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Review

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Antibodies Against SARS-CoV-2 in Human Breast Milk After Vaccination: A Systematic Review and Meta-Analysis

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Abstract

Background: CDC guidelines have recommended coronavirus disease-19 (COVID-19) vaccination for all people 5 years and older, including people who are breastfeeding. Breast milk has shown to be a valuable source of protection for immune-immature neonates. It has been shown that breast milk from mothers who have received vaccinations can transfer antibodies.
Aim/Objective: This systematic review and meta-analysis investigate the presence of antibodies to SARS-CoV-2 in human breast milk after vaccination.
Methods: Studies that evaluated immunoglobulins in breast milk of women receiving a SARS-CoV-2 vaccination were included. PubMed, Embase, Web of Science were searched for articles published between December 1, 2019 and September 30, 2021. Data from relevant articles were extracted manually or by WebPlotDigitizer version 4.1 to obtain the numeric values of antibody levels on peak days and the peak day then condensed into Excel. Additional raw data and information were supplied by corresponding authors.
Results: One hundred ninety-two articles were obtained from the search. After excluding duplicates, screening titles and abstracts, 18 cohort studies were identified. For the rate of SARS-CoV-2 antibodies in breast milk after the first vaccine dose but before the second vaccine dose, we found 64% (95% CI 51–78%) were positive for IgA and 30% (95% CI 13.1–46%) were positive for IgG. For the rate for SARS-CoV-2 antibodies in breast milk after the second vaccine dose, we found 70% (95% CI 55–86%) were positive for IgA and 91% (95% CI 80–103%) were positive for IgG.
Conclusions: Our analysis of the data published worldwide showed high rates of positivity for antibodies in breast milk following COVID-19 immunizations. Further research is necessary to find if the rate of positivity of IgA and IgG against SARS-CoV-2 in breast milk persists months after the full immunization, and their impact on the prevention of SARS-CoV-2 infection in infants.

Keywords: breast milk, SARS-CoV-2, COVID-19, antibodies

Introduction

With the arrival of immunizations to prevent the coronavirus disease-19 (COVID-19), there has been concern of whether the vaccine is safe to administer to breastfeeding mothers. Current CDC guidelines recommend COVID-19 vaccination for all people 5 years and older, including people who are breastfeeding, although there is limited data on the effect of these vaccines on breastfeeding mothers, infants, and their effects on milk production.[1]

Breast milk has been shown to be a valuable source of protection for immune-immature neonates.[2] Secretory IgA, and to a lesser extent IgG, are both secreted in breast milk and aid in protection against illnesses, for example, acute and prolonged diarrhea, respiratory tract infections, otitis media, urinary tract infection, neonatal septicemia, and necrotizing

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enterocolitis.[2,3] Furthermore, research has shown the transfer of these antibodies through breast milk in mothers who have received vaccinations.[4]

Two mRNA vaccines, BNT162b2 Pfizer/BioNTech and mRNA-1273 Moderna, and the adenovirus vector vaccine, Ad26 J&J/Janssen, are currently available in the United States for COVID-19 immunization. Access to any of these vaccines is recommended for children older than 5 years of age, leaving a public health void in infant, toddlers, and the preschool population. Fifty percent of children infected with SARS-CoV-2 are infants.[5] Although 43% of children appeared to be asymptomatic, 7% of children require ICU admission. Protection for infants is, therefore, paramount, so great amount of research is undergoing to keep this group safe. Studies on breastfeeding population began in late 2020, once emergency vaccine authorization was given by the Food and Drug Administration, after evaluating the safety and benefit of vaccinating breastfeeding women.[6]

In this systematic review and meta-analysis, we evaluated the current available literature regarding the presence of antibodies to SARS-CoV-2 in human breast milk after vaccination.

Methods

The study was conducted according to the Meta-analysis of Observational Studies in Epidemiology guidelines and reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[7]

Eligibility criteria

Studies that evaluated immunoglobulins in breast milk of women receiving a SARS-CoV-2 vaccination were included. The included studies were nonrandomized, prospective cohort studies with any COVID-19 vaccine administered before or after birth to mothers planning to breastfeed. Studies were excluded if they did not report one of three variables: the percent of women with either IgA- or IgG-positive breast milk; IgA or IgG titers; or IgA or IgG ratios as determined by enzyme-linked immunosorbent assay. Studies were also excluded if they were case studies, reviews, meta-analysis, or articles focused only on mother with preexisting conditions.

Search strategy

PubMed, Embase, and Web of Science were searched for articles published between December 1, 2019 and September 30, 2021. Additional search from bibliographies of relevant articles was conducted. No language restrictions were applied. Search terms included ''SARS-CoV-2, COVID'', ''breast milk, breastfeeding'', ''antibody, Immunoglobulin, IgA, IgG'', ''Vaccine, vaccination, Moderna, Pfizer, and J&J.'' Two authors (N.W. and J.C.) performed the literature search and review. Conflicts were decided by consensus.

Data collection

The following variables were collected from studies: authors, publication year, study design, sample size, previous or current SARS-CoV-2 infection, vaccination manufacturer,

TABLE 1. PERCENT OF SUBJECTS WITH BREAST MILK POSITIVE FOR IGA AFTER FIRST AND SECOND DOSE OF VACCINE

Author, year (country)	*Design*	N	*COVID-19 test result*	*Vaccine manufacturer*	*Positivity after 1st dose (%)*	*Collection after 1st dose*	*Positivity after 2nd dose (%)*	*Collection after 2nd dose (days)*
Baird et al., 2021 (US)[10]	Single-center, cohort	7	N.P.	Moderna/Pfizer			100	11
Calil et al., 2021 (Sao Paulo)[11]	Single-center, cohort	16	Negative	CoronaVac			62.5	49
Charepe et al., 2021 (Portugal)[12]	Single-center, cohort	14	Unknown	Pfizer	35.7	9.5 days	21.4	10
Collier et al., 2021 (US)[13]	Single-center, cohort	16	Positive in 1/16	Moderna/Pfizer			43.8	26
Fox et al., 2021 (US)[14]	Single-center, cohort	50	N.P.	Moderna/Pfizer/J&J			50	14
Golan et al., 2021 (US)[15]	Single-center, cohort	48	Negative	Moderna/Pfizer	75	3–4 weeks	75	17–74
Juncker et al., 2021 (Netherlands)[16]	Single-center, cohort	26	Positive in 1/26	Pfizer	80	15 days	100	7
Kelly et al., 2021 (US)[17]	Single-center, cohort	5	Negative	Pfizer			100	30–39
Low et al., 2021 (Singapore)[18]	Single-center, cohort	14	N.P.	Pfizer	71	7–10 days	90	3–7
Perl et al., 2021 (Israel)[19]	Single-center, cohort	84	Unknown	Pfizer	61.8	14 days	86.1	7
Romero et al. 2021 (Spain)[20]	Multicenter, cohort	93	N.P.	Moderna/Pfizer			89	14
Valcarce et al., 2021 (US)[21]	Single-center, cohort	22	N.P.	Moderna/Pfizer			85	7–10

N.P., never performed.

TABLE 2. PERCENT OF SUBJECTS WITH BREAST MILK POSITIVE FOR IGG AFTER FIRST AND SECOND DOSE OF VACCINE

Author, year (country)	*Design*	N	*COVID-19 test result*	*Vaccine manufacturer*	*Positivity after 1st dose (%)*	*Collection after 1st dose*	*Positivity after 2nd dose*	*Collection after 2nd dose (days)*
Baird et al., 2021 (US)[10]	Single-center, cohort	7	N.P.	Moderna/Pfizer			100	11
Charepe et al., 2021 (Portugal)[12]	Single-center, cohort	14	Unknown	Pfizer	7.1	9.5 days	42.9	10
Collier et al., 2021 (US)[13]	Single-center, cohort	16	Positive in 1/16	Moderna/Pfizer			75	26
Fox et al., 2021 (US)[14]	Single-center, cohort	50	N.P.	Moderna/Pfizer/J&J			86	14
Golan et al., 2021 (US)[15]	Single-center, cohort	48	Negative	Moderna/Pfizer	51.4	3–4 weeks	95.8	17–74
Jakuszko et al., 2021 (Poland)[22]	Single-center, cohort	28	N.P.	Pfizer	50	20–24 days	100	26–32
Kelly et al., 2021 (US)[17]	Single-center, cohort	5	Negative	Pfizer			100	26
Low et al., 2021 (Singapore)[18]	Single-center, cohort	14	N.P.	Pfizer	35.7	7–10 days	100	3–7
Nir et al., 2021 (Israel)[23]	Single-center, cohort	30	N.P.	Pfizer			100	21.7 (±11.0)
Perl et al., 2021 (Israel)[19]	Single-center, cohort	84	Unknown	Pfizer	18.7	14 days	97	14
Romero et al. 2021 (Spain)[20]	Multicenter, cohort	93	N.P.	Moderna/Pfizer			100	14
Valcarce et al., 2021 (US)[21]	Single-center, cohort	10	N.P.	Moderna/Pfizer			100	7–10

COVID-19, coronavirus disease-19; NP, never performed.

SARS-CoV-2 RNA in milk sample, percent of women with breast milk positive for IgA or IgG after first vaccine dose, length of time after first dose of vaccine to breast milk sample collection tested for IgA or IgG, percent of women with breast milk positive for IgA or IgG after second dose of vaccine, length of time after second dose of vaccine to breast milk sample collection tested for IgA or IgG, baseline milk-borne IgA and IgG reactive to SARS-CoV-2 concentrations or ratios, peak milk-borne IgA and IgG reactive to SARS-CoV-2 concentrations or ratios after first and second dose of vaccine, length of time after first or second dose of vaccine to breast milk sample with peak IgA or IgG.

Data from relevant articles was extracted manually or by WebPlotDigitizer version 4.1 to obtain the numeric values of antibody levels on peak days and the peak day then condensed into Excel.[8] Addition information and clarifications were supplied by corresponding authors. Analyses were conducted using the methods described by Neyeloff et al.[9]

Results

One hundred ninety-two articles were obtained from the search. After excluding duplicates and screening titles and abstracts, 18 cohort studies were identified (Tables 1 and 2). One article was removed due to reporting only total antibodies and not stratifying by class. Flow diagram of the search results is presented in Figure 1.

When analyzing the pooled breast milk sample positivity rate for SARS-CoV-2 antibodies after the first vaccine dose but before the second vaccine dose, we found that 64% (95% CI 51–78%) were positive for IgA and 30% (95% CI 13.1–46%) were positive for IgG (Figs. 2 and 3). Collection times

FIG. 1. PRISMA flow diagram depicting search results. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

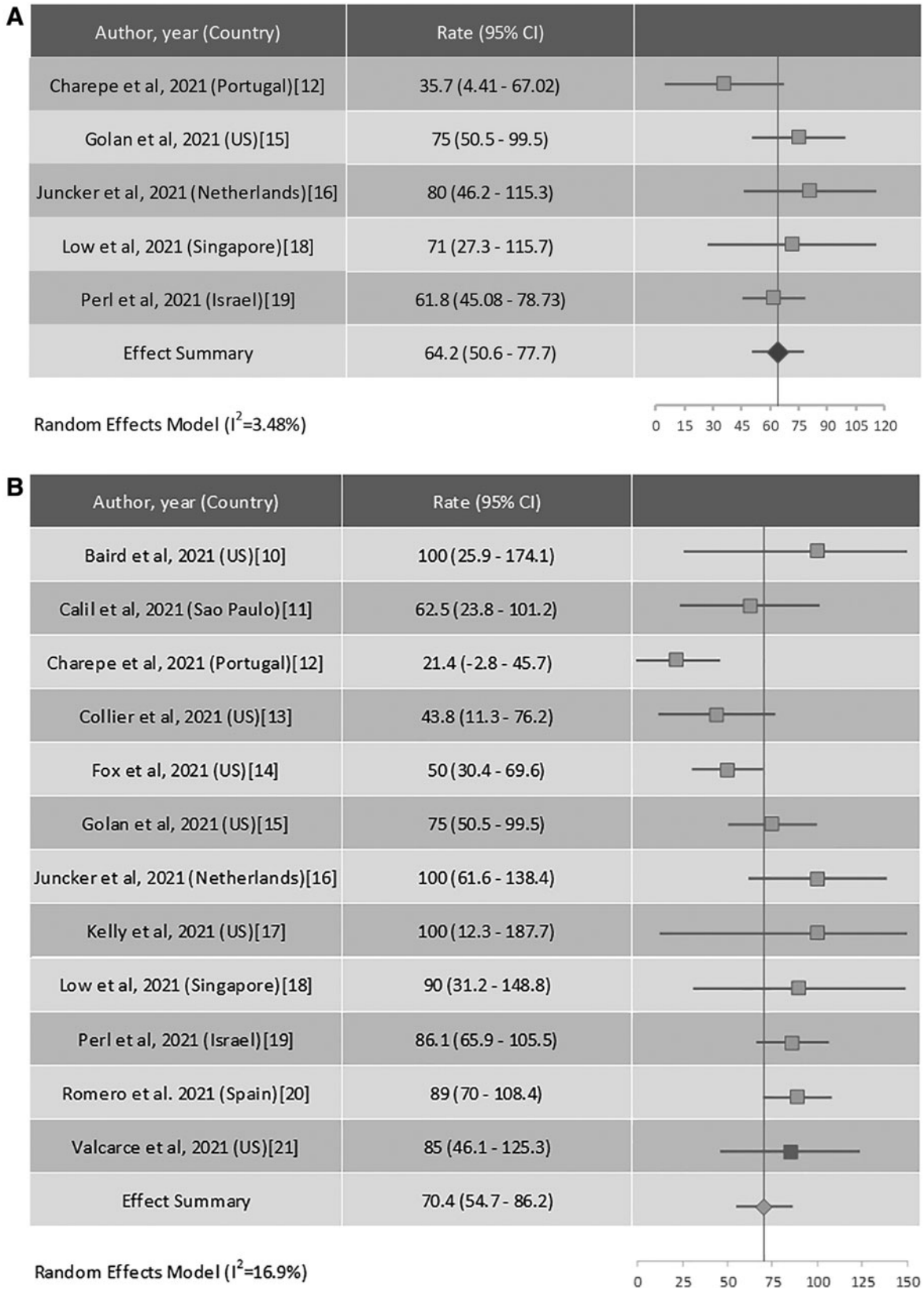

FIG. 2. Forest plot of proportion of anti-SARS-CoV-2 IgA detection in breast milk after first dose of vaccine **(A)** and after second dose of vaccine **(B)**.

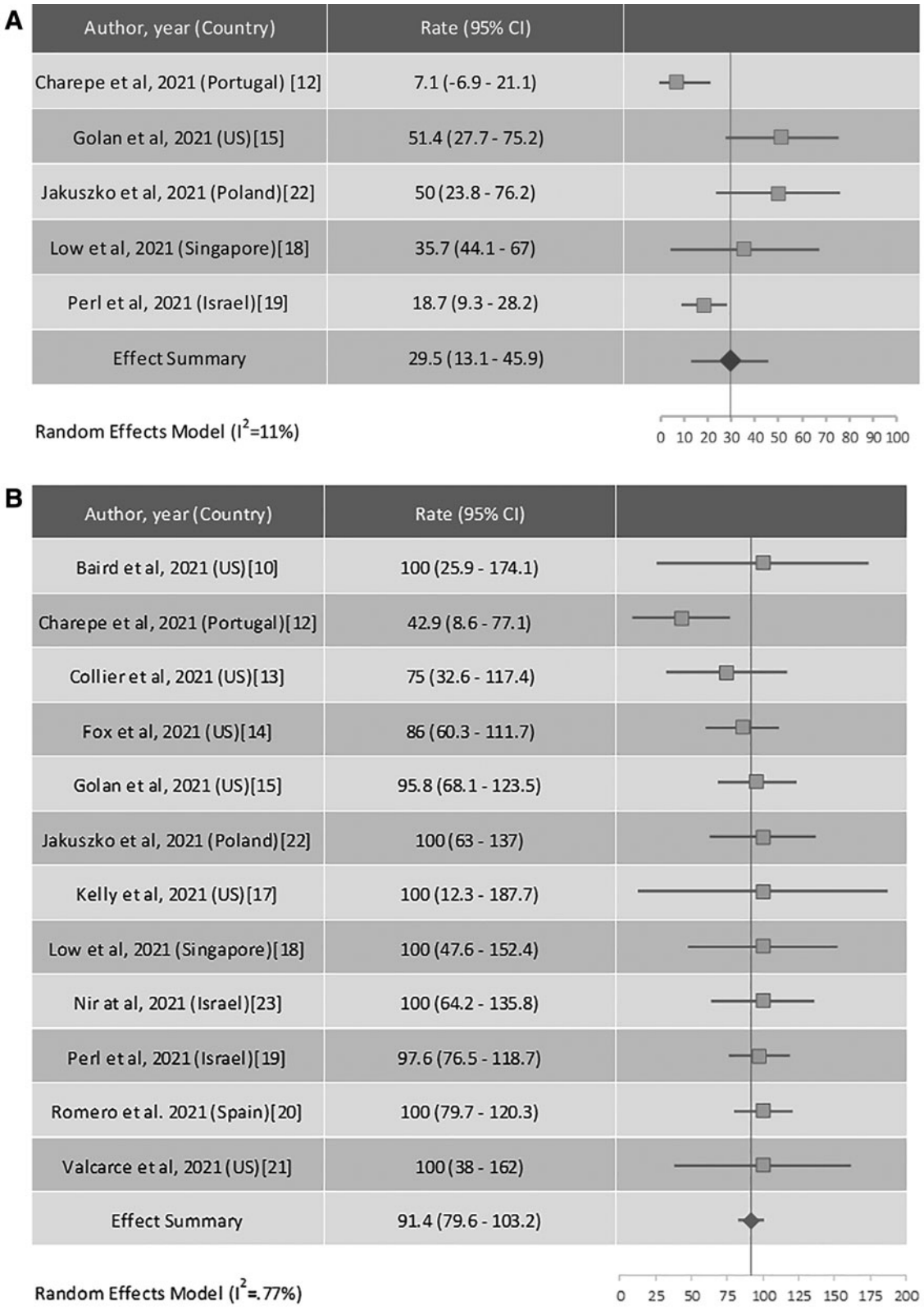

FIG. 3. Forest plot of proportion of anti-SARS-CoV-2 IgG detection in breast milk after first dose of vaccine **(A)** and after second dose of vaccine **(B)**.

Table 3. Levels of IgA in Breast Milk Reported at Baseline, Levels at Collection or Peak After First Dose of Vaccine, and Levels or Peak After Second Dose of Vaccine (Expressed as Units/mL)

Author, year (country)	*Design*	N	*COVID-19 test result*	*Vaccine manufacturer*	*Baseline IgA*	*Post 1st dose peak IgA*	*Time after 1st dose*	*Post 2nd dose peak IgA*	*Time after 2nd dose (days)*
Baird et al., 2021 (US)[10]	Single-center, cohort	7	N.P.	Moderna/Pfizer	67	666	14 days	552	11
Charepe et al., 2021 (Portugal)[12]	Single-center, cohort	14	Unknown	Pfizer		188	9.5 days	264	10
Collier et al., 2021 (US)[13]	Single-center, cohort	16	Positive in 1/16	Moderna/Pfizer				2431	26
Fox et al., 2021 (US)[14]	Single-center, cohort	50	N.P.	Moderna/Pfizer/J&J				21	14
Golan et al., 2021 (US)[15]	Single-center, cohort	48	Negative	Moderna/Pfizer	12	181	3–4 weeks	165	17–74
Valcarce et al., 2021 (US)[21]	Single-center, cohort	22	N.P.	Moderna/Pfizer	26	45	16–30 days	219	7–10

COVID-19, coronavirus disease-19; N.P., never performed.

Table 4. Levels of IgA in Breast Milk Reported at Baseline, Levels at Collection or Peak After First Dose of Vaccine, and Levels or Peak After Second Dose of Vaccine (Expressed as OD450 Ratio)

Author, year (country)	*Design*	N	*COVID-19 test result*	*Vaccine manufacturer*	*Baseline IgA*	*Post 1st dose peak IgA*	*Time after 1st dose (days)*	*Post 2nd dose peak IgA*	*Time after 2nd dose (days)*
Calil et al., 2021 (Sao Paulo)[11]	Single-center, cohort	16	No current	CoronaVac	0.44	Not significant		1.98	7
Gray et al., 2021 (US)[24]	Multicenter, cohort	31	Positive in 2/31	Moderna/Pfizer		Not significant		Not significant	
Juncker et al., 2021 (Netherlands)[16]	Single-center, cohort	26	Positive in 1/26	Pfizer	0.27	0.72	15	0.92	7
Kelly et al., 2021 (US)[17]	Single-center, cohort	5	Negative	Pfizer	1.4	4.9	10–19	5.33	9–18
Low et al., 2021 (Singapore)[18]	Single-center, cohort	14	N.P.	Pfizer	0.21	Not significant		0.7	3–7
Lechosa-Muniz et al., 2021 (Spain)[25]	Single-center, cross-sectional	38	Unknown	Moderna/Pfizer/ J&J				0.1	30
Perl et al., 2021 (Israel)[19]	Single-center, cohort	84	Unknown	Pfizer	0.65	2.05	14	4.21	7
Romero et al. 2021 (Spain)[20]	Multicenter, cohort	93	N.P.	Moderna/Pfizer				1.73	14

COVID-19, coronavirus disease-19; N.P., never performed.

Table 5. Levels of IgG in Breast Milk Reported at Baseline, Levels at Collection or Peak After First Dose of Vaccine, and Levels or Peak After Second Dose of Vaccine (AU/mL)

Author, year (country)	*Design*	N	*COVID-19 test result*	*Vaccine manufacturer*	*Baseline IgA*	*Post 1st dose peak IgG*	*Time after 1st dose*	*Post 2nd dose peak IgG*	*Time after 2nd dose*
Baird et al., 2021 (US)[10]	Single-center, cohort	7	N.P.	Moderna/Pfizer	67	420	16 days	1000	11 days
Charepe et al., 2021 (Portugal)[12]	Single-center, cohort	14	Unknown	Pfizer		11	9.5 days	179	10 days
Collier et al., 2021 (US)[13]	Single-center, cohort	16	Positive in 1/16	Moderna/Pfizer				727	26 days
Fox et al., 2021 (US)[14]	Single-center, cohort	37	N.P.	Moderna/Pfizer				157	14 days
Golan et al., 2021 (US)[15]	Single-center, cohort	48	Negative	Moderna/Pfizer	37	151	3–4 weeks	457	17–74 days
Gray et al., 2021 (US)[24]	Multicenter, cohort	13	Positive in 2/13	Moderna/Pfizer	2754	Not significant		3162	2–5.5 weeks
Esteve-Palau et al., 2021 (Spain)[26]	Single-center, cohort	33	Negative	Pfizer		1	12–17 days	78	14–15 days
Perl et al., 2021 (Israel)[19]	Single-center, cohort	84	Not tested	Pfizer	0.41	Not significant		20.5	7 days
Valcarce et al., 2021 (US)[21]	Single-center, cohort	10	N.P.	Moderna/Pfizer	1.2	3.16	16–30 days	59	7–10 days

COVID-19, coronavirus disease-19; N.P., never performed.

Table 6. Levels of IgG in Breast Milk Reported at Baseline, Levels at Collection or Peak After First Dose of Vaccine, and Levels or Peak After Second Dose of Vaccine (OD450 Ratio)

Author, year (country)	*Design*	N	*COVID-19 test result*	*Vaccine manufacturer*	*Baseline IgA*	*Post 1st dose peak IgG*	*Time after 1st dose (days)*	*Post 2nd dose peak IgG*	*Time after 2nd dose (days)*
Juncker et al., 2021 (Netherlands)[16]	Single-center, cohort	26	Positive in 1/16	Pfizer	0.2	0.79	21 days	1.14	15 days
Kelly et al., 2021 (US)[17]	Single-center, cohort	5	Negative	Pfizer		4	10–19 days	5.65	9–18 days
Low et al., 2021 (Singapore)[18]	Single-center, cohort	14	N.P.	Pfizer	0.09	Not significant		1.05	3–7 days
Lechosa-Muniz et al., 2021 (Spain)[25]	Single-center, cross-sectional	32	Unknown	Moderna/Pfizer				0.362	30 days
Nir et al., 2021 (Israel)[23]	Single-center, cohort	30	N.P.	Pfizer				5	21.7 (±11.0) days
Romero et al. 2021 (Spain)[20]	Multicenter, cohort	93	N.P.	Moderna/Pfizer				12.19	14 days

COVID-19, coronavirus disease-19; N.P., never performed.

of breast milk in these studies ranged from an average of 9.5 days in one study to the day of the second dose, which could be 3 weeks for the Pfizer vaccine or 4 weeks for the Moderna vaccine. Six studies showed statistically significant increases in IgA levels in breast milk during this first time frame (compared with baseline levels), while three other studies showed the value not to be significant (Tables 3 and 4). Similarly, IgG levels in breast milk were shown to be significantly increased from baseline in four studies, while three showed no significant change (Tables 5 and 6).

When analyzing the pooled breast milk sample positivity rate for SARS-CoV-2 antibodies after the second vaccine dose, we found 70% (95% CI 55–86%) were positive for IgA and 91% (95% CI 80–103%) were positive for IgG (Figs. 2 and 3). Collection times of these breast milk samples had a wide distribution with the earliest samples at 3 days and the latest at 10 weeks. Eight studies reported significant increases in IgA from baseline (Tables 3 and 4), and seven studies reported significant increases in IgG from baseline (Tables 5 and 6).

Discussion

Worldwide efforts to immunize individuals against COVID-19 have slowed the rate of infections and spread of the virus, as well as reducing the number of individuals with severe symptoms.[27] Data from the current pandemic have shown that the number of severe cases has a strong correlation with overall mortality as well as saturation of health care resources for adult patients across the globe. The same may hold true in the pediatric population. Currently, children 5 years and older are eligible for immunization, so little is known about the effects of COVID-19 vaccines in toddlers and infants. Breastfeeding infants permit antibody transfer from the mother to the infant through the breast milk, particularly once the vertically transmitted antibodies have waned soon after birth.[28]

Breast milk is crucial for protection against infection while the infant's immune system matures through the first year of life.[29] Our findings show that most mothers fully vaccinated against SARS-CoV-2 produce breast milk that contains both secretory IgA and IgG against SARS-CoV-2. This effect is most notable after the second dose of the Pfizer and Moderna vaccine, compared with partial immunization, emphasizing the importance of completing the vaccination schedule as recommended by the manufacturers. This may translate into massive public health impact regarding protection against SARS-CoV-2 infection and COVID-19 in infants.

Differential breast milk IgG and IgA antibody production specific to respiratory pathogens has been described in the setting of maternal infection and vaccination.[30] The clinical relevance of the levels of antibodies like IgG in breast milk remains to be elucidated. Postvaccine antibody response to SARS-CoV-2 in breast milk appeared to be IgG dominant, especially after the second vaccine dose. This IgG isotype transfer profile for breast milk observed after intramuscular vaccination, differs with the antibody profile programming in naturally mucosally acquired SARS-CoV-2 infection, which is predominantly IgA.[24] Whether breast milk IgG or IgA will be more critical for neonatal protection remains unclear.

Data on neutralizing ability of these antibodies on SARS-CoV-2 are still scarce.[31,32] van Keulen et al. found a 97% neutralizing capacity of antibodies to SARS-CoV-2 in breast milk. They also found that there was no correlation between neutralizing capacity and antibody levels.[31] This is encouraging because although many studies in this meta-analysis found statistically significant increases in antibody levels after the vaccination series, the levels of antibody varied significantly. The variation in the levels of antibodies could also be partially explained by the varying collection times of samples within individual studies and when comparing different studies. Furthermore, Baird et al. reported a decrease in the levels of SARS-CoV-2 antibodies of only by 6% after breast milk pasteurization, a procedure done widely at milk banks.[10]

These results should open the door for the consideration of the use of breast milk from vaccinated women in infants and neonates with SARS-CoV-2 infection and COVID-19.

Conclusion

Our review analyzed a great amount of data published worldwide and showed high rates of positivity for antibodies in breast milk following COVID-19 immunizations. Despite most of the studies refer to women vaccinated with either Moderna or Pfizer RNA-based COVID-19 vaccines, not all populations reported the same vaccines. Since the analysis included reports from around the world, certain populations' unique immunogenetic background particularities that could play a role in their antibody production could not be analyzed.

More research is necessary to find if the rate of positivity of IgA and IgG against SARS-CoV-2 in breast milk persists months after the full immunization, before and after the booster, the extent of their neutralizing capacity, and implications for use in treatment and prevention of SARS-CoV-2 in infants. We hope this analysis provides support for vaccination efforts in pregnant and breastfeeding mothers and encourages more research in the mother–child dyad.

Authors' Contributions

N.W. performed search. N.W. and J.C. wrote the article.

Disclosure Statement

No competing financial interests exist.

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