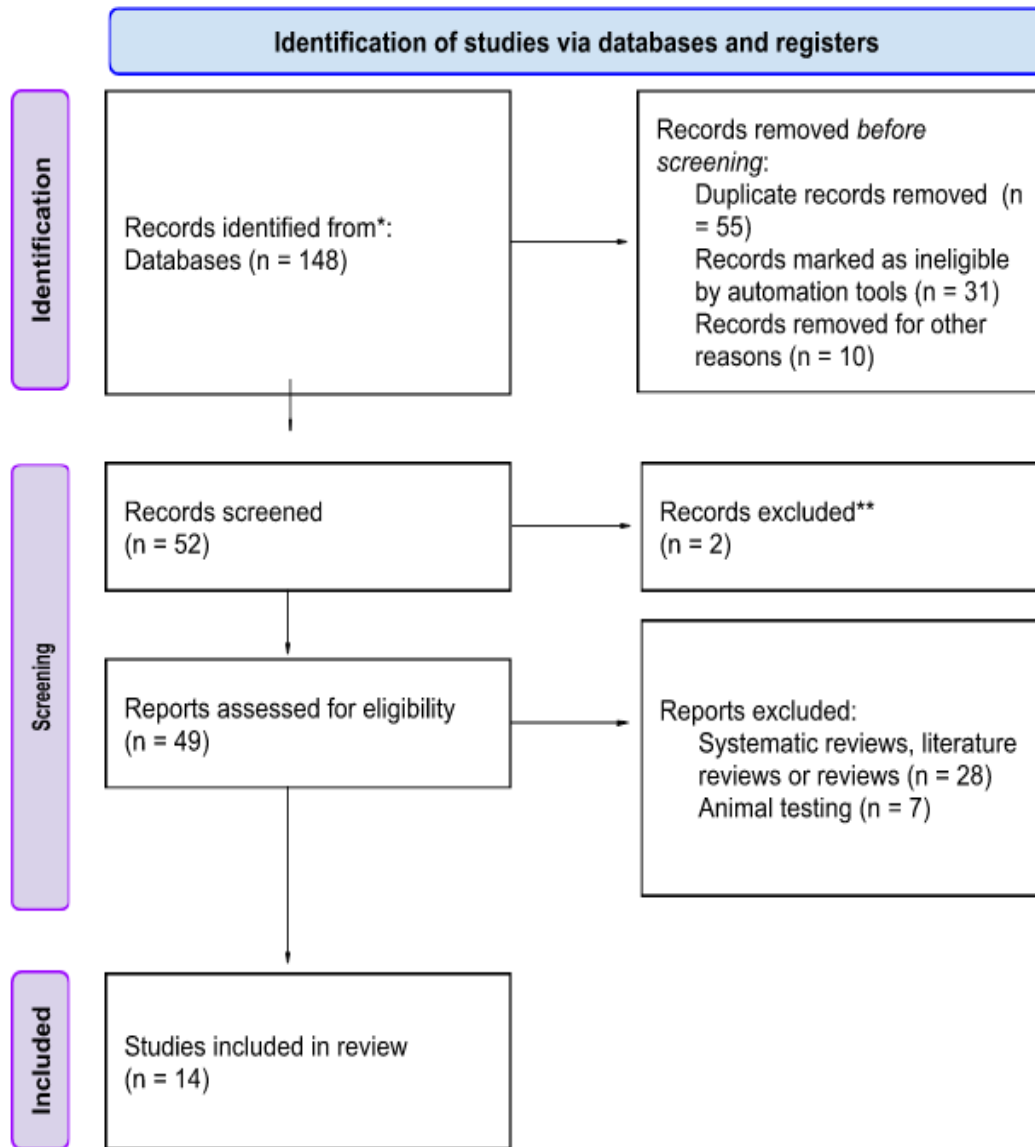
2. Methodology

This study was conducted within the protocols for systematic reviews established by the PRISMA statement (Page, et al., 2021). For the present systematic review, a broad search was conducted in the databases PubMed, Science Direct and Google Scholar, between June 15 and July 15, 2020, with the aim of identifying research that includes studies on the presence of SARS-CoV-2 in human milk, using the following keywords: Breastfeeding, Colostrum, SARS-CoV-2, Serology.

The choice of keywords was made from the following combinations: COVID-19 AND breast milk AND serology, COVID-19 AND breastfeeding AND serology, colostrum AND breast milk AND COVID-19, SARS-CoV-2 AND breast milk AND serology, SARS-CoV-2 AND breastfeeding AND serology, colostrum AND breast milk AND SARS-CoV-2, where 148 papers were located.

After checking the suitability of the studies for this review (Figure 1), 14 articles were included when considering their contributions on breast milk and COVID-19 research. No articles were located containing all the keywords.

Figure 1 - Stages of the study.



Font: Elaborated by the authors.

The inclusion criteria listed papers that performed immunological dosages in breast milk in the Table 1 presented in the results, considered study designs on breastfeeding by mothers with SARS-CoV-2, sample type (breast milk), and sample analysis methodology. Cross-sectional, observational and retrospective studies were included in this review. Systematic reviews, scope reviews, narrative reviews or overview articles were excluded.

3. Results and Discussion

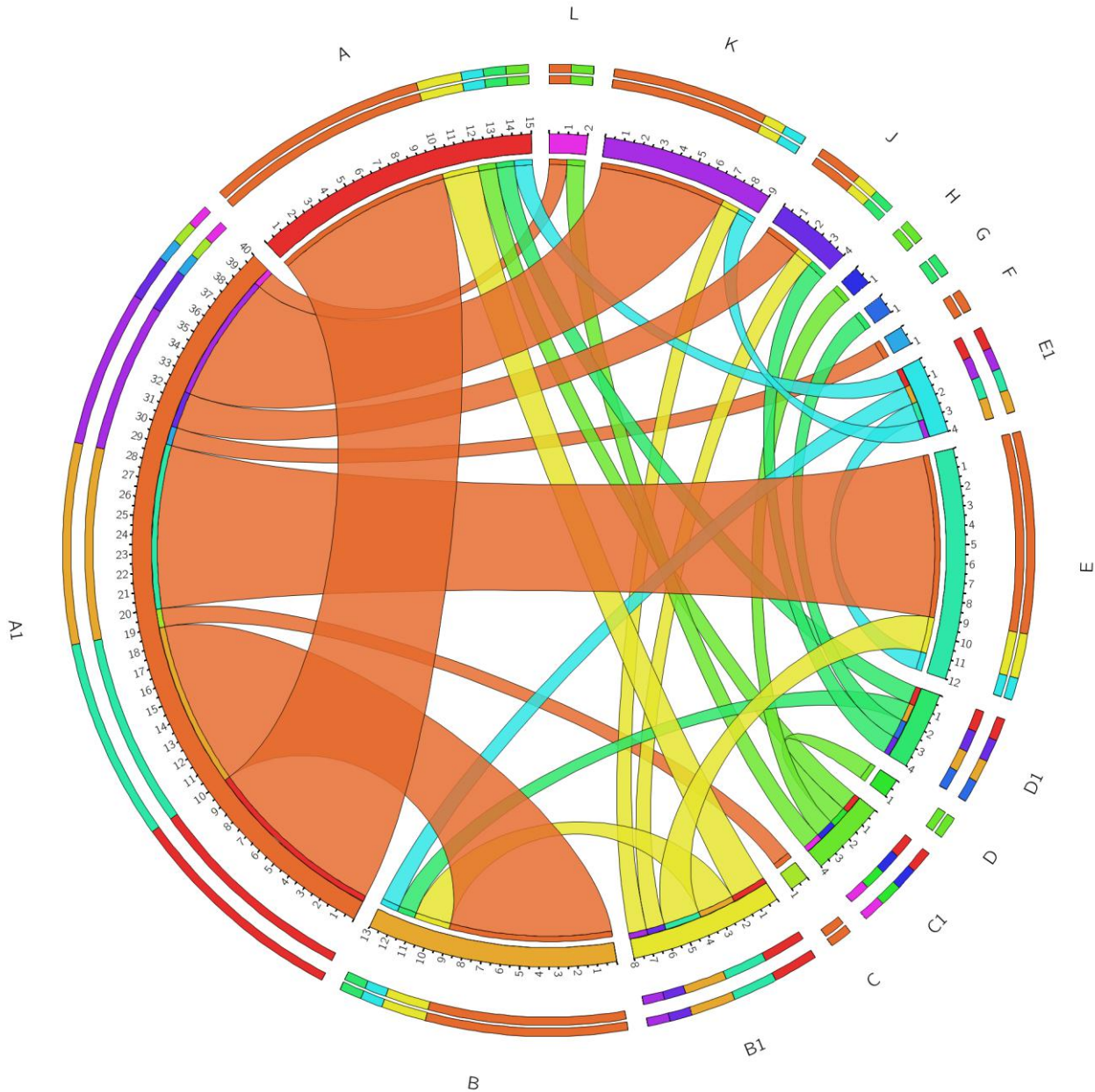
The Table 1 below presents the characteristics of the studies selected here, which address breastfeeding, COVID-19, SARS-CoV-2 and analysis methodology. Our study selected 14 articles that fit our inclusion criteria and are organized as shown in Figure 2.

Table 1 - Characteristics and clipping of the selected studies.

Date/DOI	Author	Study design	Country	Sample	Intervention group (mothers)	Analysis methodology	Result	Conclusion
17/03/2020 10.1093/cid/ciaa226	Fan <i>et al.</i>	Case study	China	Breast milk	2	RT-PCR	Negative	Breastfeeding is discouraged
26/03/2020 10.1001/jama.2020.4621	Dong <i>et al.</i>	Case study	China	Breast milk	1	RT-PCR	Negative	Additional sample examinations should be done.
26/03/2020 10.1007/s11596-020-2174-4	Wang <i>et al.</i>	Case study	China	Mother	1	RT-PCR		Diagnosed cases are not recommended for breastfeeding.
13/04/2020 10.1089/bfm.2020.0095	Salvatori <i>et al.</i>	Cohort Case study	Italy	Breast milk	2	RT-PCR	Negative	There is no reason to stop breastfeeding.
13/04/2020 10.1007/s11684-020-0772-y	Liu <i>et al.</i>	Case study	China	Breast milk	10	RT-PCR	Negative	Ten samples with negative results.
15/04/2020 10.1111/ajo.13173	Lowe & Dopp	Case report	Australia	Not informed	1	Not informed		Encouraging breastfeeding seems possible and safe.
05/05/2020 10.1111/1471-0528.16276	Wu <i>et al.</i>	Cohort study	China	Breast milk	3	RT-PCR	1 positive sample	Additional research isurgently needed.
21/05/2020 10.1016/S0140-6736(20)31181-8	Groß <i>et al.</i>	Case study	Germany	Breast milk	2	RT-qPCR	1 positive sample on days 10, 12 and 13	Further studies of milk samples are required.
30/05/2020 10.1093/cid/ciaa673	Tam <i>et al.</i>	Case study	Australia	Breast milk	1	RT-PCR	Positive	Despite detecting detected in human milk, do not interrupt breastfeeding.
8/05/2020 doi.org/10.101/2020.05.04.20089995	Fox <i>et al.</i>	Experimental study	USA	Breast milk	15	ELISA	Positive	80% of samples tested positive for IgA
17/06/2020 10.3201 / eid2606.200287	Li <i>et al.</i>	Case study	China	Breast milk	1	RT-PCR	Negative	Vertical transmission is improbable.
07/05/2020 10.1016/S2352-4642(20)30140-1	Piersigilli <i>et al.</i>	Case study	Belgium	Breast milk	1	RT-PCR	Negative	Breastfeeding has been ruled out as a transmission route.
11/04/2020 10.1016/j.jiph.2020.04.004	Peng <i>et al.</i>	Case study	China	Breast milk	1	RT-PCR	Negative	The test on breast milk was also negative.
12/02/2020 10.1016/S0140-6736(20)30360-3	Chen <i>et al.</i>	Medical record review	China	Breast milk	6	RT-PCR	Negative	All samples were negative for the virus.

Source: Elaborated by the authors.

Figure 2 - List representing the articles found by study design.



Legend: We considered the letters as the respective variables: *study design* (A), *breast milk sample* (B), *sample from the mother* (C), *uninformed sample* (D); *RT-PCR* (E), *RT-qPCR* (F) and *ELISA* (G) as analysis methodology or *uninformed methodology* (H) and *negative* (I), *positive* (J) or *uninformed* (K) results. To represent them, we organized the articles found into *case study* (A1), *cohort study* (B1), *case report* (C1), *experimental study* (D1) and *medical report review* (E1) and crossed them with the variables, presenting their respective results. Source: Elaborated by the authors.

After evaluating the studies, we can infer that: one study identified IgA reactivity in 80% of 15 breast milk samples obtained from donors previously infected with SARS-CoV-2 using the ELISA test. The others (13 case studies) used the RT-PCR analysis methodology for the detection of SARS-CoV-2 in breast milk. Thirty-two mothers were tested. Of these, 3 were positive, and one mother was positive in samples collected on 3 different days (10, 12, and 13).

Research where samples used were negative for SARS-CoV-2, adds that:

- Breast milk was negative, presumably excluding breastfeeding as a transmission route (Piersigilli, et al., 2020);
- In view of the negative result, additional examinations of maternal and newborn samples are considered necessary to

confirm this observation (Dong, et al., 2020);

- When SARS-CoV-2 is identified in both mother and child, there is no reason to stop breastfeeding and separate them. Whenever direct breastfeeding is not possible, the use of expressed breast milk should be considered and promoted to take advantage of its unquestionable benefits (Salvatori, et al., 2020);
- It considers that the mother can hypothetically produce enough neutralizing antibodies without developing severe conditions that may have a protective effect on infants through breastfeeding. However, it discourages breastfeeding even though no SARS-CoV-2 was detected in breast milk in the study (Fan, et al., 2020);
- Close attention should be paid to hand and breast hygiene during breastfeeding. Suspected cases, clinically diagnosed, not cured and confirmed cases are not recommended to breastfeed (Wang, et al., 2020).

Research that showed samples with positive results for SARS-CoV-2 suggests:

- Further studies of milk samples from breastfeeding women and possible virus transmission via breastfeeding are needed to develop recommendations to mothers with COVID-19 and the possibility of breastfeeding (Groß, et al., 2020);
- One of three breast milk samples was positive. However, additional research is urgently needed to examine breast milk and the potential risk of viral contamination (Wu, et al., 2020);
- Despite identified (RNA) virus detectable in human milk, adverse effects were nil (Tam, et al., 2020).

The test used in the samples of the 13 studies cited here, from different countries, was the RT-PCR, where positive and negative results were found for the presence of SARS-CoV-2 in breast milk. It was observed in this study that the researches of Fan et al. (2020) of Dong et al. (2020) and of Wang et al. (2020), did not demonstrate safety regarding the recommendation of breastfeeding by mothers with SARS-CoV-2, even in the face of the negative results of the RT-PCR tests, in their respective samples.

The research of Lowe and Dopp (2020), Salvatori et al. (2020), and Tam et al. (2020), consider that there is no reason to interrupt breastfeeding.

Ten breast milk samples from mothers with SARS-CoV-2 were obtained after the first lactation and tested negative, according to Liu et al. (2020). These results were also found by Peng et al. (2020) and Chen et al. (2020).

The research by Li et al. (2020), Piersigilli et al. (2020), and Tam et al. (2020), do not consider breastfeeding to transmit the new coronavirus.

According to Wu et al. (2020) and Groß et al. (2020), additional research is needed on breast milk samples and on breastfeeding as a transmission route.

It is important to note the non-validation of the RT-PCR methodology of analysis for human milk samples. No study detailed the processing of the samples, and no standardization for performing the test was identified in these studies.

A study of 15 breast milk samples obtained from donors previously infected with SARS-CoV-2, 80% exhibited reactivity for IgA. According to Fox et al. (2020), this study demonstrates a strong immune response to SARS-CoV-2, dominant in sIgA in human milk after infection.

There is no consensus among authors on the conduct for breastfeeding by mothers with SARS-CoV-2. Although some studies identify the presence of the virus in breast milk and consider breastfeeding to be a possible route of transmission of the new coronavirus, most studies recommend breastfeeding.

No conclusive studies were found on the presence of IgM, IgG, and IgA antibodies in breast milk and no studies were

located on testing in colostrum from mothers with COVID-19.

The absence of robust evidence on the transmission of the new coronavirus through breast milk makes the guidelines about the safety of breastfeeding and milk donation for women diagnosed with COVID-19 non-consensual so far. The articles studied comprise publications available between February and June 2020, aimed at testing for SARS-CoV-2 in breast milk samples. Most of these papers analyzed other samples (saliva, amniotic fluid, urine, and feces) from mothers and infants. There is a lack of studies in the literature so far on the detection of antibodies in breast milk.

We can observe, through this systematic review, negative and positive results for SARS-CoV-2 in the analysis of milk samples, which raise more questions about the action of this virus in breast milk and consequences for the baby's health. The positive samples by the RT-PCR method raise doubts about the potential infectious risk for the child and whether this method has been validated for these samples.

The WHO guides breastfeeding even in the face of these uncertainties. Therefore, more studies are needed in the area of antibody detection in breast milk to understand the immune response to SARS-CoV-2 and the safety of breastfeeding for both mother and baby.

4. Final Considerations

This study was conducted in a context where COVID-19 vaccines were not available and where breastfeeding was a possible transfer of antibodies to infants. Our study concluded that no completed research involving serological testing for antibodies in human colostrum was located. Therefore, more serological studies on breastfeeding are needed. We suggest that future studies on the topic should attempt to demonstrate that breastfeeding induces a better immune response to SARS-CoV-2 infection.

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