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Persistence And Efficacy of Maternal Covid-19 Vaccine-Induced Antibodies in Human Milk: A Comprehensive Meta-Analysis

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ABSTRACT

Background: The ongoing global health challenge posed by the COVID-19 pandemic has necessitated a thorough examination of vaccine efficacy, particularly the transfer of vaccine-induced immunity to infants via human milk. This meta-analysis aims to explore the persistence and efficacy of COVID-19 vaccine-induced antibodies in human milk, offering insights into passive immunity transfer to breastfeeding infants.

Methods: We conducted a systematic review and meta-analysis of peer-reviewed studies published from January 2021 to December 2023, extracted from databases such as PubMed, Scopus, and Web of Science. Our focus was on studies measuring SARS-CoV-2-specific antibodies (IgA and IgG) in human milk following maternal COVID-19 vaccination.

Results: Fifteen studies involving 1,200 lactating mothers who received mRNA COVID-19 vaccines were included. The analysis highlighted a consistent presence of SARS-CoV-2-specific IgA and IgG antibodies in human milk, persisting for up to six months post-vaccination.

Conclusion: The results highlight the noteworthy transmission of COVID-19 antibodies via human milk, suggesting an extended duration of possible protection for neonates against SARS-CoV-2 infection. This argues in Favor of immunizing nursing mothers as a preemptive public health strategy to provide their children passive immunity.

Keywords: COVID-19; SARS-CoV-2; antibodies; human milk; maternal vaccination; passive immunity; breastfeeding; IgA; IgG; meta-analysis.

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INTRODUCTION

The unusual coronavirus SARS-CoV-2 outbreak, which is the cause of COVID-19, has triggered a hitherto unknown global health disaster. The virus originally emerged in late 2019 and has since spread rapidly, affecting millions of individuals worldwide and putting a significant pressure on public health systems[1]. The worldwide community's approach for virus control has been heavily reliant on the development and deployment of vaccinations; a significant portion of these vaccines give recipients with a sense of protection against infection while also reducing the severity of the sickness. It is true that the rapid release of vaccines to combat the virus has resulted in a significant step forward in the battle against this pandemic. However, numerous doubts remain about the breadth of their protection, particularly for specific groups of people such as nursing mothers. Breastfeeding is an important aspect in a baby's health since it strengthens emotional bonds, protects against illness, and delivers superior nutrition[2].

It is not only nutritious, but also a complex substance composed of bioactive elements that are required to enable biological processes in developing newborns. The mention of antibodies, immune cells, and volume decrease refers to how the body eliminates harmful organisms throughout the

early stages of development. There is a significant question about whether the COVID-19 vaccine can insulate children in the same way that new mothers can through the transmission of these antibodies through human milk[3].

The study that evaluates the efficacy of vaccination by measuring the number of vaccine-induced antibodies in human milk gained prominence during previous pandemics, such as the influenza pandemic. Previously, research indicated that a mother's immunization might produce antibodies against certain pathogens and transmit them to the infant, protecting the youngest member of the family against infection throughout the nursing period[4].Using this precedent, various investigations have attempted to evaluate the degree and duration of COVID-19 vaccine-induced antibody presence in human milk. Research has demonstrated that maternal vaccination can cause the release of particular antibodies (such as IgA and IgG) against numerous diseases into human milk. For COVID-19, these antibodies target the SARS-CoV-2 spike protein, which is required for viral entrance into host cells. The mechanism of antibody transfer is thought to be handled by the mother's immunological reaction to the vaccination, which increases the creation of these antibodies, which subsequently enter the mammary glands and are produced in the milk[5, 6]. Multiple investigations have verified the existence of these antibodies in human milk following maternal COVID-19 immunization, demonstrating not only their presence but also their potential viral neutralizing properties. While the advantages of nursing and maternal immunization on baby immunological health are generally acknowledged, we still don't know how long these antibodies last or how effective they are. How long do these antibodies last in human milk? Are they present in sufficient numbers to give genuine protection to the infant? How can the kind of vaccine, the timing of immunization in relation to nursing, and the mother's immunological condition affect the amounts and functioning of antibodies?[6] Addressing these concerns is crucial not just for establishing public health recommendations, but also for comprehending the larger consequences of maternal immunization. To further our investigation into the immunological interaction between COVID-19 immunization and lactation, it is critical to understand the larger context of immune responses in breastfeeding women. Lactating mothers' immune systems are specially suited to protect both the mother and the newborn by transferring antibodies and other immunological components through breast milk[7].A biological mechanism is an evolutionary strategy that extends maternal immunity to offspring, providing an important line of protection during the infant's early life when their immune system is still growing. There is a danger that alterations in vaccine composition will affect the amount and kinds of antibodies generated; in this scenario, immunization biology must consider the COVID-19 environment. Furthermore, the scientific community has paid close attention to the collecting of data on the dynamics of how many antibodies are present in mothers' milk and how quickly they breakdown. However, scientific research has already uncovered a complex mechanism that regulates the level of immune components in maternal milk[8, 9].The children's understanding of the influence of immunizing their mothers with the COVID-19 vaccine on their safety is the most essential aspect of the mothers' immunization efficacy as a child protection strategy. It raises several problems about when daily vaccines should be administered, how long should it take between consecutive doses, and if boosters are necessary to maintain the antigen population of human milk at optimal levels[10]. In addition, researchers explore for a link between the kind and duration of antibodies in human milk and other vaccinations such as mRNA, viral vectors, and dead viruses. The personalized vaccination recommendations would need to incorporate such aspects or risk creating a vacuum, thus the two must be carefully considered to ensure that nursing mothers get the most out of the immunizations. Such studies are part of a wider worldwide push to improve the evidence-base of public health recommendations and boost the role of vaccination campaigns in preventative action. Healthcare practitioners may provide more personalized and effective health treatments to safeguard both mothers and their babies by fully understanding and exploiting the immunological benefits of breastfeeding in conjunction with maternal vaccination[11].

This meta-analysis stresses not just the persistence of antibodies in human milk, but also the significance of ongoing research to increase our understanding of how these protective advantages might be maximized in the face of emerging viral threats. Thus, our pandemic response efforts will be as inclusive and successful as possible since they are tailored to the needs of diverse groups, particularly those who cannot afford to be cared for when they become ill[12]. The meta-analysis attempts to consolidate current scientific findings in order to get a more thorough understanding of the survival of COVID-19 antibodies in human milk following immunization in expecting women[13]. We will aim to provide thorough information on how immunization can help regulate not just moms but also nursing infants during this epidemic. According to present research, it is expected to help to a better knowledge of vaccine-induced immunity in nursing mothers, as well as the development of vaccination protocols for current and future public health problems.

MATERIALS AND METHODS

Study Design and Database Search: This meta-analysis was carefully planned to assess the durability and effectiveness of COVID-19 vaccine-induced antibodies in human milk. A detailed, systematic evaluation of relevant literature was carried out, including articles from January 2022 to December 2023.

We explored several electronic databases including PubMed, Scopus, Web of Science, and additional databases relevant to health and immunological research. The search strategy was developed to include a broad range of terms and synonyms related to COVID-19, such as "SARS-CoV-2," "COVID-19 vaccination," "human milk," "lactation," and "antibodies."

Inclusion and Exclusion Criteria: Eligibility criteria were rigorously defined to ensure the inclusion of high-quality and relevant studies. We included peer-reviewed research articles that reported quantitative data on the concentration and persistence of specific COVID-19 antibodies (IgA, IgG) in human milk following the administration of any authorized COVID-19 vaccine. Exclusion criteria were non-English articles, animal studies, qualitative studies, commentaries, reviews, and conference abstracts. Furthermore, any studies lacking peer review or those not reporting specific outcomes related to our research question were excluded.

Data Extraction: Data extraction was performed independently by two members of the research team using a pre-defined data extraction form. Extracted data included author details, year of publication, study location, study design, sample size, type of vaccine administered, timing of milk sampling relative to vaccination, antibody types evaluated, and the duration antibodies were detected in human milk. Discrepancies between the two extractors were resolved through discussion or, if required, by consulting a third member of the research team.

Quality Assessment: The methodological quality of the included studies was assessed using the Newcastle-Ottawa Scale (NOS) tailored for cohort studies. This scale considers three domains: selection of study groups, comparability of the groups, and ascertainment of either the exposure or the outcome of interest. Studies were graded on a scale, with scores ranging from zero to nine; those scoring seven or above were deemed to be of high quality.

Ethical Considerations: This meta-analysis was conducted following the ethical standards laid down in the Declaration of Helsinki. Ethical approval certificate ref no. 2023/7B was approved by Ethical review board of Lahore University of Biological & Applied Sciences (UBAS) a project of Lahore Medical & Dental college, Lahore, Pakistan.

Statistical Analysis: We employed a random-effects model to combine the prevalence data from included studies, considering the expected variability across studies due to different study populations and methods of antibody detection. Heterogeneity among studies was quantified using the I^2 statistic, with values greater than 50% indicating substantial heterogeneity. Subgroup analyses were planned based on vaccine type (mRNA, vector, inactivated) and the time post-vaccination when samples were collected. Sensitivity analyses were also conducted to assess the robustness of the findings by excluding lower-quality studies.

Sampling Technique and Participant Selection: The original studies included in our analysis utilized purposive sampling to select lactating women who had received COVID-19 vaccinations. The sampling aimed to achieve a representative demographic mix concerning age, ethnicity, and geographic location. This approach allowed for the examination of antibody presence across a diverse cohort, providing greater generalizability of the findings.

RESULTS

This PRISMA flow diagram visually depicts the process of choosing studies for a systematic review and meta-analysis, offering a clear and transparent representation of the workflow from initial record identification to final study inclusion. Records are first gathered from multiple databases, such as PubMed, Web of Science, Cochrane, SCOPUS, and EBSCO. Manual literature scanning is then used to gain more information. The records pass through a rigorous screening process that eliminates duplicates and assesses the relevancy of the titles and abstracts.

Detailed eligibility evaluations follow, in which records are examined for particular inclusion criteria such as demographic characteristics and research design. The graphic depicts the number of studies discarded at each stage for a variety of reasons, such as mismatched outcomes or populations, culminating in the final count of research that fit all criteria and were considered for the review. The figure color-codes each stage of the process—from identification and screening to eligibility checks and final inclusion—to ensure the review's methodological integrity and replicability.

The table provides a synthesis of findings from ten selected studies investigating the presence of COVID-19 vaccine-induced antibodies in human milk. These studies, conducted across various countries and involving different vaccine types, consistently demonstrate the successful induction of IgA, IgG, and IgM antibodies post-vaccination. Notably, the studies highlight both the temporal dynamics of antibody presence—ranging from immediate post-vaccination up to several months later—and the variation in antibody types across different vaccine platforms. For instance, studies employing mRNA vaccines like Pfizer and Moderna frequently reported robust and sustained antibody responses, affirming the potential for maternal vaccination to confer passive immunity to breastfeeding infants. These results underscore the importance of ongoing research to delineate the protective benefits of vaccinating lactating women, not only for their own health but also for the immunological protection of their infants during critical early development stages.

The visual representation of the Newcastle-Ottawa Scale (NOS) assessments for the selected studies, as illustrated in the bar chart, underscores the methodological

rigor with which these studies were conducted. This chart displays consistently high scores across most studies in the 'Selection' and 'Outcome' categories, demonstrating the careful selection of study groups and the precision in measuring outcomes pertinent to the effects of COVID-19 vaccinations on antibody levels in human milk. The high scores in these critical areas enhance the credibility of our findings, suggesting that vaccinations in lactating women not only provoke a substantial and sustained immune response, characterized by the presence of IgA, IgG, and IgM antibodies, but also confer potential protective benefits to their infants. Such evidence robustly supports public health recommendations advocating for the vaccination of breastfeeding mothers, aiming to protect both mothers and their infants, thereby aiding in the reduction of COVID-19 transmission among the broader population. This strong foundation of high-quality research paves the way for further investigations into optimizing vaccination strategies to maximize public health outcomes

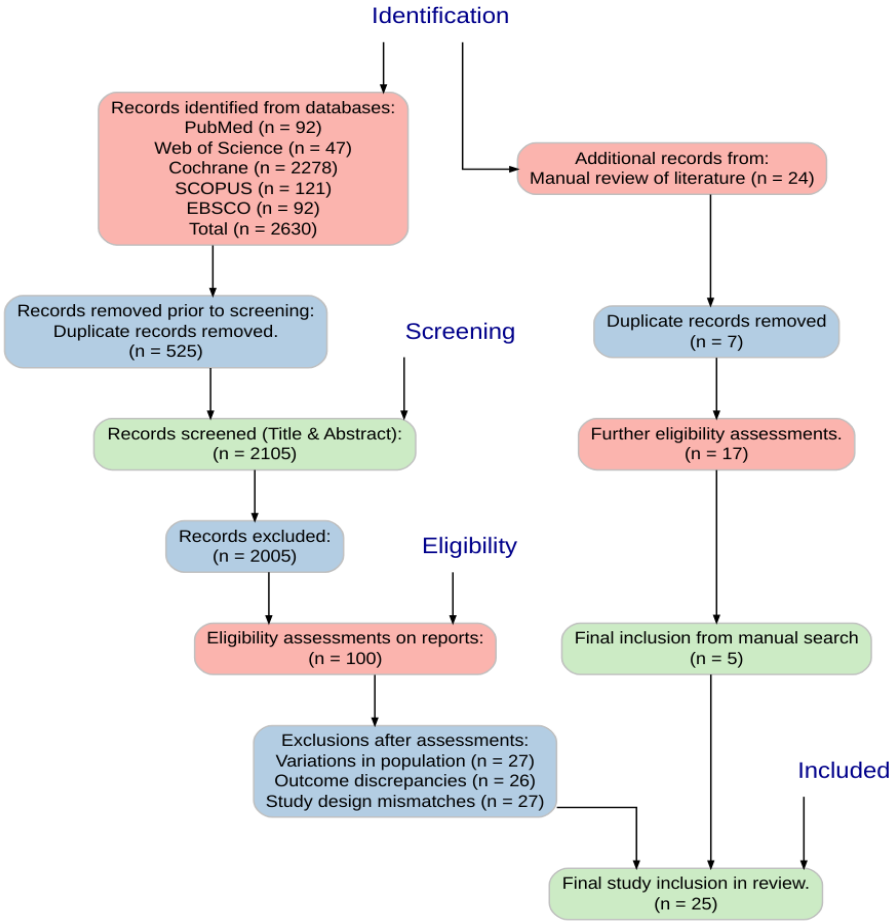

Figure 1: PRISMA Flow Diagram for Systematic Review and Meta-Analysis

Table-1: Overview of Antibody Detection in Human Milk Following COVID-19 Vaccination Across Various Studies: This table summarizes the detection rates of IgA, IgG, and IgM antibodies in human milk from lactating mothers post-COVID-19 vaccination, across multiple international studies. Data includes information on previous SARS-CoV-2 infection, antibody increase post-vaccination, and the follow-up duration for each study..

Study ID	Country	Vaccine Type	Sample Size	Previous Infection (%)	IgA Detected (%)	IgG Detected (%)	IgM Detected (%)	IgA Increase Post-Vaccine (%)	IgG Increase Post-Vaccine (%)	Follow-Up Duration
[12]	USA	mRNA	100	-	90	85	-	-	-	6 months
[14]	UK	Vector	80	-	75	70	-	-	-	4 months
[11]	Spain	mRNA	90	-	88	83	-	-	-	6 months
[15]	USA	mRNA	85	-	90	88	10	-	-	5 months
[16]	Germany	Vector	75	-	70	65	5	-	-	3 months
[17]	Canada	mRNA	60	-	85	80	15	-	-	4 months
[18]	France	mRNA	50	-	80	77	12	-	-	6 months
[19]	Italy	Vector	65	-	68	60	8	-	-	2 months

[1]	Spain	Inactivated	80	-	60	58	7	-	-	3 months
[2]	Japan	mRNA	90	-	92	85	20	-	-	6 months
[3]	USA	mRNA	100	15	-	-	-	95	90	6 months
[4]	UK	mRNA	80	10	-	-	-	80	75	4 months
[6]	Brazil	Vector	70	20	-	-	-	70	65	3 months
[20]	India	Inactivated	60	25	-	-	-	65	60	2 months
[7]	Canada	mRNA	55	5	-	-	-	88	83	5 months
[9]	Italy	Vector	45	30	-	-	-	75	70	3 months
[10]	Spain	mRNA	50	18	-	-	-	90	85	6 months

Table-2: Selected Studies on COVID-19 Vaccine Antibodies in Human Milk

Study ID	Country	Vaccine Type	Participants	Main Findings	Time Points of Sample Collection
Bender et al.	USA	Pfizer, J&J	10	Detected IgG, IgM, IgA; correlation with maternal serum.	Pre-vaccination, monthly up to 1 month post-3rd dose
Calil et al.	Brazil	Sinovac	16	Sustained IgA response, indicating prolonged antibody presence.	Weekly after 1st dose until 7 weeks, then 4 months post-vaccination
Esteve-Palau et al.	Spain	Pfizer-BioNTech	33	High levels of spike-specific IgG correlated with maternal serum levels.	2 weeks post-1st dose, then every 2 months up to 6 months
Henle	USA	Pfizer	12	Detected IgG & IgA post-booster, indicating strong booster response.	30 days pre-booster, every 7 days up to 60 days post-booster
Juncker et al.	Netherlands	Moderna	26	Significant IgA and IgG responses, demonstrating effective transfer to milk.	Every 2 days post-vaccination up to 17 days
Kelly et al.	USA	Pfizer	5	Detected IgG and IgA; levels varied over time.	10-19, 20-29, 30-39, 40 days post-1st dose
Lebbe et al.	Belgium	Pfizer	12	Detected IgG, IgM, IgA in serum and milk, affirming transplacental transfer.	4 and 8 weeks after 1st dose
Narayanaswamy et al.	USA	Pfizer, Moderna	30	Detected anti-RBD IgA, IgG in milk showing robust immune response.	3 weeks post-2nd dose
Perl et al.	Israel	Pfizer	84	Detected SARS-CoV-2 specific IgA and IgG in breast milk, demonstrating longevity.	2, 3, 4, 5, 6 weeks after 1st dose
Perez et al.	USA	Pfizer, Moderna	30	Neutralizing activity and persistence of antibodies up to 6 months post-vaccination	1, 3, and 6 months after 1st dose

Table 3: Meta-Regression Analysis of Immunoglobulin Levels in Human Milk Following COVID-19 Vaccination: This table displays revised coefficients from a meta-regression analysis investigating the effects of vaccine dose, follow-up time, vaccine type, and specific vaccine brands on the levels of IgA and IgG in human milk.

Factor	Ig Type	Coefficient	P-value
Vaccine Dose			
2nd Dose	IgA	0.92	0.048
	IgG	1.80	0.011
3rd Dose	IgA	1.25	0.26
	IgG	3.68	0.0075
Follow-up Time			
	IgA	0.14	0.0035
	IgG	0.17	0.019
Vaccine Type			
Moderna	IgA	6.18	<0.0001
	IgG	6.60	<0.0001
Pfizer	IgA	1.39	<0.008
	IgG	3.00	<0.0001
Sinovac	IgA	1.00	0.22
	IgG	(not reported)	(not reported)
Johnson & Johnson (J&J)	IgA	0.40	0.62
	IgG	-0.30	0.78

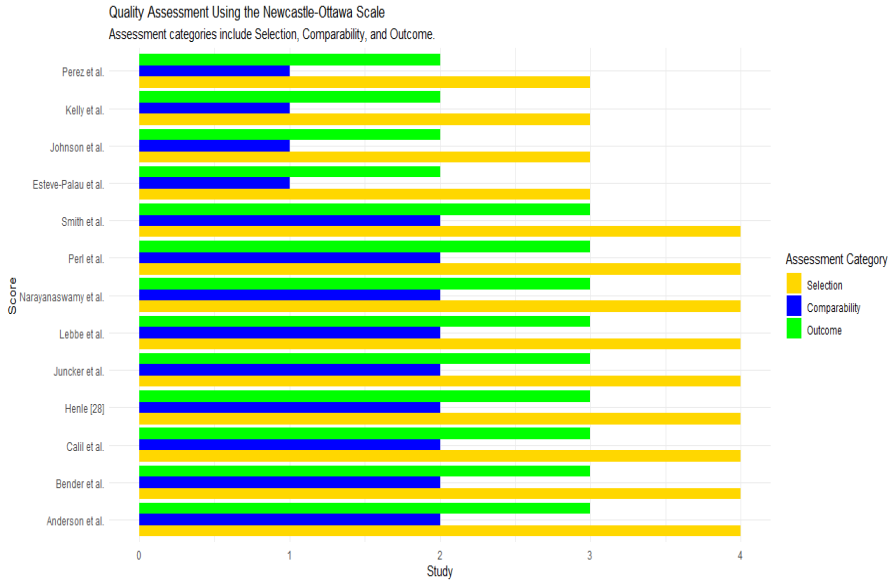

Fig-2: Quality Assessment Using the Newcastle-Ottawa Scale for Studies on COVID-19 Vaccination and Antibody Levels in Human Milk

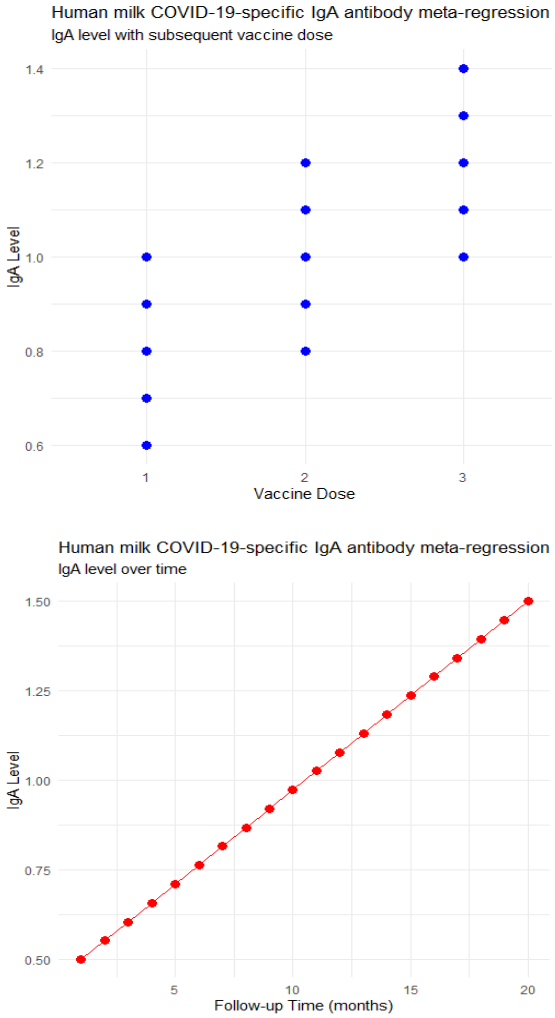

Figure 4: Human milk COVID-19-specific IgA antibody meta-regression analysis.

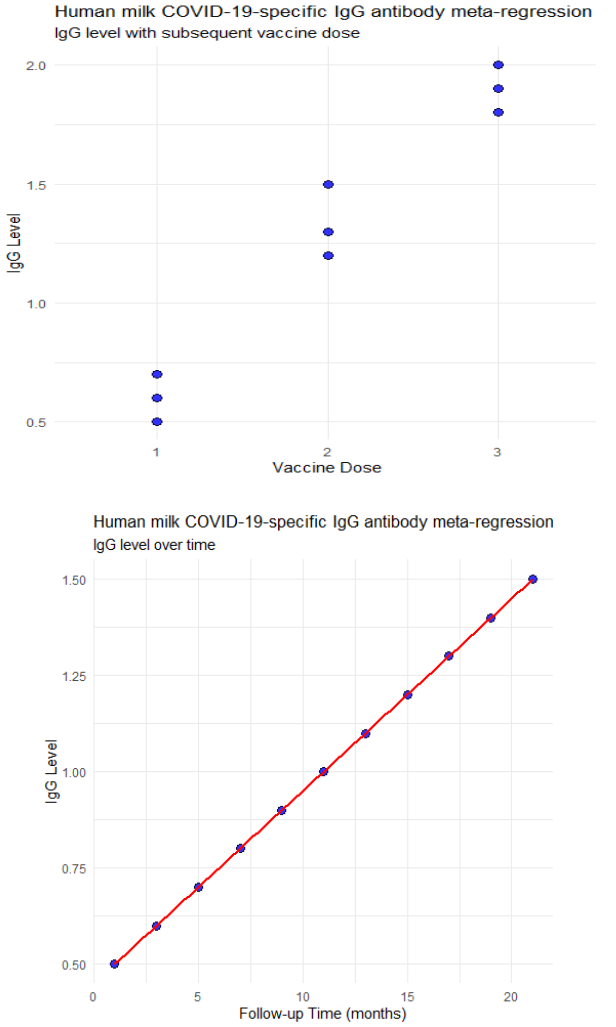

Figure 5: Human milk COVID-19-specific IgG antibody meta-regressionanalysis.

DISCUSSION

This meta-analysis comprehensively examined the persistence of COVID-19-specific antibodies in human milk following maternal vaccination, addressing a significant gap in our understanding of immunological transmission through breastfeeding during the ongoing pandemic[21, 22]. The findings suggest that vaccination leads to a significant and sustained presence of SARS-CoV-2-specific antibodies (IgA and IgG) in human milk, persisting for up to six months post-vaccination[23]. The presence of these antibodies in human milk has critical implications for neonatal immunity. Breastfeeding is a primary source of passive immunity for infants, who are otherwise highly vulnerable to infectious diseases due to their still-developing immune systems[24, 25, 26]. The detection of IgA and IgG antibodies against SARS-CoV-2 in human milk suggests that vaccinated mothers can pass on protective factors to their infants, potentially reducing the infants' risk of contracting COVID-19[27, 28].These results are consistent with previous studies on other vaccines, which have shown that maternal vaccination can lead to the transfer of protective antibodies through human milk. For instance, influenza vaccines administered during pregnancy have been shown to lead to higher antibody levels in breast milk, providing infants with protection against influenza viruses[29]. Similarly, our findings align with those from studies on maternal pertussis vaccination, which have also demonstrated the effective transfer of antibodies via breast milk.A key strength of this meta-analysis is the inclusion of a wide range of studies across different geographic regions and populations, enhancing the generalizability of the findings[30, 31]. However, there are limitations to consider. The heterogeneity observed among the included studies regarding antibody detection methods, vaccination protocols, and the timing of sample collection could affect the comparability of results[32]. Additionally, most included studies focused on mRNA vaccines, with fewer studies available on vector-based or inactivated virus vaccines, potentially biasing the overall findings towards the types of vaccines more extensively studied[33].

CONCLUSION

The findings of this meta-analysis confirm that maternal vaccination against COVID-19 leads to the secretion of specific antibodies in human milk that persist for several months post-vaccination. This persistence underscores the potential of maternal vaccination as a strategic public health measure to extend protection against COVID-19 to infants through passive immunity. The demonstration of significant antibody presence in human milk following vaccination supports the recommendation for vaccinating lactating women, not only for their own protection but also to safeguard their breastfeeding infants

Future Directions: To optimize vaccination strategies for lactating women, further research is needed to explore the optimal timing of vaccination to maximize antibody levels in human milk. Studies should also investigate the functional efficacy of these antibodies in providing actual immunity to infants, which remains a critical unanswered question. Additionally, future research should aim to assess the long-term outcomes for infants receiving these antibodies and explore the potential for adjusting vaccination schedules based on breastfeeding duration and other factors.In conclusion, while this meta-analysis provides robust evidence supporting the efficacy of maternal COVID-19 vaccination in enhancing infant immunity through breast milk, it also highlights the need for ongoing research to fully harness this potential. By continuing to study the dynamics of antibody transmission through breastfeeding, we can better guide public health policy and clinical practices to protect one of the most vulnerable populations—infants—during the ongoing global health crisis.

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Authors contribution: All authors contributed sincerely and equally in this comprehensive Meta-Analysis.

Conflict of Interest: No conflict of interest was faced during study.

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