Titres and neutralising capacity of SARS-CoV-2-specific antibodies in human milk: a systematic review

Jia Ming Low [1,2] Yue Wey Low,[3] Youjia Zhong,[2,4] Cheuk Yiu Charlotte Lee,[5] Ming Chan,[5] Nicholas Beng Hui Ng [2,4] Zubair Amin [1,2] Yvonne Peng Mei Ng [1,2]

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/archdischild-2021-322156).

[1]Neonatology, Khoo Teck Puat-National University Children's Medical Institute, National University Health System, Singapore
[2]Paediatrics, National University Singapore, Yong Loo Lin School of Medicine, Singapore
[3]Yong Loo Lin School of Medicine, National University of Singapore, Singapore
[4]Khoo Teck Puat – National University Children's Medical Institute, National University Health System, Singapore
[5]Alice Lee Centre for Nursing Studies, National University of Singapore, Singapore

Correspondence to
Dr Zubair Amin, Neonatology, Khoo Teck Puat-National University Children's Medical Institute, National University Health System, 119228, Singapore; paeza@nus.edu.sg

Received 28 March 2021
Accepted 23 June 2021

To cite: Low JM, Low YW, Zhong Y, *et al*. *Arch Dis Child Fetal Neonatal Ed* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/archdischild-2021-322156

ABSTRACT

Objective Synthesise evidence on production of SARS-CoV-2 antibodies in human milk of individuals who had COVID-19, and antibodies' ability to neutralise SARS-CoV-2 infectivity.

Design A systematic review of studies published from 1 December 2019 to 16 February 2021 without study design restrictions.

Setting Data were sourced from PubMed, MEDLINE, Embase, CNKI, CINAHL and WHO COVID-19 database. Search was also performed through reviewing references of selected articles, Google Scholar and preprint servers. Studies that tested human milk for antibodies to SARS-CoV-2 were included.

Patients Individuals with COVID-19 infection and human milk tested for anti-SARS-CoV-2 neutralising antibodies.

Main outcome measures The presence of neutralising antibodies in milk samples provided by individuals with COVID-19 infection.

Results Individual participant data from 161 persons (14 studies) were extracted and re-pooled. Milk from 133 (82.6%) individuals demonstrated the presence of anti-SARS-CoV-2 immunoglobulin A (IgA), IgM and/or IgG. Illness severity data were available in 146 individuals; 5 (3.4%) had severe disease, 128 (87.7%) had mild disease, while 13 (8.9%) were asymptomatic. Presence of neutralising antibodies in milk from 20 (41.7%) of 48 individuals neutralised SARS-CoV-2 infectivity in vitro. Neutralising capacity of antibodies was lost after Holder pasteurisation but preserved after high-pressure pasteurisation.

Conclusion Human milk of lactating individuals after COVID-19 infection contains anti-SARS-CoV-2-specific IgG, IgM and/or IgA, even after mild or asymptomatic infection. Current evidence demonstrates that these antibodies can neutralise SARS-CoV-2 virus in vitro. Holder pasteurisation deactivates SARS-CoV-2-specific IgA, while high-pressure pasteurisation preserves the SARS-CoV-2-specific IgA function.

What is already known on this topic?

► Human milk of lactating individuals with COVID-19 infection contains anti-SARS-CoV-2-specific immunoglobulin G (IgG), IgM and/or IgA.

What this study adds?

► Evidence demonstrates that these antibodies from human milk of lactating individuals can neutralise SARS-CoV-2 virus in vitro.
► Widely used Holder pasteurisation deactivates SARS-CoV-2-specific IgA, while high-pressure pasteurisation preserves antibody activity.

INTRODUCTION

Neonates can contract COVID-19 infection via vertical transmission or acquire it from the community.[1] While the risk of vertically transmitted COVID-19 infection to the neonate appears to be low,[2–4] neonates who get infected de novo were more likely to develop severe disease compared with older children.[5 6]

Human milk offers protection against gastrointestinal and respiratory tract infections.[7 8] A meta-analysis[9] in October 2020 showed that SARS-CoV-2 genome is generally not found in human milk of COVID-19 infected individuals, yet SARS-CoV-2 antibodies are produced in human milk.[9] Since then, there have been further studies investigating the characteristics of the SARS-CoV-2-specific antibodies in human milk, providing valuable information on the functional and kinetic details of these antibodies. This information is critical to evaluate whether these antibodies protect at-risk neonates from COVID-19 infection.

A thorough understanding of SARS-CoV-2 antibodies in human milk would provide support to the recommendation for infected individuals to continue breast feeding.[10–12] An overview of the functional and kinetic features of COVID-19 infection-induced antibodies secreted will help investigators design studies to investigate antibody production induced by vaccination. This would guide recommendations on vaccination of lactating individuals and if human milk in vaccinated mothers may confer protection to their infants. Hence, we conducted this review to examine the presence, isotypes and binding characteristics of antibodies against SARS-CoV-2 in human milk, and to assess the neutralising capacity of these antibodies in vitro.

MATERIALS AND METHODS

Design

A systematic review protocol was developed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P)[13] and registered in the International Prospective Register of Systematic Reviews (PROSPERO database registration number: CRD42020213075).

Search strategy

Articles were retrieved from PubMed, MEDLINE, Embase, China National Knowledge Infrastructure, CINAHL and WHO COVID-19 database. We searched for grey literature through Google Scholar, preprint servers (ie, Research Square, medRxiv) and screened through the reference lists. Studies in which human milk was tested for SARS-CoV-2 antibodies from 1 December 2019 to 16 February 2021 were included. The strategy was developed for PubMed/MEDLINE using keywords and MeSH (MEDLINE) terms then adapted to other databases (online supplemental material 1). The search strategy included broad terms of human milk immunity and infection among lactating individuals with COVID-19. Search terms included 'COVID-19, Severe Acute Respiratory Syndrome Coronavirus 2, SARS-CoV-2, Novel Coronavirus, 2019-nCov, Wuhan pneumonia', 'antibodies, neutralising antibodies, IgG, IgA, breastmilk, human milk, passive transfer' and 'pregnancy, pregnant women, mother, fetus, neonate, newborn, infant'.

Eligibility criteria and study selection

Two reviewers (JML and YWL) independently screened titles and abstracts, and full-text articles were assessed for inclusion. A third reviewer (NBHN) resolved any disagreements on study eligibility. Study authors were contacted for clarification if information on eligibility was unavailable/unclear. Inclusion criteria were lactating individuals with laboratory-confirmed COVID-19 infection using either quantitative real-time reverse transcription PCR (qRT-PCR) for SARS-CoV-2, or immunoassay such as ELISA for SARS-CoV-2 specific immunoglobulin G (IgG)/immunoglobulin M (IgM), who were infected during pregnancy or postpartum period. To ensure a comprehensive search on this topic, it was determined a priori that the review would include case reports, case series, cohort, case–control, cross-sectional studies and clinical trials. Review articles or articles written based on secondary data were excluded.

Data management and extraction

Citations of articles retrieved from database searches were exported into EndNote software V.X7 where duplicates were removed. Two reviewers (JML and YWL) independently extracted individual participant data from selected articles. Primary endpoint was presence of SARS-CoV-2-specific IgG and/or IgA in human milk of individuals with active COVID-19 or convalesced from COVID-19; where data regarding IgM were reported, these data were extracted.

Quality appraisal of included studies

The Murad reporting tool was used to assess quality of case series and case reports which include eight items under four domains (selection, ascertainment, causality, reporting).[14] Two reviewers (YWL and JML) completed the quality appraisal, with a third reviewer (NBHN) resolving inconsistencies.

RESULTS

One hundred and three articles were obtained from the systematic search and five articles from other sources (ie, reference lists of selected articles). After excluding duplicates and screening for titles and abstracts for articles that met inclusion criteria, 14 articles[15–28] were analysed; 6 were case reports, 3 were case–control studies, 5 were case series (table 1). Flow diagram is presented in figure 1.

Quality assessment of included studies

Six studies fulfilled all domains, while 8 studies fulfilled three domains in quality assessment. Quality selection for the domain of subject selection was high in six studies (42.9%) with low risk of sampling bias where patients represented the whole experience of the investigator/centre. All studies diagnosed SARS-CoV-2 infection using RT-PCR and/or ELISA (ascertainment of exposure), and accurately ascertained outcome measures. All studies described cases with sufficient details for replication or allow practitioners to make inferences related to their own practice (high quality) (online supplemental material 2).

Demographics and clinical manifestations of lactating individuals with SARS-CoV-2 infection

Individual participant data from 161 subjects who had human milk tested for SARS-CoV-2 antibodies following COVID-19 infection were extracted and pooled for reanalysis. COVID-19 was diagnosed with qRT-PCR test in 156 (96.9%) individuals[15–19 22 23 25 27 28] and by ELISA in 5 (3.1%) individuals.[19 20] Ninety-two individuals (57.1%) had antenatal COVID-19 infection, mostly in the second and third trimesters,[15 17–20 23 25] while the remaining 69 (42.9%) contracted COVID-19 infection in the postpartum period.[16 18 22 27 28]

COVID-19 disease severity was defined according to the WHO COVID-19 severity criteria.[29] Illness severity data were available in 146 women from nine studies; 5 (3.4%) had severe disease, 128 (87.7%) had mild disease (ie, fever, loss of smell/taste, headache and fatigue), while 13 (8.9%) were asymptomatic. Samples were collected between 1 and 195 days post COVID-19 infection. Repeated samples were collected from most participants.

The type of infant feeding was stated in 110 individuals; 66 (60.0%) were breast feeding exclusively,[16 17 19 20 22 24 26 27] 31 (28.2%) breastfed and supplemented their infants with formula milk,[21–23] and 13 (11.8%) fed only formula to their infants.[17] Four infants were infected with COVID-19; three were likely a result of vertical transmission. One infant was symptomatic at the same time as his mother via community transmission.[15 23 27] All four infants were breastfed and had mild disease.

Anti-SARS-CoV-2 immunoglobulin A (IgA), IgM and IgG in human milk

One hundred and thirty-three of 161 (82.6%) individuals had either anti-SARS-CoV-2 IgA, IgM or IgG in human milk.[15–19 22 25 27 28] Eighty-six of 161 (53.4%) individuals had human milk tested for SARS-CoV-2 IgA. One hundred and forty-four of 161 (89.4%) individuals had human milk tested for SARS-CoV-2 IgG. Human milk from 106 of 144 individuals (73.6%) contained SARS-CoV-2-specific IgG,[15–17 19 22 25 27 28] and human milk from 69 of 86 (80.2%) individuals contained SARS-CoV-2-specific IgA.[15 16 18 20 22 28] Twenty-nine out of 71 (40.8%) samples contained SARS-CoV-2 IgM.[17–19 21 23 26–28] The longest duration of antibody persistence in human milk reported from onset of COVID-19 infection until end of study was 195 days in a single individual (table 2).[16]

Specific IgG antibodies against the nucleocapsid protein and spike protein regions of the virus (ie, anti-SARS-CoV-2

Table 1 Demographics and clinical manifestations of lactating individuals with COVID-19 infection

Author	Publication date	Country	n=X	Study type	Diagnosis of COVID-19 in individual	Timing of COVID-19 infection	Illness severity	Infant's age at collection of milk sample	Feeding mode	Infected infants	Timing of milk collection (active infection/ convalescent/ unknown)
Dong *et al*[15]	March 2020	China	1	Case report	RT-PCR	Antenatal	Mild	<28 days (term baby)	Formula fed	0	Active infection and convalescent
Luo *et al*[21]	June 2020	China	4	Case series	RT-PCR	Antenatal	1 asymptomatic; 3 mild	<28 days (term baby)	Mixed feeding with formula	0	Unknown
Walczak *et al*[26]	July 2020	Australia	1	Case report	RT-PCR	Antenatal	Mild	<28 days (term baby)	Breastfed	0	Unknown
Yu *et al*[27]	August 2020	China	1	Case report	RT-PCR	Postnatal	Mild	13 months old	Breastfed	1	Active infection and convalescent
Lebrão *et al*[20]	August 2020	Brazil	1	Case report	ELISA	Antenatal	Severe	<28 days (term baby)	Breastfed	0	Convalescent
van Keulen *et al*[25]	August 2020	Netherlands	29	Case–control	RT-PCR	Postnatal	Mild	1.5 months old	Not stated	Not stated	Likely active infection and convalescent
Gao *et al*[19]	September 2020	China	14	Case Series	10 by RT-PCR; 4 by ELISA	Antenatal	Mild	<28 days (term baby)	Breastfed	1	Likely active infection
Julia Preßler *et al*[24]	October 2020	Germany	14	Case Series	RT-PCR	Antenatal	Mild	<28 days (Term baby)	Breastfed	0	Unknown
Fenizia *et al*[17]	October 2020	Italy	31	Case-control	RT-PCR	Antenatal	4 severe; 27 mild	<28 days (all term babies except 1 preterm at gestational age of 34+4 weeks)	29 breastfed; 2 formula fed	2	Likely active infection
Peng *et al*[23]	November 2020	China	24	Case Series	RT-PCR	Antenatal	15 mild; 9 asymptomatic	<28 days (7 preterm; 17 term)	14 mixed feeding; 10 formula fed	0	Active infection and convalescent
Favara *et al*[16]	November 2020	UK	1	Case report	RT-PCR	Postnatal	Mild	6 months old	Breastfed	0	Active infection and convalescent
Fox *et al*[18]	November 2020	USA	15	Case series	RT-PCR	2 antenatal; 13 postnatal	Not stated	Data not collected	Not stated	Not stated	Unknown
Pace *et al*[22]	February 2021	USA	18	Case series	RT-PCR	Postnatal	3 asymptomatic; 15 mild	Not stated	5 breastfed; 13 mixed feeds	0	Active infection
Demers-Mathieu *et al*[28]	February 2021	USA	7	Case–control	RT-PCR	Postnatal	7 mild	Not stated	Not stated	Not stated	Convalescent

RT-PCR, reverse transcription PCR.

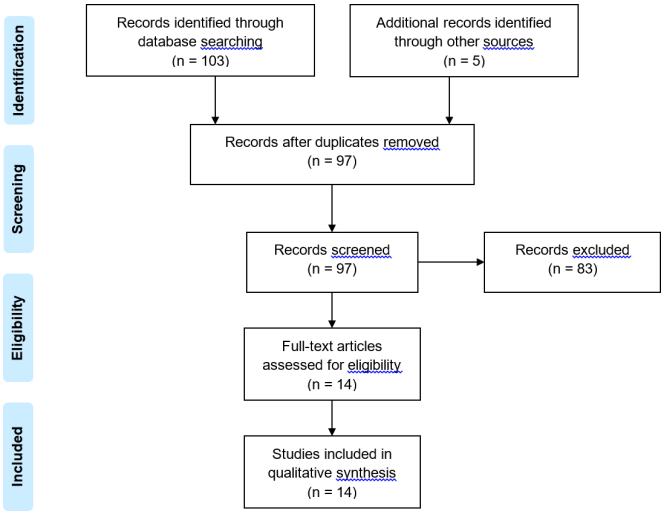

Figure 1 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart. (Editor to note: 1. Kindly remove blue underlines from various words in the boxes like searching, removed, screened, eligibility, synthesis, excluded. 2. Kindly remove the word "qualitative" from the bottom box)

nucleocapsid IgG and anti-SARS-CoV-2 S2 IgG) was present in all 48 samples tested.

Anti-SARS-CoV-2 nucleocapsid IgA was present in human milk samples provided by 51 of 56 (91.1%) individuals. Antibody reactivity against the receptor-binding domain (RBD) of the SARS-CoV-2 spike protein was present in human milk samples provided by 55 of 63 (87.3%) individuals.

Anti-SARS-CoV-2 spike IgM was found in human milk of 12 of 23 (52%) individuals who were evaluated for this.

Included studies mostly used ELISA to determine presence of specific IgA, IgM and IgG. A study used microsphere immunoassay and two studies used an unspecific chemiluminescence assay (table 2).

The neutralising capacity of human milk

The neutralising capacity of human milk against SARS-CoV-2 was tested in three studies (table 3). Samples from 20 of 48 individuals (41.7%) were found to neutralise SARS-CoV-2 infectivity in vitro.[16 22 25] In two studies, the neutralising capacity of these samples was also tested before and after pasteurisation using two methods, that is, Holder pasteurisation and high-pressure pasteurisation.[16 23 25] Holder pasteurisation uses heat treatment at 62.5°C for 30 min and is traditionally used in donor banks, whereas high-pressure pasteurisation is an alternative method which inactivates pathogens using cold water and hydrostatic pressure with no heat-induced damage to the milk.[30]

Van Keulen *et al*[25] used a SARS-CoV-2 clinical isolate on modified Vero E6 cells to interrogate neutralising activity using 50% neutralising titres as the endpoint. Unsurprisingly, viral neutralisation was better in the presence of higher IgA levels in human milk. Non-pasteurised and high pressure pasteurised samples were effective at neutralising the virus. However, samples treated by Holder pasteurisation lost neutralising capacity.[25]

Favara *et al* performed neutralisation assays on antibodies in human milk using a SARS-CoV-2 S-antigen-expressing pseudovirus.[16] IgA was the predominant antibody isotype found. The antibodies in the human milk sample were strongly neutralising but showed reduced neutralising capacity after Holder pasteurisation.[16]

Pace *et al* showed that 21 of 34 (61.7%) samples possessed neutralising capacity[22] using microneutralisation assays (Vero E6/TMPRSS2 cells), with 50% neutralising titres as the readout. Through a multivariable regression model, it was found that neutralisation was mainly mediated by anti-RBD IgA antibodies. Samples in this study were unpasteurised.[22]

In summary, the viral neutralising capacity of human milk was evaluated after Holder pasteurisation in the samples from 30 individuals[16 25] and high-pressure pasteurisation in samples from 29 individuals.[25] Although IgA levels as measured by ELISA remained unchanged, the neutralising function was significantly reduced or lost after Holder pasteurisation. High-pressure pasteurised-treated milk was effective at neutralising the virus.

DISCUSSION

This review summarises data of 161 lactating individuals with COVID-19 infection, extracted from 14 papers focusing on presence, isotype and binding characteristics of anti-SARS-CoV-2 antibodies in human milk, and neutralising capacity of human milk in vitro. Neutralisation is the ability of an antibody to block the infection process. In the context of COVID-19, this translates into the ability of an antibody to bind to the RBDof the surface spike proteins of SARS-CoV-2 and preventing its interaction with the ACE-2 receptor of target cells like respiratory epithelial cells.[28] By preventing infection of target cells, the neutralising activity of such antibodies is likely to correlate with immunity against future infection.

Despite majority (96.6%) of individuals only having mild or asymptomatic COVID-19 disease, most produced detectable SARS-CoV-2-specific antibodies (of either IgG, IgA or IgM subtype) in human milk. This is consistent with time to seroconversion in serum IgG responses after mild COVID-19 infections.[31] The potential protective capacity of human milk may also be long lasting, reported duration of milk antibody is currently 195 days after infection in one individual. While durations from first infective symptoms until testing of antibody are reported in table 2, median durability of human milk antibody production could not be reported due to heterogeneity of reporting.

Antigen-specific antibodies are enriched in human milk; of these isotypes, generally about 90% of the total antibodies is secretory IgA. IgA is the predominant antibody isotype conferring mucosal immunity and passive transfer during breast feeding would patrol mucosal surfaces of the breastfeeding infant for potential pathogens.[32] In our review, 82.6% of lactating individuals demonstrated presence of SARS-CoV-2 antibodies in human milk. In terms of isotype, milk of 62 of 79 (78.5%) tested individuals contained SARS-CoV-2-specific IgA. In fact, it has been demonstrated that for SARS-CoV-2, the majority of antibodies (60%) are IgA or secretory IgA.[33] As majority of studies in our review did not test for the presence of IgA, the true proportion of individuals who have SARS-COV-2-specific IgA is likely to be higher.

In terms of specificity, milk of 63 of 154 women were tested for RBD-specific antibodies, and the majority (87.3%) were found to be positive. Many studies found nucleocapsid and S2 subunit specific IgG or IgA, with a positivity ranging from 78.8% to 100%. Since these antibodies can be cross-reactive with non-SARS-CoV-2 coronaviridae, it is unclear whether these antibodies may confer protection against SARS-CoV-2.[28 34] Ultimately, neutralisation assays are the gold standard for estimation of functional capacity of antibodies. Although neutralisation tends to correlate with RBD-specific antibody levels in various serological studies,[35] our review found that only 20 of

Table 2 SARS-CoV-2 antibody tests of human milk in included studies

Author	n=X	Method used	SARS-CoV-2 IgG (unspecified)	Anti-SARS-CoV-2 nucleocapsid IgG	Anti-SARS-CoV-2 S2 IgG	Anti-SARS-CoV-2 IgA (unspecified)	Anti-SARS-CoV-2 nucleocapsid IgA	SARS-CoV-2 IgM (unspecified)	Anti- SARS-CoV-2 spike protein IgM	Total antibody reactivity against the RBD of the SARS-CoV-2 spike protein	SARS-CoV-2 neutralisation ability	Interval between onset of symptoms and presence of antibody	Duration antibody persisted from onset of COVID-19 until end of study
Dong *et al*[15]	1	ELISA. Specificity: S-protein.	Yes	NA	NA	Yes	NA	NA	NA	NA	NA	26 days	42 days
Yu *et al*[27]	1	Not stated	Yes	NA	NA	NA	NA	Yes	NA	NA	NA	30 days	30 days
Luo *et al*[21]	1	ELISA. Specificity: not stated.	No	NA	NA	No	NA	100%, 4/4 individuals	NA	NA	NA	7 days	Not known
Walczak *et al*[26]	1	Microsphere immunoassay. Specificity: not stated.	Yes	NA	NA	No	NA	Yes	NA	NA	NA	10 days	25 days
Lebrão *et al*[20]	1	ELISA Specificity: Not stated	No	NA	NA	Yes	Yes	NA	NA	NA	NA	3 days	6 days
van Keulen *et al*[25]	29	ELISA and bridging ELISA. Specificity: S-protein, RBD and N protein.	Yes	Yes	Yes	83%; 24 individuals	83%; 24 individuals	NA	NA	83%; 24 individuals	28%; 8 individuals	Mean 5.9 (SD 2.6) weeks	Not known
Gao *et al*[19]	14	Chemiluminescence immunoassay. Specificity: not stated.	Yes	NA	NA	NA	NA	14%, 2 individuals	NA	NA	NA	17–22 days	28 days
Preßler *et al*[24]	14	Not stated. Specificity: nucleocapsid.	14%; 2 individuals	NA	NA	14%; 2 individuals	NA	NA	NA	NA	NA	14 days	Not known
Fenizia *et al*[17]	31	Chemiluminescence immunoassay. Specificity: nucleocapsid and S-protein.	Yes	NA	NA	NA	NA	10%, 1/10 individuals	NA	NA	NA	Not known	Not known
Peng *et al*[23]	24	ELISA. Specificity: not stated.	Negative	NA	NA	NA	NA	42.1%, 8/19 individuals	NA	NA	NA	3–79 days	1–70 days
Favara *et al*[16]	1	Not stated. Specificity: N-antigen, S-antigen and RBD-antigen.	Yes	Yes	Yes	Yes	Yes	NA	NA	Yes	Yes	28 days	195 days
Fox *et al*[18]	15	ELISA. Specificity: trimeric S-protein, RBD of S-protein	NA	NA	NA	Yes	NA	33.3%, 5 individuals	33.3%, 5 individuals	80%; 12 individuals	NA	Not known	Not known
Pace *et al*[22]	18	ELISA. Specificity: Spike (S2 and RBD) and nucleocapsid.	Yes	Yes	Yes	Yes	Yes	NA	NA	Yes	62%;11 individuals	0–22 days (3 asymptomatic)	Not known
Demers-Mathieu *et al*[28]	7	ELISA. Specificity: Spike (S1 or S2)	100%; 7 individuals	NA	100%; 7 individuals	100%; 7 individuals	NA	100%; 7 individuals	100%; 7 individuals	NA	NA	Mean 47 (SD 24) days	Not known
Number of individuals who tested positive for antibodies/individuals who were tested for antibodies (%)			106/144 (73.6%)	48/48 (100%)	55/55 (100%)	69/86 (80%)	44/49 (89.8%)	29/71 (40.8%)	12/22 (54.5%)	55/63 (87.3%)	20/48 (41.6%)		

NA, not tested; RBD, receptor binding domain; S-protein, spike protein.

Table 3 Neutralising SARS-CoV-2 antibodies of human milk in included studies

Author	Neutralisation assay	Number of individuals	Neutralising threshold	Pasteurisation methods	SARS-CoV-2 neutralisation	Correlation of neutralisation abilities	Ratio of neutralisation IC_{50} values of serum: human milk	Ratio of neutralisation IC_{50} values of serum: human milk after Holder pasteurisation
Van Keulen *et at*[25]	SARS CoV-2 clinical isolate on Vero E6 cell lined-based pseudovirus	29	50% as compared with control	Holder and high-pressure	26%; 8 individuals	Higher neutralisation titres correlated with higher concentration of IgA	NA	NA
Favara *et al*[16]	SARS-CoV-2 S-antigen-expressing pseudovirus	1	50% as compared with control	Holder	Yes	NA	1:1	Neutralisation decreased to 20% from pre-Holder pasteurisation
Pace *et al*[22]	Microneutralisation assays (using Vero E6/TMPRSS2 cells)	18	50% as compared with control	Not done	61%;11 individuals	Higher neutralisation titre were correlated with higher concentration of RBD-reactive IgA	NA	NA

NA, not tested; RBD, receptor binding domain; S-protein, spike protein.

48 subjects (41.7%) with positive antibodies could neutralise SARS-CoV-2 infectivity in vitro. This underscores the importance of performing functional characterisation of antibodies and not just quantitative analysis.

At present, there is a lack of standardisation for neutralisation assays. While the US Food and Drug Administration (FDA) has issued recommendations on titres of neutralising antibodies in convalescent plasma, it did not specify the level of virus neutralisation that should be achieved at these titres or how to measure it.[36] In addition, several strains of pseudovirus and live SARS-COV-2 variants, and modified target cells, are being used to measure neutralisation in laboratories.[25] Studies in our review also used multiple methods to determine neutralising activity of human milk antibodies, rendering it difficult to compare antibody function across studies. To be able to compare antibody function across centres, such standardisation is urgently needed. There is also uncertainty on whether in vitro neutralisation correlates with in vivo protection against infection.

The study of SARS-CoV-2-specific neutralisation capacity of human milk has presented a unique opportunity to revisit methods of pasteurisation that are used in donor human milk banks (HMB) worldwide. Holder pasteurisation is recommended in all international HMB guidelines.[37] It has been shown to effectively inactivate SARS-CoV-2 in human milk.[38] However, our review shows that Holder pasteurisation significantly reduces neutralisation capacity of SARS-CoV-2-specific IgA. The high temperature of 62.5°C has been shown to denature secretory IgA.[39] The issue of Holder pasteurisation being detrimental to the bioactivity of human milk deserves to be revisited, and alternative methods such as high-pressure pasteurisation should be judiciously explored for HMBs. At present, data are scarce on the safety for microbiological control for alternative methods of pasteurisation.[40]

As COVID-19 immunisations are rolled out, the risk–benefit ratio of vaccinating lactating mothers remains unclear owing to paucity of real-world data. However, in the context of a pandemic, the American College of Obstetricians and Gynaecologists[41] recommends that vaccines be offered to lactating individuals, based on the principle[42] that non-live vaccines are safe in lactation in general. Studies have shown that lactating individuals who received the mRNA vaccines have SARS-CoV-2-specific antibodies in human milk for up to 6 weeks after vaccination.[43] If human milk post vaccination is found to contain SARS-CoV-2-specific IgA with neutralizing function, this would lend further strengths to the recommendation to vaccinate lactating mothers. Since the kinetics of antibody production after natural infection and vaccination are closely related, our review informs future studies on this.

In summary, this review provides a snapshot of a dynamic milk immune response in lactating individuals with COVID-19. The majority of lactating individuals with COVID-19 produce human milk containing SARS-CoV-2-specific IgA, which in about half demonstrate in vitro neutralisation capacity. Larger studies on the quantity, function and durability of SARS-CoV-2-specific antibodies in human milk from COVID-19 convalescent and vaccinated individuals are warranted. More studies are required to determine if these antibodies confer passive immunity to breastfed infants.

Acknowledgements The authors wish to thank Dr Dimple Rajgor for helping with reviewing, formatting and in submission of the manuscript for publication.

Contributors JML and YWL designed, analysed and interpreted the data. CYCL, MC and NBHN drafted the work and contributed to the design and conception of the study. JML, ZA, YPN and YZ analysed and revised the manuscript critically for important intellectual content.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplemental information. The data were extracted from the published literature. The details of all such literature used are included in the manuscript.

ORCID iDs
Jia Ming Low http://orcid.org/0000-0002-4351-8606
Nicholas Beng Hui Ng http://orcid.org/0000-0002-7948-8891
Zubair Amin http://orcid.org/0000-0002-4430-5012
Yvonne Peng Mei Ng http://orcid.org/0000-0003-0497-0306

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