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Article

Reactogenicity of mRNA and non-mRNA based COVID-19 vaccines among lactating mother and baby dyads

Beth Jacob-Chow[1^], Kandarpa Lakshmi Vasundhara[1^], Cheang Hon Kit (MD, MRCP (UK)[2], M Med (Paeds)), Lee Le Ye[1,3] (MRCPCH, MMED (Paeds), FAMS (Paeds)), Jia Ming Low (MRCPCH, MMED (Paeds), MCI)[3*+], and Zubair Amin (MBBS, Board Cert (Paeds))[1,3+]

[1] Yong Loo Lin School of Medicine, National University of Singapore, Singapore
[2] Department of Paediatrics and Neonatology, Lam Wah Ee Hospital, Malaysia
[3] Department of Neonatology, Khoo Teck Puat-National University Children's Medical Institute, National University Health System, Singapore
[*] Correspondence: Email: jia_ming_low@nuhs.edu.sg; Tel.: 65 6772 5075; Fax.: 65 6872 1908; Address: Department of Neonatology, Khoo Teck Puat-National University Children's Medical Institute, National University Health System, Singapore, 1E Kent Ridge Road, NUHS Tower Block, Level 12, Singapore 119228.
[^] Both first authors contributed equally
[+] Both last authors contributed equally

Abstract: The aims of the study are: a) Describe the reactogenicity of WHO-approved two mRNA (Pfizer-BioNTech, Moderna) and two non-RNA vaccines (Oxford-AstraZeneca, Sinovac) among lactating mother and baby pairs; and b) compare and contrast the reactogenicity between mRNA and non-mRNA vaccines. A cross-sectional, self-reported survey was conducted amongst 1784 lactating women who received COVID-19 vaccinations. The most common maternal adverse reaction was a local reaction at the injection site; the largest minority of respondents, 43.7% (780/1784), reported experiencing worse symptoms when receiving the second dose compared to the first dose. There were no major reported adverse effects or behavioural changes in the breastfed infants. Among the respondents who received non-mRNA COVID-19 vaccinations, a majority reported no change in lactation but those who did more commonly reported an increase in milk supply, decrease in milk supply and pain in the breast. The more commonly reported lactation changes (fluctuations in breastmilk supply and pain in the breast) for the non-mRNA vaccines were similar to that of respondents who received mRNA vaccines. Our study, with a large cohort and wide geographical and racial mix, further augments earlier reported findings that COVID-19 vaccines are safe for breastfeeding mothers and her children.

Keywords: COVID-19 vaccines; SARS-CoV2; lactation; mother-child dyads; reactogenicity

1. Introduction

Although children are mostly asymptomatic or have mild COVID-19 infections, in some cases a more severe clinical picture has been described [1,2]. It is thus important to protect both mother-child dyads from COVID-19 infection as maternal vaccination during lactation leads to antibody transfer through breastmilk [3,4].

At the start of the pandemic, countries adopted varying strategies in the roll out of their national immunisation programs among breastfeeding mothers. These varied responses were in part due to the paucity of robust data on the safety of COVID-19 vaccines. Singapore, for example, adopted a cautious approach towards vaccination whereby breastfeeding mothers were asked to suspend breastfeeding for up to 7 days after any COVID-19 vaccination [5]. This advisory has since been revised since June 2021 to allow

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for breastfeeding after receipt of mRNA COVID-19 vaccinations. In contrast, the Malaysian Ministry of Health recommended continual breastfeeding following COVID-19 vaccinations [6].

Varying national policies and conflicting consent forms which state that breastfeeding is a contraindication for COVID-19 vaccinations [7], coupled with anecdotal reports of mastitis after mRNA COVID-19 vaccinations [8] contributed to lower vaccine acceptance rates in breastfeeding mothers.

In contrast to mRNA vaccines, there is a severe paucity of cross-sectional studies with adequate participants comparing the reactogenicity of different non-mRNA COVID-19 vaccines for breastfeeding mother-child dyads. For example, a single study of 20 mother-child dyads vaccinated with CoronaVac (produced by Sinovac) has been published which showed no adverse effects in the breastfed children [9]. Hence, it is crucial to address the information gap by researching the reactogenicity of non-mRNA vaccines and comparing mRNA and non-mRNA vaccines.

The aims of the study are two-fold: a) Describe the reactogenicity of WHO-approved two mRNA (Pfizer-BioNTech, Moderna) and two non-RNA vaccines (Oxford-AstraZeneca, Sinovac) among lactating mother and child pairs; and b) compare and contrast the reactogenicity between mRNA and non-mRNA vaccines. We also report a separate sub-group analysis of non-mRNA vaccines.

2. Materials and Methods

2.1 Design

This is a descriptive, cross-sectional, self-reported survey-based research with a non-probability sampling method conducted in Singapore and Malaysia. The National Healthcare Group's Domain Specific Review Board (DSRB) categorised the study as exempt for the Singapore site (DSRB reference number: 2021/00708). In Malaysia, similar exempt status was approved by the Joint Ethics Committee on Clinical Studies of School of Pharmaceutical Sciences, USM - Hospital Lam Wah Ee.

2.2 Settings

In Singapore, 99% of new mothers attempt to breastfeed their children. By 6 months of age, 42% children receive some form of human milk and only 1% children are exclusively breastfed [10]. Similarly, 98.1% of Malaysian mothers make at least one attempt at breastfeeding their infants; but unlike Singapore, the prevalence of exclusive breastfeeding up to 6 months is much higher at 47.1% [11]. Majority of the vaccinations administered in the early part of the pandemic in both Singapore and Malaysia were mRNA vaccines as they were the first to achieve emergency authorisation status.

2.3 Sample

Lactating women ≥ 21 years of age who received at least one dose of any of the following WHO-approved COVID-19 vaccines (Pfizer-BioNTech, Moderna, Oxford-AstraZeneca, Sinovac) were eligible for the study. The survey was distributed online through social media and advertisements.

2.4 Measurements

Demographics, past medical history, and clinical outcomes of mother-child dyads at least 7 days after the vaccine dose were determined through a structured questionnaire designed specifically for the study. The survey instrument was developed through a multi-staged process: a preliminary draft was developed from known side effects of COVID-19 vaccines reported in pre-approval trials. Severe adverse effects were defined as cardiovascular or cerebral accidents. We also reviewed available reports of adverse

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events from post-approval research. The preliminary draft was further reviewed by the research team consisting of four specialist paediatricians and neonatologists. Thereafter, it was pilot tested among three lactating mothers. The administered questionnaire is available in Appendix A.

2.5 Data Collection

Survey was administered from 14th August 2021 to 5th January 2022 through an online secured, specialised electronic platform (Qualtrics®). Respondents' confidentiality was maintained as only anonymised data were collected.

2.6 Data Analysis

Data were analysed using descriptive statistics to calculate rate and proportions with STATA® version 13. Continuous data were reported as mean and standard deviations. Discontinuous data were reported as median and interquartile range. Chi-square or Fisher exact tests assessed the association between vaccine types, dose, impact on breastfeeding and covariables. A p-value <0.05 was considered significant.

3. Results

3.1. Demographics of Breastfeeding Mother-Child Dyads

Table 1 shows the demographic data of mother and child dyads. In total, 2612 responses were received, out of which 828 (31.7%) responses were excluded. Reasons for exclusions were as follows: 673 had incomplete or missing data, 2 had taken vaccines that were not included in our study, 63 took the vaccine in a country other than Singapore/Malaysia, and 90 were vaccinated during pregnancy but not during lactating period. This resulted in a total of 1784 responses for analysis.

Only 2.2% (40/1784) respondents had a prior COVID-19 infection out of which 12.5% (5/40) required intensive care admission.

Table 1. Demographic Characteristics of Breastfeeding Mother-Child Dyads (n=1784)

Characteristics of Respondents [n (%)]	
Mean age of mothers in years (SD)	32.7 +/- 3.9
Age range of the youngest child who was breastfed	
<1 month	81 (4.5)
1-6 months	714 (40.0)
7-12 months	509 (28.5)
13-18 months	290 (16.3)
19-24 months	124 (7.0)
25-36 months	56 (3.1)
> 36 months	10 (0.6)

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Highest education level of mother	
Primary school	4 (0.2)
Secondary school	53 (3.0)
High school diploma or equivalent	264 (14.8)
Undergraduate degree	813 (45.6)
Postgraduate degree	604 (33.9)
Others	46 (2.5)
Brand of vaccine	
Pfizer-BioNTech (mRNA vaccine)	1409 (79.0)
Moderna (mRNA vaccine)	130 (7.3)
Sinovac (non-mRNA vaccine)	162 (9.1)
Oxford-AstraZeneca (non-mRNA vaccine)	83 (4.6)
Participating country	
Singapore	1225 (68.7)
Malaysia	559 (31.3)
Ethnic group	
Chinese	1078 (60.4)
Malay	496 (27.8)
Indian	62 (3.5)
Others	148 (8.3)
COVID-19 Vaccines Received and Breastfeeding History [n (%)]	
1 dose	213 (11.9)
2 doses	1571 (88.1)
Milk intake of the child	
Totally breastfed	1010 (56.6)
Half human milk, half other liquids	336 (18.8)
Some human milk, mostly other liquids	36 (2.0)

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Some human milk, mostly other solid feeds	396 (22.2)
Indeterminate	6 (0.4)
Medical History of Respondents [n (%)]	
Significant maternal past medical history	
NIL	1622 (91.0)
Asthma	34 (1.9)
Cardiovascular diseases	12 (0.7)
Type 2 diabetes mellitus	8 (0.4)
Autoimmune diseases	8 (0.4)
Others	100 (5.6)
Maternal medications	
None	1691 (94.8)
Medications (e.g., Domperidone) to improve milk supply	4 (0.2)
Immunosuppressant	7 (0.4)
Medications for asthma	6 (0.3)
Oral contraceptive	18 (1.0)
Others	58 (3.3)
Maternal allergy history	
None	1427 (80.0)
Drug allergy	179 (10.0)
Food allergy	78 (4.4)
Environmental allergy	61 (3.4)
Multiple allergies	39 (2.2)

3.2. Reactogenicity of COVID-19 Vaccines

Table 2 shows the reactogenicity of COVID-19 vaccines among mother and baby dyads.

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3.2.1 Impact on Lactating Mothers

The commonest symptom reported was local reaction at the injection site at 66.3% (1183/1784) and 57.7% (906/1571) after the first and second dose of COVID-19 vaccinations respectively. 43.7% (780/1784) of the respondents reported experiencing worse symptoms when receiving the second dose compared to the first dose.

Other commonly reported symptoms were fatigue {(32.4% (578/1784) versus 42.4% (666/1571)} and headache {(22.7% (405/1784) versus 31.4% (494/1571)} for the first and second dose respectively. When analysing mRNA and non-mRNA respondents separately, this trend remained consistent. The incidence of fatigue, headache, increased tactile body temperature, enlarged lymph nodes, nausea, and fever over 38°C were significantly higher after the second dose compared to the first dose ($p<0.05$). This trend was consistent in the subgroup analysis of the breastfeeding mothers who received mRNA COVID-19 vaccines. In contrast, mothers who received non-mRNA vaccines reported fewer side effects {(i.e., significant local reactions, fatigue, headache, increased tactile body temperature, lymph node reaction, nausea, and fever ($p<0.05$)} when receiving their second dose compared to the first dose.

Some other minor and less common post-vaccination reactions were also reported by 4.4% (79/1784) and 8.5% (133/1571) respondents following the first and second dose respectively. These reactions included body aches, bloating, chills, giddiness, insomnia, joint pains, and menstrual disturbances, palpitations for less than an hour, tingling limbs, and sore throat. 1.1% (19/1784) and 1.0% (16/1571) of respondents reported allergy-related symptoms (i.e., hives, itchy eyes) after the first and second dose respectively. Reassuringly, no respondent developed anaphylaxis or other severe adverse reactions such as myocarditis or cerebrovascular accidents.

3.2.2 Impact on Lactation

11.9% (213/1784) of respondents received one dose while 88.1% (1571/1784) of respondents received two doses of COVID-19 vaccination while breastfeeding. About half (51.7%; 923/1784) of respondents did not experience any change in lactation outcomes, remaining 48.3% (861/1784) of respondents reported a change in lactation outcomes. The commonest reported change was related to breastmilk supply. 11.7% (25/213) and 13.6% (214/1571) of respondents reported a reduction in breastmilk supply following one and two doses respectively. Whereas, an increase in breastmilk supply was reported by 12.7% (27/213), and 11.8% (186/1571) of those who received one or two doses of vaccines respectively. A minority of the respondents (1.4%; 25/1784) reported other less common side effects including the sensation of clogged ducts, thicker breastmilk consistency, and variations in breastmilk supply (e.g., decrease in milk supply after dose 1 followed by an increase in supply after dose 2). 2.3% (5/213) and 2.4% (37/1571) reported a change in milk colour following one or two doses respectively.

Respondents who received non-mRNA vaccines were less likely to report any change in lactation outcomes or soreness in the breast compared to those who received mRNA vaccine ($p<0.05$). Respondents who exclusively breastfed were more likely to report breast engorgement and changes in breastmilk supply ($p<0.05$). The length of reported symptoms related to lactation was median 3 days, IQR 3 days. 1.2% (21/1784) reported that their breastmilk supply was perpetually altered by the vaccine; out of which 38.1% (8/21) reported an increase, while 61.9% (13/21) experienced a reduction.

6.2% (110/1784) of respondents stopped breastfeeding for at least 24 hours after COVID-19 vaccination. Far more respondents who received mRNA vaccines stopped breastfeeding: 97.2% (107/110) compared to 2.8% (3/110) of those who received non-mRNA vaccines ($p <0.05$). The reasons stated included advice from medical experts

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(26.4%; 29/110), abundance of caution (25.5%; 28/110), limited availability of clinical research data (12.7%; 14/110), fear of potential negative impact on the breastfed child (12.7%; 14/110) while 22.7% (25/110) did not specify any reason for cessation of breastfeeding.

In addition, 8.0% (143/1784) respondents expressed and discarded their breastmilk for a mean of 7.5 +/- 5.5 days following vaccination. 0.8% (14/1784) chose to discard the first pump of expressed breastmilk after their COVID-19 vaccination and then continued to breastfeed as per normal.

3.2.3 Impact on Child

There were no major reported adverse effects in the breastfed children of mothers who received COVID-19 vaccination. The more common symptoms reported were rashes {(6.6% (14/213) versus 2.2% (34/1571)}, diarrhoea {(1.9% (4/213) versus 2.0% (32/1571)}, fever {(1.9% (4/213) versus 2% (33/1571)} and runny nose {(2.8% (6/213) versus 1.2% (19/1571)} for mothers receiving one and two doses of vaccinations respectively. There was no significant difference in child's outcomes when comparing mRNA and non-mRNA vaccine cohorts.

92.9% (1658/1784) of these breastfed children had no reported changes in behaviour after their mothers received COVID-19 vaccine. The more commonly reported behavioural symptoms were being sleepier than usual {(2.8% (6/213) and 2.4% (38/1571)} and increased fussiness {(3.3% (7/213), 2.8% (44/1571)} following first and second dose respectively. There was no significant difference in any behavioural outcomes for the children between mothers who received one or two doses of vaccine, regardless of the type of vaccine. Of the 126 respondents who reported changes in their child's symptoms, 11.9% (15/126) acknowledged that their assessment of their child's behavioural change might be confounded by other events such as teething, intercurrent illness, administration of other routine childhood vaccinations, etc.

Table 2. Maternal-Child Outcomes of Respondents Who Received COVID-19 Vaccine(s)

Adverse Reactions Among Lactating Mothers Who Received COVID-19 Vaccine(s)

Type of Adverse Reactions	Dose 1 mRNA [n (%)] n=1539	Dose 2 mRNA [n (%)] n= 1344	P value	Dose 1 non-mRNA [n (%)] n=245	Dose 2 non-mRNA [n (%)] n= 227	P value	Dose 1 overall [n (%)] n=1784	Dose 2 overall [n (%)] n= 1571	P value
No symptoms	256 (16.6)	147 (10.9)	*<0.05*	91 (37.1)	115 (50.6)	*<0.05*	347 (19.5)	262 (16.7)	*<0.05*
Reaction at the injection site	1110 (72.1)	858 (63.8)	*<0.05*	73 (29.8)	48 (21.1)	*<0.05*	1183 (66.3)	906 (57.7)	*<0.05*
Fatigue or low mood	503 (32.7)	627 (46.7)	*<0.05*	75 (30.6)	39 (17.2)	*<0.05*	578 (32.4)	666 (42.4)	*<0.05*
Headache	326 (21.2)	460 (34.2)	*<0.05*	79 (32.2)	34 (15.0)	*<0.05*	405 (22.7)	494 (31.4)	*<0.05*

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Body temperature up to 38C	171 (11.1)	369 (27.5)	*<0.05*	47 (19.2)	8 (3.5)	*<0.05*	218 (12.2)	377 (24.0)	*<0.05*
Soreness and enlarged lymph node	55 (3.6)	95 (7.1)	*<0.05*	1 (0.4)	1 (0.4)	*1.00*	56 (3.1)	96 (6.1)	*<0.05*
Nausea	47 (3.1)	73 (5.4)	*<0.05*	14 (5.7)	3 (1.3)	*<0.05*	61 (3.4)	76 (4.8)	*<0.05*
Fever (over 38°C)	33 (2.1)	148 (11.0)	*<0.05*	15 (6.1)	2 (0.8)	*<0.05*	48 (2.7)	150 (9.5)	*<0.05*
Runny nose	25 (1.6)	46 (3.4)	*<0.05*	6 (2.5)	1 (0.4)	*0.07*	31 (1.7)	47 (3.0)	*<0.05*
Diarrhoea	22 (1.4)	27 (2.1)	*0.23*	4 (1.6)	3 (1.3)	*0.54*	26 (1.5)	30 (1.9)	*0.31*
Chest pain	23 (1.5)	28 (2.1)	*0.23*	6 (2.5)	6 (2.6)	*0.56*	29 (1.6)	34 (2.2)	*0.25*
Cough	10 (0.7)	13 (0.9)	*0.34*	3 (1.2)	0 (0)	*0.14*	13 (0.8)	13 (0.8)	*0.74*
Vomiting	7 (0.5)	12 (0.8)	*0.15*	2 (0.8)	1 (0.4)	*0.52*	9 (0.5)	13 (0.8)	*0.25*
Allergic symptoms	17 (1.1)	12 (0.9)	*0.57*	2 (0.8)	4 (1.8)	*0.31*	19 (1.1)	16 (1.0)	*0.89*
Others	74 (4.8)	128 (9.5)	*<0.05*	5 (2.0)	5 (2.2)	*0.58*	79 (4.4)	133 (8.5)	*<0.05*

Comparison of Dose 1 vs Dose 2 of Vaccines Received

Comparison	mRNA [n (%)] n=1539	non-mRNA [n (%)] n=245	P value	Total [n (%)] n=1784
No symptoms experienced either time	74 (4.8)	73 (29.8)	<0.05	147 (8.2)
Reaction same for both doses	248 (16.1)	41 (16.7)	0.06	289 (16.2)
Reaction worse for first dose	231 (15.0)	64 (26.1)	<0.05	295 (16.5)
Reaction worse for second dose	744 (48.3)	36 (14.7)	<0.05	780 (43.7)

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Not applicable (only one dose received, or unable to make a comparison)	242 (15.7)	31 (12.7)	0.22	273 (15.3)					
Lactation-related Outcomes of Mothers Who Received COVID-19 Vaccine(s) [n (%)]									
Type of Outcome	Received only one mRNA dose [n (%)] n=195	Received two mRNA doses [n (%)] n=1344	P value	Received only one non-mRNA dose [n (%)] n=18	Received two non-mRNA doses [n (%)] n=227	P value	Received only one vaccine dose (overall) [n (%)] n=213	Received two vaccine doses (overall) [n (%)] n=1571	P value
No change in milk supply	104 (53.3)	638 (47.5)	*0.13*	11 (61.1)	147 (64.8)	*0.76*	115 (54.0)	785 (50.0)	*0.27*
Reduction in milk supply	24 (12.3)	194 (14.4)	*0.43*	1 (5.6)	20 (8.8)	*0.63*	25 (11.7)	214 (13.6)	*0.49*
Increase in milk supply	24 (12.3)	159 (11.8)	*0.85*	3 (16.7)	27 (11.9)	*0.55*	27 (12.7)	186 (11.8)	*0.72*
Breast engorgement	9 (4.6)	81 (6.0)	*0.43*	0 (0)	10 (4.4)	*0.46*	9 (4.2)	91 (5.8)	*0.25*
Change in milk colour	5 (2.6)	36 (2.7)	*0.93*	0 (0)	1 (0.4)	*0.92*	5 (2.3)	37 (2.4)	*0.99*
Soreness of breast	11 (5.6)	62 (4.6)	*0.53*	1 (5.6)	2 (0.9)	*0.20*	12 (5.6)	64 (4.1)	*0.29*
Nipple pain	9 (4.6)	72 (5.4)	*0.66*	2 (11.1)	10 (4.4)	*0.22*	11 (5.2)	82 (5.2)	*0.97*
Lymph node swelling at the neck or axillary areas	2 (1.0)	31 (2.3)	*0.25*	0 (0)	3 (1.3)	*0.79*	2 (0.9)	34 (2.2)	*0.23*
Breast redness	2 (1.0)	30 (2.2)	*0.27*	0 (0)	5 (2.2)	*0.68*	2 (0.9)	35 (2.2)	*0.22*
Others	5 (2.6)	41 (3.1)	*0.71*	0 (0)	2 (0.9)	*0.86*	5 (2.3)	43 (2.7)	*0.74*
Outcomes of Breastfed Children Whose Mothers Received At Least One Dose of COVID-19 Vaccine While Breastfeeding [n (%)]									

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Type of Infant Outcome	Received only one mRNA dose [n (%)] n=195	Received two mRNA doses [n (%)] n=1344	P value	Received only one non-mRNA dose [n (%)] n=18	Received two non-mRNA doses [n (%)] n=227	P value	Received only one vaccine dose (overall) [n (%)] n=213	Received two vaccine doses (overall) [n (%)] n=1571	P value
Rash	13 (6.6)	29 (2.2)	*<0.05*	0 (0)	5 (2.2)	*0.52*	14 (6.6)	34 (2.2)	*<0.05*
Diarrhoea	4 (2.1)	28 (2.1)	*0.98*	0 (0)	4 (1.8)	*0.57*	4 (1.9)	32 (2.0)	*0.88*
Fever	4 (2.1)	28 (2.1)	*0.98*	0 (0)	5 (2.2)	*0.52*	4 (1.9)	33 (2.1)	*0.83*
Runny nose	6 (3.1)	17 (1.3)	*0.05*	0 (0)	2 (0.9)	*0.69*	6 (2.8)	19 (1.2)	*0.06*
Cough	3 (1.5)	15 (1.1)	*0.61*	0 (0)	2 (0.9)	*0.69*	3 (1.4)	17 (1.1)	*0.67*
Vomiting	2 (1.0)	6 (0.4)	*0.29*	0 (0)	0 (0)	*N/A*	2 (0.9)	6 (0.4)	*0.25*
Refusal to feed	0 (0)	1 (0.1)	*0.70*	0 (0)	0 (0)	*N/A*	0 (0)	1 (0.1)	*0.71*
Behavioural Outcomes of Breastfed Children Whose Mothers Received At Least One Dose of COVID-19 Vaccine While Breastfeeding [n (%)]									
Type of Outcome	Received only one mRNA dose [n (%)] n=195	Received two mRNA doses [n (%)] n=1344	P value	Received only one non-mRNA dose [n (%)] n=18	Received two non-mRNA doses [n (%)] n=227	P value	Received only one vaccine dose (overall) [n (%)] n=213	Received two vaccine doses (overall) [n (%)] n=1571	P value
No significant behavioural changes	177 (90.8)	1244 (92.6)	0.38	17 (94.4)	220 (96.9)	0.57	194 (91.1)	1464 (93.2)	0.26
Sleepier than usual	6 (3.1)	36 (2.7)	0.75	0 (0)	2 (0.8)	0.86	6 (2.8)	38 (2.4)	0.73
Increased fussiness	6 (3.1)	42 (3.1)	0.97	1 (5.6)	2 (0.8)	0.21	7 (3.3)	44 (2.8)	0.69
Refusal to feed	1 (0.5)	5 (0.4)	0.56	0 (0)	1 (0.4)	0.93	1 (0.4)	6 (0.4)	0.85

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Others	5 (2.6)	17 (1.3)	0.15	0 (0)	2 (0.8)	0.86	5 (2.3)	19 (1.2)	0.18

3.2.4 Subgroup Analysis of non-mRNA Vaccines

Table 3 shows selected maternal and child outcomes among non-mRNA vaccines recipients.

Among the 13.7% (245/1784) respondents who received non-mRNA COVID-19 vaccinations, the commoner symptoms were an increase in milk supply {(16.7%; 3/18 versus 11.9% (27/227)}, decrease in milk supply {(5.6% (1/18) versus 8.8% (20/227)} and pain in the breast {(11.1% (2/18), 4.4% (10/227)} following first and second dose respectively. Less common symptoms reported were change in milk colour (0.4 % (1/227) and local lymph node swelling (1.3% (3/227) respectively. When comparing lactation outcomes between respondents who received the Sinovac and Oxford-AstraZeneca vaccines, there were no significant differences. The more commonly reported lactation changes (fluctuations in breastmilk supply and pain in the breast) for the non-mRNA vaccines were similar to that of respondents who received mRNA vaccines. None of the mothers who took the Oxford-AstraZeneca vaccine experienced changes in breastmilk colour, local lymph node swelling or breast redness. There were no differences in child outcomes comparing the Sinovac and Oxford-AstraZeneca vaccines. However, there were significantly fewer children with any behavioural changes in the Oxford-AstraZeneca cohort ($p<0.05$) compared to the Sinovac vaccine.

Table 3. Maternal-Child Outcomes of Respondents Who Received non-mRNA Vaccine

Lactation-related Outcomes of Mothers Who Received COVID-19 Vaccine [n (%)]			
Type of Outcome	Received one or two doses of Sinovac vaccine [n (%)] n=162	Received one or two doses of Oxford-AstraZeneca vaccine [n (%)] n=83	Comparison (p value)
No change in milk supply	98 (60.4)	60 (72.3)	*0.07*
Reduction in milk supply	16 (9.9)	5 (6.0)	*0.31*
Increase in milk supply	19 (11.7)	11 (13.3)	*0.73*
Breast engorgement	7 (4.3)	3 (3.6)	*0.54*
Change in milk colour	1 (0.6)	0 (0)	*0.66*
Soreness of breast	2 (1.2)	1 (1.2)	*0.73*

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Nipple pain	9 (5.6)	3 (3.6)	*0.37*
Lymph node swelling at the neck or axillary areas	3 (1.9)	0 (0)	*0.29*
Breast redness	5 (3.1)	0 (0)	*0.13*
Other lactation complaints	2 (1.2)	0 (0)	*0.43*
Outcomes of Breastfed Children Whose Mothers Received At Least One Dose of COVID-19 Vaccine While Breastfeeding [n (%)]			
Type of Outcome	Received one or two doses of Sinovac vaccine [n (%)] n=162	Received one or two doses of Oxford-AstraZeneca vaccine [n (%)] n=83	Comparison (p value)
Rash	3 (1.9)	1 (1.2)	*0.58*
Diarrhoea	4 (2.5)	1 (1.2)	*0.45*
Fever	2 (1.2)	3 (3.6)	*0.22*
Runny nose	2 (1.2)	1 (1.2)	*0.73*
Cough	2 (1.2)	0 (0)	*0.44*
Vomiting	0 (0)	1 (1.2)	*0.34*
Refusal to feed	0 (0)	1 (1.2)	*0.34*
Behavioural Outcomes of Breastfed Children Whose Mothers Received At Least One Dose of COVID-19 Vaccine While Breastfeeding [n (%)]			
Type of Outcome	Received one or two doses of Sinovac vaccine [n (%)] n=162	Received one or two doses of Oxford-AstraZeneca vaccine [n (%)] n=83	Comparison (p value)
No significant behavioural changes reported	146 (90.1)	81 (97.6)	*<0.05*

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Sleepier than usual	1 (0.6)	1 (1.2)	*0.56*
Increased fussiness	2 (1.2)	1 (1.2)	*0.73*
Refusal to feed	1 (0.6)	0 (0)	*0.66*
Others	2 (1.2)	0 (0)	*0.44*

4. Discussion

There is no biological plausibility that COVID-19 vaccines would cause harm to the breastfed children as the vaccines do not contain live components and there is no known risk associated with being given a non-live vaccine while breastfeeding [12]. However, there is a paucity of data reporting both non-mRNA and mRNA COVID-19 vaccination of lactating women with representation from wider geographical locations and ethnicities to further boost vaccination rates among lactating women. In particular, the data reporting side effects of non-mRNA vaccines, such as the widely-used Sinovac, among lactating mother and child dyads are lacking. COVID-19 vaccines are currently not authorised to be used for infants and toddlers [13], hence passive transplacental transfer of antibody coupled with breastfeeding from immunised mothers remains the only viable option for protecting this vulnerable group. Thus, this study lends a unique perspective on the short-term COVID-19 vaccine reactogenicity by surveying a large Southeast Asian population of breastfeeding mother-child dyads, whereby about 1 in 10 (9.1%; 162/1784) received the Sinovac vaccination.

In this study, most respondents reported only suspected reactions in themselves which were similar to reports for the general population. Approximately 80% of respondents reported some reactions for both doses at a rate that is similar to several other studies among breastfeeding mothers [14-17]. In general, respondents receiving non-mRNA vaccines reported less frequent adverse events compared to mRNA vaccines. For example, about 50% of non-mRNA vaccine recipients did not experience any symptoms after the second dose; the corresponding number for mRNA vaccine recipients was 10.9%. Similarly, 64.8% of the mothers did not report any change in milk supply after the second dose of non-mRNA vaccine compared to 47.8% among mRNA vaccine recipients. The reported rate of change in child behaviour was low in our study with over 90% mothers reported no change following the first and second dose of either mRNA or non-mRNA vaccines.

In sub-group analysis with 310 breastfeeding mothers, both Oxford-AstraZeneca and Sinovac vaccines fared favourably with more widely used mRNA vaccines. Our study demonstrated that non-mRNA vaccines, especially the Oxford-AstraZeneca vaccine, appear to have better reactogenicity, lactation-related outcomes and child outcomes compared to mRNA vaccines. Between the two non-mRNA vaccines, Oxford-AstraZeneca was better in terms of adverse events experienced by mothers, lactational outcomes, and incidence of change in child behaviours. Our study augments findings from another smaller study with 20 nursing mothers who received 2 doses of the Sinovac vaccine in which the mothers did not report any adverse effects in their breastfed children [9].

Symptoms reported for the breastfed children such as increased fussiness, rashes, diarrhoea and respiratory tract symptoms are common among young children, hence the effects reported may have no causal relationship to the COVID-19 vaccination of the breastfeeding mother. Our findings are in keeping with other reported literature whereby

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the majority surveyed reported no or minor side effects among breastfed children following maternal vaccination [14-16].

The majority respondents reported no change to their lactation quantity or quality following vaccination. The commonest effect experienced was a transient change in the quantity of breastmilk supply, with increased or decreased supply reported at similar frequencies. This is in keeping with reported literature [14-16].

A few plausible mechanisms whereby maternal symptoms may impact lactation exist. A myriad of factors can affect breastmilk supply, including general maternal health, amount of sleep, and anxiety. Maternal fever could have a detrimental impact on breastfeeding by reducing the total body water available for milk production as fever increases metabolic demands [16]. Secondly, fatigue may contribute to a reduction in breastmilk supply [18]. Hence, it may be helpful for breastfeeding women to be counselled on strategies to maintain their breastmilk, particularly if they are feeling unwell following vaccination.

Limitations in our study include subjective reports from study participants; for example, there was no measurement of milk volume to quantify any perceived change in milk supply. Participants' reported symptoms and signs were not verified by healthcare professionals. As with self-reported surveys, there is a possibility of recall bias resulting in over- or underestimation of the events reported.

Nevertheless, our study allows a better understanding of the effects and safety of four commonly used mRNA and non-RNA COVID-19 vaccines among lactating mothers and their infants. Our study lends further support to other published studies with more study participants and wider geographical and racial mix. In the face of potential threat for new COVID-19 variants, further studies appraising adverse events incidence in relation to booster doses and vaccine interchangeability are still needed to provide a broader safety aspect for the vaccines currently being used for this population.

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References

1. Jiang, L., Tang, K., Levin, M., Irfan, O., Morris, S., Wilson, K., Klein, J. and Bhutta, Z. COVID-19 and multisystem inflammatory syndrome in children and adolescents. *The Lancet Infectious Diseases* **2020**, 20(11), pp. 276-e288.
2. Bixler, D., Miller, A., Mattison, C., Taylor, B., Komatsu, K., Peterson Pompa, X., Moon, S., Karmarkar, E., Liu, C., Openshaw, J., Plotzker, R., Rosen, H., Alden, N., Kawasaki, B., Siniscalchi, A., Leapley, A., Drenzek, C., Tobin-D'Angelo, M., Kauerauf, J., Reid, H., Hawkins, E., White, K., Ahmed, F., Hand, J., Richardson, G., Sokol, T., Eckel, S., Collins, J., Holzbauer, S., Kollmann, L., Larson, L., Schiffman, E., Kittle, T., Hertin, K., Kraushaar, V., Raman, D., LeGarde, V., Kinsinger, L., Peek-Bullock, M., Lifshitz, J., Ojo, M., Arciuolo, R., Davidson, A., Huynh, M., Lash, M., Latash, J., Lee, E., Li, L., McGibbon, E., McIntosh-Beckles, N., Pouchet, R., Ramachandran, J., Reilly, K., Dufort, E., Pulver, W., Zamcheck, A., Wilson, E., de Fijter, S., Naqvi, O., Nalluswami, K., Waller, K., Bell, L., Burch, A., Radcliffe, R., Fiscus, M., Lewis, A., Kolsin, J., Pont, S., Salinas, A., Sanders, K., Barbeau, B., Althomsons, S., Atti, S., Brown, J., Chang, A., Clarke, K., Datta, S., Iskander, J., Leitgeb, B., Pindyck, T., Priyamvada, L., Reagan-Steiner, S., Scott, N., Viens, L., Zhong, J., Koumans, E., Blythe, D., Harduar Morano, L., Black, C., McCabe, C. and Lin, X. SARS-CoV-2–Associated Deaths Among Persons Aged <21 Years — United States, February 12–July 31, 2020. *MMWR. Morbidity and Mortality Weekly Report* **2020**, 69(37), pp.1324-1329.
3. Low, J., Gu, Y., Ng, M., Amin, Z., Lee, L., Ng, Y., Shunmuganathan, B., Niu, Y., Gupta, R., Tambyah, P., MacAry, P., Wang, L. and Zhong, Y. Codominant IgG and IgA expression with minimal vaccine mRNA in milk of BNT162b2 vaccinees. *npj Vaccines* **2021**, 6(1).
4. Juncker, H., Mulleners, S., Coenen, E., van Goudoever, J., van Gils, M. and van Keulen, B. Comparing Human Milk Antibody Response After 4 Different Vaccines for COVID-19. *JAMA Pediatrics* **2022**.
5. Ministry of Health Singapore. Expert Committee on COVID-19 vaccination expands medical eligibility for mRNA vaccines. Available online: https://www.moh.gov.sg/news-highlights/details/expert-committee-on-covid-19-vaccination-expands-medical-eligibility-for-mrna-vaccines (accessed on 23/02/2022).
6. Ministry of Health Malaysia. Guidelines for COVID-19 vaccination 02/03/2021. Available online: https://covid-19.moh.gov.my/garis-panduan/garis-panduan-kkm/Annex_48b_CLINICAL_GUIDELINES_ON_COVID-19_VACCINATION_AstraZeneca_2802021.pdf (accessed on 01/02/2022).
7. Mayo, S. and Monfort, S. Letter to the Editor: Breastfeeding and COVID-19 Vaccine: Yes We Can. *Journal of Human Lactation* **2021**, 37(2).
8. The Breastfeeding Network. Update on Coronavirus and breastfeeding. Available online: https://www.breastfeedingnetwork.org.uk/coronavirus/ (accessed on 25/02/2022).
9. Calil, V., Palmeira, P., Zheng, Y., Krebs, V., de Carvalho, W. and Carneiro-SampaioI, C. CoronaVac can induce the production of anti-SARS-CoV-2 IgA antibodies in human milk. *Clinics (Sao Paolo)* **2021**, 76.
10. Chua, L. and Win, A. Prevalence of breastfeeding in Singapore. Available online: https://www.singstat.gov.sg/-/media/files/publications/society/ssnsep13-pg10-14.pdf (accessed on 28/02/2022).
11. Ministry of Health Malaysia. V. Nutrition. In National Health and Morbidity Survey 2016: Maternal and Child Health, *Volume 2: Maternal and Child Health Findings*; Publisher: Institute for Public Health, National Institutes of Health (NIH), Ministry of Health, Malaysia, 2016; Volume 2, pp. 23-24.
12. National Library of Medicine (US). COVID-19 vaccines [Updated 2022 Mar 21], Drugs and Lactation Database (LactMed), National Center for Biotechnology Information. Available online: https://www.ncbi.nlm.nih.gov/books/NBK565969/ (accessed on 22/02/2022).
13. Centers for Disease Control and Prevention: COVID-19 Vaccination for Children. Available online: https://www.cdc.gov/vaccines/covid-19/planning/children.html#covid19-vax-recommendations (accessed on 24/04/2022)
14. Bertrand, K., Honerkamp-Smith, G. and Chambers, C. Maternal and Child Outcomes Reported by Breastfeeding Women Following Messenger RNA COVID-19 Vaccination. *Breastfeeding Medicine* **2021**, 16(9), pp.697-701.
15. Gray, K., Bordt, E., Atyeo, C., Deriso, E., Akinwunmi, B., Young, N., Baez, A., Shook, L., Cvrk, D., James, K., De Guzman, R., Brigida, S., Diouf, K., Goldfarb, I., Bebell, L., Yonker, L., Fasano, A., Rabi, S., Elovitz, M., Alter, G. and Edlow, A. Coronavirus disease 2019 vaccine response in pregnant and lactating women: a cohort study. *American Journal of Obstetrics and Gynecology* **2021**, 225(3), pp.303.e1-303.e17.
16. McLaurin-Jiang, S., Garner, C., Krutsch, K. and Hale, T. Maternal and Child Symptoms Following COVID-19 Vaccination Among Breastfeeding Mothers. *Breastfeeding Medicine* **2021**, 16(9), pp.702-709.
17. Low, J., Lee, L., Ng, Y., Zhong, Y. and Amin, Z. Breastfeeding Mother and Child Clinical Outcomes After COVID-19 Vaccination. *Journal of Human Lactation* **2021**, p.089033442110565.
18. Callahan, S., Séjourné, N. and Denis, A. Fatigue and Breastfeeding: An Inevitable Partnership?. *Journal of Human Lactation* **2006**, 22(2), pp.182-187.