

Infant Feeding Type of Children Who Qualify For SARS-CoV-2 Testing: An Observational Study.

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Short report

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Abstract

Background: It has been demonstrated that children who had been breastfed remain better protected against various infections, and notably respiratory tract infections, well beyond infancy. Since the role of breastfeeding to explain why children are less affected by COVID-19 has not been studied until now, the aim of this study was to determine whether any history of breastfeeding reduces the incidence rate of COVID-19 in children.

Methods: This was a secondary analysis of an observational study on clinical and epidemiological characteristics of pediatric COVID-19 in Majorca. A total of 691 children were recruited. Eligible participants were children under 14 who were tested for SARS-CoV-2 in pediatric emergency services. The independent explanatory variable was initial breastfeeding. Bivariate analyses were conducted through the Chi-square test, the Fisher's Exact test or the Student's T test.

All children had the same demographic, epidemiological and clinical data collected through a study team member interview and via the participants medical records. Aspredicted Trials Registry number is #62721.

Results: Within the sample of children who visited emergency services with symptoms of potential COVID-19, we found higher prevalence of positive SARS-CoV-2 RT-PCR test results among those who were exclusively formula fed compared with those who were ever breastfed (OR, 2.48; 95%CI, 1.45-3.51; $P=0.036$).

Conclusions: Since approximately 1 in 60 ever breastfed symptomatic children had tested positive for SARS-CoV-2 versus 1 in 25 never breastfed symptomatic children, this study shows that initially breastfed children remain at lower risk of COVID-19.

Background

In contrast to other respiratory viruses, children have been less affected by COVID-19 than adults. Furthermore, for reasons that remain elusive, the vast majority of reported infections in children are mild or asymptomatic. Recent reviews have proposed a wide range of mechanisms for this difference, including factors such as concurrent infections, differences in microbiota, anti-oxidative properties, or protective effects of vaccine [1].

However, as far as we know, the role of pre-exposure to mother's milk as a protective factor against COVID-19 has not been critically reviewed. Human milk contains an array of antimicrobial, anti-inflammatory, and immunomodulatory compounds that confer long-term benefits against infections years after lactation is terminated [2].

Given this latter possibility and that a detailed examination of risk factors for COVID-19 in this unique population is needed, we used a cohort of children to explore the hypothesis that the risk of pediatric

COVID-19 is attenuated among children who were ever breastfed. The secondary aim of this study was to compare the clinical spectrum of children attending emergency services (ESs) during the COVID-19 pandemic according to infant feeding categories. We expect to provide new insight into the emergence and early outcomes of children infected with COVID-19.

Methods

This is a secondary analysis of COVID IB4221/20PI, an ongoing multicentric observational study of clinical and epidemiological features of children who present for care in one of thirteen participating pediatric ESs located in Majorca, Spain, during the late summer and autumn 2020 period of the COVID-19 pandemic.

Study strategy

This study was conducted in two University Hospitals, a District Hospital, nine healthcare centers for community Pediatrics, and a Private Hospital, where COVID-19 testing was conducted free of charge.

Study design and participants

The first aim of our study was to analyze the effect of exclusive formula-feeding on the risk of testing positive for SARS-CoV-2. The secondary aim was to examine the relationship between breastfeeding type and symptoms or diagnosis of children attending ESs during the COVID-19 pandemic. Eligible participants were those younger than 14 years of age who presented to a participating ES for care and who were tested for SARS-CoV-2 because of suspected COVID-19, ambulatory care or scheduled hospital procedures on the 2nd and 16th of each month from August to December 2020. The assay intended for nucleic acid detection was the SARS-CoV-2 test (E, N and RdRP gene detection) from nasopharyngeal swab specimens.

Data collection

At enrollment in the ES, regardless of SARS-CoV-2 test results, all children had the same information collected, including demographic, epidemiological and clinical data. Baseline data: A study team member completed the enrollment form using the participants medical records and through a caregiver interview. Data collected: calendar date and site of enrollment, recent travel, exposures, household conditions, age, sex, health information (e.g., infant feeding, past medical history, weight, height), onset of current illness (e.g., timing, symptoms), and laboratory investigations performed in the ES. Study team members asked specifically about fever, asthenia, pain, diarrhea or respiratory symptoms, as well as other new or worsening health problems, and recorded the discharge diagnoses. Any episode of acute otitis media (AOM) was validated with clinical examination.

Growth patterns. Percentiles of body mass index (BMI) were determined according to the Spanish Orbegozo Foundation growth charts [3]. A child's weight status was established as defined by the Centers

of Disease Control [4]: individuals who had BMI values below the 5th percentile were classified as underweight, healthy weight was defined as a BMI at or above the 5th percentile and below the 85th percentile, overweight was defined as a BMI at or above the 85th percentile and below the 95th percentile, and obesity was defined as a BMI at or above the 95th percentile.

Estimation of breastfeeding rate. The independent explanatory variable was initial breastfeeding. A brief interviewer-administered question was used to collect quality data recalled about lactation: "Was [child] ever breastfed directly at the breast?" Answer options: Yes / No / Don't know / Refused. This is the first question of the validated Brief Breastfeeding and Milk Expression Recall Survey [5].

Sample size

At the time of study development, the wide variation of COVID-19 incidence rate in pediatric patients (1%-16%) [6] precluded a robust sample size estimate. Hence, we have opted for a convenience sample of children screened for COVID-19 at the ES of Majorca during five months (August-December 2020) of the COVID-19 pandemic.

Data analysis

Statistical analyses were performed with IBM SPSS v.23 statistical software. Categorical data were presented as percentages. Normally distributed variables were described by means \pm standard deviations. Proportions were compared using the Pearson's chi-squared or the Fisher's exact tests. Differences between means were studied through the Student's T test. A *P* value < 0.05 was considered statistically significant.

Ethics

The study was approved by the Balearic Conjoint Health Research Ethics Review Board. There is no direct benefit of study participation. Weekly interim analysis allowed for real-time data sharing with regional policy makers. A research team member at each institution contacted in-person the guardian/caregiver/child to obtain written informed consent and assent, as appropriate.

Preregistration: Aspredicted Trials Registry number is #62721.

Results

This sample consisted of 691 children with consistent information regarding infant feeding. The mean age of recruited children was 67.8 (standard deviation 52.5) months. Most children had no known comorbidities (81%), and they were predominantly male (55%). Sixty eight per cent of participant children were initially breastfed, and thirty two per cent were never breastfed. There were no differences between the groups in terms of age, sex, comorbidity, height or weight. However, there were some differences among breastfed and formula-fed groups in terms of BMI and housing. Lower BMI of children was

positively linked to breastfeeding rates. In addition, breastfed children were found to live in households with fewer children, as opposed to formula-fed children. The baseline characteristics of the study sample compared by feeding categories are available in Table 1.

Table 1
Baseline and demographic characteristics of patients

Variables	No breastfeeding	Any breastfeeding	P value
Number (%)	220 (32%)	471 (68%)	
CHILDREN'S CHARACTERISTICS			
Age (months)	67.2 ± 51.7	69.3 ± 54.3	0.611
Female/male gender	97/123	211/260	0.862
Height (cm)	120.9 ± 28.9	116.8 ± 33.9	0.515
Weight (kg)	24.0 ± 15.9	23.6 ± 16.1	0.762
Body mass index ^a (kg/m ²)	0 (0%)	8 (8.3%)	0.042*
• underweight	24 (65%)	50 (52%)	
• healthy weight	5 (13.5%)	27 (28%)	
• overweight	8 (21.5%)	11 (11.7%)	
• obese			
Known comorbidities	46 (20.4%)	88 (18.7%)	0.535
HOUSING CONDITIONS			
Children under 5 in the household	0.78 ± 0.72	0.80 ± 0.69	0.742
Children under 10 in the household	1.30 ± 0.95	0.97 ± 0.84	< 0.0001***
Children under 15 in the household	2.25 ± 1.53	1.61 ± 1.31	< 0.0001***
HEALTH CARE FACILITY			
Private pediatric settings	77 (35.0%)	139 (30.1%)	0.073
Public pediatric settings	143 (65.0%)	322 (69.9%)	
• Urban pediatric settings	186 (84.5%)	384 (81.5%)	0.331
• Rural pediatric settings	34 (14.5%)	87 (18.5%)	
Values are presented as number (%) or means ± standard deviations.			
^a according to the Centers of Disease Control percentiles.			
ABBREVIATIONS: * ≤ 0.05.			

Clinical outcomes. Our study showed that exclusive formula-feeding was associated with a significant increase in the risk of headache (OR, 4.40; 95%CI, 1.31–14.79; $P=0.016$), AOM (OR, 2.04; 95%CI, 1.08–3.82; $P=0.026$), and positive SARS-CoV-2 RT-PCR test results in symptomatic children (OR, 2.48; 95%CI, 1.45–3.51; $P=0.036$). The proportion of all exclusively formula-fed children (with or without symptoms) who tested positive for SARS-CoV-2 was also higher compared with the group of ever breastfed children (with or without symptoms); this difference did not reach statistical significance (OR, 2.18; 95%CI, 1.19–3.17; $P=0.056$) but may be clinically significant. Only one patient who tested positive for SARS-CoV-2 was admitted into hospital; he was a never breastfed 13 years old boy. There were no significant differences between the two groups for the rest of observed clinical outcomes (Table 2).

Table 2
Identified medical problems by feeding type

Clinical or laboratory features	No breastfeeding	Any breastfeeding	P value	OR (95%CI)
Number (%)	220 (32%)	471 (68%)		
PRESENTING SYMPTOMS				
Fever	86 (39.1%)	184 (39.1%)	0.995	1.00 (0.72–1.38)
Asthenia	20 (9.1%)	48 (10.2%)	0.651	0.88 (0.50–1.52)
Dyspnea	9 (4.1%)	33 (7.0%)	0.069	0.50 (0.23–1.05)
Coughing	64 (29.1%)	133 (28.2%)	0.817	1.04 (0.73–1.48)
Sore throat	30 (13.6%)	70 (14.9%)	0.669	0.90 (0.57–1.43)
Ear ache	14 (6.4%)	19 (4.0%)	0.184	1.61 (0.79–3.28)
Abdominal pain	28 (12.7%)	48 (10.2%)	0.321	1.28 (0.78–2.11)
Diarrhoea	25 (11.4%)	40 (8.5%)	0.230	1.38 (0.81–2.34)
DIAGNOSIS				
Acute pharyngitis	9 (4.1%)	20 (4.2%)	0.924	0.96 (0.43–2.14)
Bulging hyperemic tympanic membrane	20 (9.1%)	22 (4.7%)	0.026*	2.04 (1.08–3.82)
Laryngitis	3 (1.4%)	7 (1.5%)	0.900	0.91 (0.23–3.57)
Asthma	8 (3.6%)	27 (5.7%)	0.245	0.62 (0.27–1.38)
Acute gastroenteritis	20 (9.1%)	31 (6.6%)	0.241	1.41 (0.78–2.55)
Seizures	1 (0.5%)	4 (0.8%)	0.332	0.23 (0.01–4.39)

ABBREVIATIONS: * ≤ 0.05 ; confidence interval, CI; odds ratio, OR; real-time polymerase chain reaction, RT-PCR; severe acute respiratory syndrome coronavirus 2, SARS-CoV-2.

Clinical or laboratory features	No breastfeeding	Any breastfeeding	P value	OR (95%CI)
Headache	8 (3.6%)	4 (0.8%)	0.016*	4.40 (1.31–14.79)
Febrile syndrome	22 (10%)	37 (7.9%)	0.348	1.30 (0.74–2.26)
Fracture	1 (0.5%)	7 (1.5%)	0.265	0.302 (0.03–2.47)
Dermatitis	4 (1.8%)	13 (2.8%)	0.459	0.65 (0.21–2.02)
Rash	2 (0.9%)	6 (1.3%)	0.677	0.71 (0.14–3.55)
Symptomatic patients	203 (92.3%)	431 (91.5%)	0.73	0.90 (0.49–1.63)
EXPOSURE HISTORY				
COVID-19 confirmed test in close contacts	10 (4.5%)	23 (4.9%)	0.846	0.93 (0.43–1.98)
Positive results of SARS-CoV-2 RT-PCR tests				
From symptomatic and asymptomatic patients	8 (3.6%)	8 (1.6%)	0.056	2.18 (1.19–3.17)
From symptomatic patients	8 (3.9%)	7 (1.6%)	0.036*	2.48 (1.45–3.51)
ABBREVIATIONS: * ≤ 0.05 ; confidence interval, CI; odds ratio, OR; real-time polymerase chain reaction, RT-PCR; severe acute respiratory syndrome coronavirus 2, SARS-CoV-2.				

Discussion

We confirm that the risk of any COVID-19, AOM, or headache in children is amplified for those who were never breastfed.

Concerning ear infections, a 2015 meta-analysis [7] found consistent evidence of a protective effect of breastfeeding on AOM occurrence. In general, there was an effect of breastfeeding on the risk of AOM during the first two years of life, but an effect lasting for 6 years was also found. Regarding the diagnosis of AOM, a few studies assessed children like we do, with clinical examination to validate an episode of AOM.

The protective effect of breastfeeding on the development of headache remains controversial. Breastfeeding was found associated with reduced recurrent primary headache prevalence in a case-control study in which 61% of cases versus 95% of controls had been breastfed ($p < 0.0005$) [8]. Our results agree with this report despite the fact that we focus on acute headache instead of recurrent

headache. However, a subsequent study failed to find a link between breastfeeding duration and headache development [9]. To our knowledge, there is no further research on this association.

We have not identified previous studies that have examined whether breastfeeding affords long-term protection from SARS-CoV-2. The risk of COVID-19 presumably reflects a balance between the rate of SARS-CoV-2 transmission to close contacts, and the individual protective immune response to respiratory viruses.

With regards to the household characteristics, Woods et al. have recently reported that living with children was associated with an attenuated risk of any COVID-19 among adults in the household [10]. Given that we report that households with never breastfed children were more likely to include more children under 15, the higher rate of COVID-19 among never breastfed children in our sample is not likely to be associated to their specific indoor exposures.

Another important question is whether breastfeeding from the start could modulate the immune response to fight SARS-CoV-2 a few years later. There is good evidence for enhanced protection against infections years after lactation is terminated [11]. A systematic review has concluded that 13 out of 16 studies show that breastfeeding protects infants against respiratory tract infections [12]. Children who had been breastfed remain better protected against respiratory tract infections for seven years compared with those not breastfed. Breastfeeding predicts lower incidence of wheezing bronchitis for up to six years and of meningitis for up to ten years [13]. Early consumption of mother's milk also confers long-term benefits against acute appendicitis [14] and tonsillitis [15]. The mechanisms through which breastfeeding could have a long lasting impact on infectious disease are multiple [2] including interfering with the oxidative stress, which is a key player in severe COVID-19. Oxidative stress is a characteristic of the obese state, and it is to note that the prevalence of obesity among never breastfed is approximately twice as much as among ever breastfed children of our cohort (21.5% versus 11.7%).

To sum up, our current study reports for the first time that initially breastfed children remained at lower risk of COVID-19 during August–December 2020 than formula fed children. And adds to a large body of evidence that has been accumulating for three decades to suggest a strong (negative) correlation between breastfeeding and incidence of infection 5 to 10 years later.

LIMITATIONS

This is an observational study of less than one thousand children, our results may not be applicable to different populations. The wide variation of pediatric COVID-19 incidence does not allow for optimal sample size calculation, and the low number of positive SARS-CoV-2 RT-PCR results precludes a multivariate analysis of our data. There are several possible explanations for any patterns found. This study cannot establish whether any link is due to direct effects (breastfeeding) or indirect effects (environmental exposures of breastfed children). In addition, we have not data about the mitigation measures in the childcare/educational settings they attended (eg masking, and smaller, cohorted groups). These variables may be relevant to get a sense of risk of exposure to SARS-CoV-2. Finally, it is also to be

noted that the effects of breast-feeding are dose-dependent, hence we must acknowledge that “ever breastfeeding” is a generally problematic variable.

Conclusions

This study has raised a new question about COVID-19 in children. By studying children who attended emergency services at a time of community transmission of COVID-19, we found that among ever breastfed children, approximately 1 in 60 had tested positive for SARS-CoV-2; on the other hand, among never breastfed children, 1 in 25 had tested positive for SARS-CoV-2. The results of this small trial point at one of the potentially important links between breastfeeding and COVID-19 spread. Given the potentially harmful and costly effects of this infection, further work is needed in this area as it could have major policy implications.

Abbreviations

AOM, otitis media; BMI, body mass index; ESs, emergency services.

Declarations

Ethics approval and consent to participate

The Manuscripts includes a statement on ethics approval and consent, it includes the name of the ethics committee that approved the study.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analysed during this study are included in this published article [and its supplementary information files].

Competing interests

The authors declare that they have no competing interests.

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Ruth Díez received a scholarship from IdISBa (Balears Medical Research Institute), Government of Balears, Spain. No competing financial interests exist for the remaining authors.

Authors' contributions

RD and JR had full access to all the data in the study and take responsibility for the integrity of the data. Study concept and design: RD and SV. Acquisition, analysis, or interpretation of data: IV and SV. Literature review and drafting of the manuscript: JR, IV, AP, and M-IM-D. All authors approved the final manuscript for submission.

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References

1. Zimmermann P, Curtis N. Why is COVID-19 less severe in children? A review of the proposed mechanisms underlying the age-related difference in severity of SARS-CoV-2 infections. Vol. 106, *Archives of Disease in Childhood*. BMJ Publishing Group 2020 Dec. doi: 10.1136/archdischild-2020-320338. Epub ahead of print.
2. Li R, Dee D, Li CM, Hoffman HJ, Grummer-Strawn LM, et al. Breastfeeding and risk of infections at 6 years. *Pediatrics*. Sep 1;134(Suppl 1):S13–20.
3. Sobradillo B, Aguirre A, Aresti U, et al. *Curvas y tablas de crecimiento. Estudios longitudinal y transversal*. Bilbao. Fundación Faustino Orbeagozo; 2004.
4. Centers for Disease Control and Prevention. *Overweight & Obesity. Defining childhood obesity*. Atlanta: U.S. Department of Health and Human Services; 2018. <https://www.cdc.gov/obesity/childhood/defining.html>.
5. Keim SA, Smith K, Ingol T, et al. Improved Estimation of Breastfeeding Rates Using a Novel Breastfeeding and Milk Expression Survey. *Breastfeed Med* 2019 Sep 1;14(7):499–507.
6. Han X, Li X, Xiao Y, Yang R, Wang Y, Wei X. Distinct Characteristics of COVID-19 Infection in Children. *Frontiers in Pediatrics*. Frontiers Media SA. 2021;Vol. 9:619738. 9.
7. Bowatte G, Tham R, Allen K, Tan D, Lau M, Dai X, et al. Breastfeeding and childhood acute otitis media: A systematic review and meta-analysis *Acta Paediatrica, International Journal of Paediatrics*. Blackwell Publishing Ltd; 2015. pp. 85–95.
8. Pogliani L, Spiri D, Duca PG, et al. Breastfeeding and headache, is there a protective effect? *Arch Dis Child*. 2008;93:pw480.
9. Pogliani L, Spiri D, Penagini F, Nello F, Di, Duca P, Zuccotti GV. Headache in children and adolescents aged 6–18 years in Northern Italy: Prevalence and risk factors. *Eur J Paediatr Neurol*. 2011 May;15(3):234–40.

10. Wood R, Thomson E, Galbraith R, Gribben C, Caldwell D, Bishop J, et al. Sharing a household with children and risk of COVID-19: a study of over 300 000 adults living in healthcare worker households in Scotland. *Arch Dis Child Arch Dis Child* 2021:archdischild-2021-321604. doi: 10.1136/archdischild-2021-321604. Epub ahead of print.
11. Hanson L, Hahn-Zoric M, Berndes M, et al. Breast feeding: overview and breast milk immunology. *Acta Paediatr Jpn.* 1994;36:557–61.
12. Duijts L, Ramadhani MK, Moll HA. Breastfeeding protects against infectious diseases during infancy in industrialized countries. A systematic review. *Maternal Child Nutrition.* 2009;5:199–210.
13. Silfverdal SA, Bodin L, Hugosson S, Garpenholt Ö, Werner B, Esbjörner E, et al. Protective effect of breastfeeding on invasive *Haemophilus influenzae* infection: A case-control study in Swedish preschool children. *Int J Epidemiol.* 1997;26(2):443–50.
14. Pisacane A, de Luca U, Impagliazzo N, Russo M, de Caprio C, Caracciolo G. Breast feeding and acute appendicitis. *BMJ* 1995 Apr 1; 310:836–837.
15. Pisacane A, Impagliazzo N, De Caprio C, Criscuolo L, Inglese A, Pereira Da Silva MCM. Breast feeding and tonsillectomy. *Br Med J.* 1996;312:746–7.

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