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Original Article

Impact of Breast Feeding On Diarrhea and Pneumonia Among Vaccinated Children: Single Center Study

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INTRODUCTION

The best way to give babies the nutrition they need to grow and develop is through breast milk. It has been associated with lower incidence of illnesses such diarrhea and respiratory tract infections, which reduce hospitalization and mortality[1]. Its significance is widely acknowledged in middle- and low-income countries [2]. Every year, 8% of deaths in children under the age of five are caused by diarrhea. Due to severe gastroenteritis and rapid dehydration, rotavirus, one of the leading causes of diarrhea in children, can be fatal [3]. Breastfeeding may lower the risk of diarrhea, according to several studies [4-7]. There is a higher risk of morbidity from diarrhea in

ABSTRACT

The best way to give babies the nutrition they need to grow and develop is through breast milk. Objective: To assess the combine effect of breast feeding, Rota virus vaccine and Pneumococcal vaccine on frequency of Diarrhea and Pneumonia in children less than 5 years of age. Methods: A descriptive cross-sectional study conducted at Department of Pediatrics at Darul sehat hospital, Karachi. Participants were selected by convenience sampling and interview-based questionnaire was used. 196 Participants were interviewed which included mothers of infant and children from 6 months to 5 years of age, who received complete or partial vaccination according to Expanded program of Immunization (EPI) schedule with information on history of diarrhea and pneumonia. Infant and children with bloody diarrhea were excluded. Results: Among the 196 participants, 152 (77.6%) children received breast feed, 72(47.4%) children received two doses of Rota vaccine and 128 (84.2%) children received three doses of Pneumococcal vaccines. Significant impact was seen with breast feeding and Rota vaccine on the frequency of diarrhea with p value of 0.0001. Breastfeeding and the pneumococcal vaccine both had a similar potent effect on the prevalence of pneumonia, with a p-value of 0.006. **Conclusions:** Our study highlights the importance of breast feeding in vaccinated children, with incidence of diarrhea in breastfed, vaccinated children decreased to (32%), compared to 93% in non-breastfed, unvaccinated infants. Similarly, only 33% of breastfed, vaccinated children developed pneumonia, compared to 85% of unvaccinated, non-breastfed infants.

> children who were not exclusively breastfed for the first six months of life and who have not received the Rota virus vaccine. Rotavirus vaccination is crucial for children since study reveal that breastfeeding alone is insufficient to prevent diarrhea caused by the rotavirus [8]. More over half of pneumonia-related deaths worldwide are caused by streptococcus pneumonia [9]. After the Pneumococcal Conjugate Vaccine (PCV) was added to the vaccination schedule to lower pneumococcal associated morbidity and mortality, there was a notable decrease in hospitalizations [10]. The fatality rates caused by pneumonia are highest in developing and underdeveloped nations. Low- and middle

income countries have been described as frequently experiencing issues such inadequate breastfeeding, overcrowding, poor nutrition, low socioeconomic status, and insufficient immunization [11]. The objective of this study was to determine how breastfeeding affected the incidence of diarrhea and pneumonia in children who had received the Pneumococcal and Rotavirus vaccines. To the best of our knowledge, there hasn't been a local study that has evaluated the combined impact of breastfeeding and immunization on the frequency of diarrhea and pneumonia in children under the age of five.

METHODS

From 1st October 2019 till 31st December 2019, a crosssectional survey was carried out at the Darul Sehat hospital in Karachi's pediatrics department. The Raosoft® sample size software was used to determine the sample size. In Pakistan, it is believed that 40% of children exclusively breastfeed [12]. An estimated sample of 196 patients was gathered for the study by taking into account the 95% confidence interval (CI), 5% margin of error, and 80% power to detect such difference. Data were stored and analyzed using IBM-SPSS version 23.0. Counts with percentages were reported on Age group, sex, name of vaccine received, breastfeeding status and reason of not breastfeeding for studied children. Pearson Chi-square test was used to check the association of breastfeeding with vaccinations done, reason of vaccination and reason of no vaccination. Binary logistic regression was performed to build two models for estimating risk of Pneumonia Model-I and Diarrhea Model-II and impact of breast feeding, rota and pneumococcal vaccination, reason of vaccination and reason of not vaccination was studied using odds ratio with 95% confidence interval. Pvalue less than 0.05 were considered statistically significant, bar diagram and odds ratio charts were also used to give graphical presentation of data. Convenience sampling was used to choose the respondents, and an interview-based questionnaire was filled out. The subjects were children from the outpatient department who accompanied their mother and other family members for medical advice regarding any illness. Infants and children aged 6 months to 5 years old who had completed or partially completed the Expanded Program of Immunization (EPI) schedule and provided information on previous episodes of pneumonia and diarrhea were included as participants. Diarrhea is defined as child having more than 3 episodes of stool per day [13]. Children and infants who had bloody diarrhea were excluded. Pneumonia is categorized as child with cough and fast breathing requiring treatment and no pneumonia is defined as cough and flu according to IMNCI [14]. After receiving all necessary information, parents provided their signed consent. Ethical approval was sought from the ethical review committee of our institution.

RESULTS

In the present study there were one hundred and ninety-six children with a mean age of 25 (SD = \pm 18.3) months, 89 (45.4%) received Pneumonia vaccine, 3 (1.5%) received Rota vaccine, 82(41.8%) received both Pneumonia and Rota vaccine and 22 (11.2%) were unvaccinated. 152 (77.6%) children received breastfeed. Table 1 shows the association of breastfeeding with studied factors. Rota vaccination and grades of diarrhea showed significant association with breastfeeding,(p<0.05).

Table 1: Association of Breastfeeding with Studied Variables

Characteristics							
		No (n=44)		Yes (n=152)		p-value	
		n	%	n	%		
	≤6 Months	9	20.5	28	18.4		
	7 - 12 Months	5	11.4	26	17.1	0.52	
Age Groups	13 - 24 Months	7	15.9	37	24.3		
	25 - 48 Months	16	36.4	45	29.6		
	49 - 60 Months	7	15.9	16	10.5		
Sex	Boy	21	47.7	81	53.3	0.51	
Sex	Girl	23	52.3	71	46.7		
Categories of Rota vaccine	Partial	4	9.1	5	3.3	<0.01*	
	Complete	9	20.5	72	47.4		
	None	31	70.5	75	49.3		
Categories of Pneumonia vaccine	Partial	7	15.9	13	8.6	0.12	
	Complete	31	70.5	128	84.2		
vacenie	None	6	13.6	11	7.2		
Grading of Pneumonia	Pneumonia	18	40.9	55	36.2	0.56	
	No pneumonia	26	59.1	97	63.8		
Grading of	Diarrhea	35	79.5	77	50.7	<0.01*	
diarrhea	No diarrhea	9	20.5	75	49.3		
*p<0.05 was considered statistically significant using Pearson Chi-square test							

Pneumococcal vaccine, frequency of pneumonia, and breastfeeding were all found to be significantly correlated, with a p value of 0.006 as shown in Table 2.

Table 2: Association of Grading of Pneumonia with Breastfeedingand Pneumonia Vaccination

	Grading of Pneumonia					
Breastfeed/ Pneumonia Vaccine		No (n=44)		Yes =152)	p-value	Odds Ratio (95% C.I)
	n	%	n	%		
Breastfeed and Pneumonia Vaccinated	94	66.7	47	33.3		Reference
Breastfeed and No Pneumonia Vaccinated	3	27.3	8	72.2	0.006*	5.33* (1.35-21.0)
No Breastfeed and Pneumonia Vaccinated	25	65.8	13	34.2		1.04 (0.48-2.21)
No Breastfeed and No Pneumonia Vaccinated	1	16.7	5	83.3		9.99*(1.13-88.0)
*n<0.05 was considered statistically significant1						

*p<0.05 was considered statistically significant1

Table 3 shows Rota vaccination, frequency of diarrhea, and breastfeeding were found to be significantly correlated, with a p value of <0.01.

Table 3: Association of Grading of Diarrhea with Breastfeeding

 and Diarrhea Vaccination

	Grading of Diarrhea					
Breastfeed/ Rota Vaccine		No (n=84)		Yes 1=112)	p-value	Odds Ratio (95% C.I)
	n	%	n	%		
Breastfeed and Rota Vaccinated	52	67.5	25	32.5		Reference
Breastfeed and No Rota Vaccinated	23	30.7	52	69.3	<0.01*	4.70*(2.37-9.32)
No Breastfeed and Rota Vaccinated	7	53.8	6	46.2		1.78 (0.54-5.86)
No Breastfeed and No Rota Vaccinated	2	6.5	29	93.5		30.1*(6.66-136.5)
*p<0.05 was considered statistically significant using Pearson Chi-square test						

Table 4 shows the result from binary logistic regression analysis. Children who were not breastfed and unvaccinated have higher risk of developing pneumonia and diarrhea.

Table 4: Risk Estimation of Pneumonia and Diarrhea using BinaryLogistic Regression

Risk Factors	Model -I Pneumonia OR (95% C.I)	Model-II Diarrhea OR (95% C.I)				
No Breastfeeding	1.22(0.61-2.42)	3.78*(1.70-8.41)				
Partially Vaccinated	0.30(0.07-1.27)	0.61(0.14-2.64)				
Completely Vaccinated	0.14*(0.04-0.45)	0.13*(0.07-0.26)				
Not Vaccinated	4.72*(1.42-15.6)	10.8*(1.39-85.0)				
*odds ratio considered statistically significant with p<0.05 Model-I : Dependent variable Pneumonia Model-II : Dependent variable Diarrhea						

In Model-I for Pneumonia, partial vaccination lowers the odd of developing pneumonia by 70% (OR: 0.30 (CI: 0.07 -1.27)) and complete vaccination lowers the odd of developing pneumonia by 86% (OR: 0.14 (C.I 0.04 - 0.45) when compared with unvaccinated children. On the contrary the children who did not breastfeed had 1.22 times higher risk of developing the disease (OR: 1.22[C.I. 0.61 -2.42]),) while children who were unvaccinated had 4.72 times higher likelihood of having pneumonia (OR: 4.72 (C.I. 1.42 - 15.6)). While in model-II for diarrhea, complete vaccination lowers the odd of developing diarrhea by 87% (OR: 0.13 (CI:. 0.07 - 0.26) when compared with unvaccinated children. On the contrary children who were not breastfed had a 3.78 times greater likelihood of developing the diarrhea (OR: 3.78 (CI: 1.70 - 8.41)) and children who were unvaccinated had 10.8 times significantly higher risk of contracting diarrhea (OR: 10.8 (CI: 1.39-85.0)).

DISCUSSION

This study was conducted with the understanding that, despite being part of our tradition, our religion, and physician advice in accordance with WHO criteria, the practice of breastfeeding is still infrequent in our society. The preventive effect of breastfeeding cannot be underestimated in the presence of these vaccines, despite DOI: https://doi.org/10.54393/pjhs.v4i04.702

the fact that immunization against diseases like Rota virus diarrhea and pneumonia offer immunity against such illnesses, hence reducing the burden of disease globally [15]. According to a survey conducted by Unicef in Pakistan, 48.4% of children are exclusively breastfed, compared to 68.4% who continue to breastfeed until one year of age [16]. In our study, the prevalence of breastfeeding was 77.6%, which may be attributable to mothers in the study's catchment area having higher levels of education and awareness. Our research has demonstrated a favorable correlation between breast-fed infants who have received two doses of the Rota vaccination and a reduction in diarrheal episodes. This finding was reinforced by a study conducted in Ethiopia that revealed infants who had only one dose of the Rota vaccination experienced a three-fold rise in diarrhea incidents, while infants who were not breastfed experienced a two-fold increase [8]. Additionally, a Mozambigue study revealed that children who received the Rota vaccination experienced fewer hospitalizations for diarrhoea [17]. However, a study conducted in the Kingdom of Saudi Arabia, where children have received the Rota vaccine as part of EPI, does not support the impact of Rota vaccine on diarrhoeal cases. But it was discovered that these infants were receiving mixed feeding [18]. The effectiveness of breastfeeding in preventing diarrheal illnesses is still up for debate. Indian research has demonstrated the protective effects of anti-Rota virus antibodies in mother milk, consequently decreasing the incidence of Rota virus diarrhea, [19] which is consistent with our study that breastfeeding has a significant impact on reducing the frequency of diarrhea. Additionally, study has shown that breastfeeding improves the effectiveness of vaccines. According to a metaanalysis comprising 17 articles, there is no connection between Rota virus gastroenteritis and breast-feeding. Although there are theoretical advantages to breastfeeding, in practice we need preventative measures like rotavirus immunization to prevent diarrhea [20]. Similarly Malaysian study also suggests that that breast feeding and Rota vaccination both can have beneficial effect against these viruses. The vaccination requires multiple dosing and time to produce its protective effects, during which beneficial and protective effect of breastfeeding help gives the immunity and hence magnifies the effect of vaccination [15]. These studies suggests that immune protective composition of breast feeding provides the early immune response to the infant which is enhanced by the protective effects of two doses of Rota vaccine given before 6 months of age, reducing the frequency of Rota associated diarrhea. In our study, a similar substantial correlation between breastfeeding, the frequency of pneumonia, and pneumococcal vaccination was observed,

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getting immunized is necessary.

Authors Contribution

Conceptualization: SQB Methodology: SQB, UHAS Formal analysis: UHAS, MFR

Writing-review and editing: SQB, FS, NA, MFR

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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REFERENCES

- [1] World Health Organization. Continued breastfeeding for healthy growth and development of children. Retrieved June. 2019 Jun; 17: 2021.
- [2] Victora CG, Bahl R, Barros AJ, França GV, Horton S, Krasevec J, et al. Breastfeeding in the 21st century: epidemiology, mechanisms, and lifelong effect. The lancet. 2016 Jan; 387(10017): 475-90. doi: 10.1016/ S0140-6736(15)01024-7
- [3] Steele AD, Victor JC, Carey ME, Tate JE, Atherly DE, Pecenka C, et al. Experiences with rotavirus vaccines: can we improve rotavirus vaccine impact in developing countries?. Human Vaccines & Immunotherapeutics. 2019 Jun; 15(6): 1215-27. doi: 10.1080/21645515.2018.1553593
- [4] Wright MJ, Mendez MA, Bentley ME, Adair LS. Breastfeeding modifies the impact of diarrhoeal disease on relative weight: a longitudinal analysis of 2–12 month-old Filipino infants. Maternal & child nutrition. 2017 Apr; 13(2): e12312. doi: 10.1111/mcn. 12312
- [5] Santos FS, Santos LH, Saldan PC, Santos FC, Leite AM, Mello DF. Breastfeeding and acute diarrhea among children enrolled in the family health strategy. Texto & Contexto-Enfermagem. 2016 Apr; 25. doi: 10.1590/0104-070720160000220015
- [6] Isyti'aroh Isyti'aroh SR and Widyastuti W. Breastfeeding and the Risk for Diarrhea Morbidity Among Children in Indonesia. Malaysian Journal of Medicine and Health Sciences. 2022; 18(SUPP18): 96-100.
- [7] Mulatu T, Yimer NB, Alemnew B, Linger M, Liben ML. Exclusive breastfeeding lowers the odds of childhood diarrhea and other medical conditions: evidence from the 2016 Ethiopian demographic and health survey. Italian Journal of Pediatrics. 2021 Dec; 47(1): 1-6. doi: 10.1186/s13052-021-01115-3

out of 63 children with pneumonia, 48 (76.1%) were breastfed whereas 15 (23.8%) were not [21]. According to Lamberti et al., systemic review of the literature, the absence of exclusive breastfeeding is the primary cause of the rise in morbidity from pneumonia and mortality from severe pneumonia in infants [22]. Similar findings were also reported from a study conducted in Brazil, which revealed a notable decrease in pneumonia-related hospitalizations among infants under 6 months of age who were exclusively breastfed and in children 9 to 12 months of age who were breastfed [23]. These studies demonstrate that breastfeeding exclusively has a better effect on boosting infants' immunity before the age of six months. Breastfed newborns at 4 months of age have been proven to have larger thymuses and higher antibody titers, producing a more potent immunological response than non-breastfed babies. According to a Kenyan study, babies who were breastfed had a 47% lower risk of having pneumonia [24]. Due to the pneumococcal vaccine's positive impact, the incidence of pneumonia has significantly decreased in our study. According to an Australian study, the pneumococcal vaccine offers higher protection and reduces the number of paediatric pneumonia hospitalization's [25]. Similar to the Gambian trial, after receiving the recommended dose of the pneumococcal vaccine, pneumonia cases significantly decreased by 22% [26]. Although breastfeeding offers immunity through anti-inflammatory, immunological modulatory, and antibacterial activity, adequate vaccination coverage and dosages considerably increase the benefit to battle the mortality and morbidity linked to pneumococcal disease. As far as we are aware, no study has been conducted to date to assess the combined impact of breastfeeding and the contribution of vaccinations to the prevention of diarrhea and pneumonia in children under the age of five. Our study is not without limitations. The study being of short duration and hence we could not assess the long-term effect. Our study represents a certain catchment area with middle class population so this cannot be a representation for overall population.

which contrasted with a study from India that found that

CONCLUSIONS

Our study highlights the importance of breast feeding in vaccinated children, with incidence of diarrhea in breastfed, vaccinated children decreased to 32%, compared to 93% in non-breastfed, unvaccinated infants. Similarly, only 33% of breastfed, vaccinated children developed pneumonia, compared to 85% of unvaccinated, non-breastfed infants. Effective measures should be undertaken to encourage breastfeeding, especially during the first six months of life. Effective parental education regarding the advantages of immunization and risks of not

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- [8] Shumetie G, Gedefaw M, Kebede A, Derso T. Exclusive breastfeeding and rotavirus vaccination are associated with decreased diarrheal morbidity among under-five children in Bahir Dar, northwest Ethiopia. Public health reviews. 2018 Dec; 39(1): 1-0. doi: 10.1186/s40985-018-0107-6
- [9] Troeger C, Forouzanfar M, Rao PC, Khalil I, Brown A, Reiner RC, et al. Estimates of global, regional, and national morbidity, mortality, and aetiologies of diarrhoeal diseases: a systematic analysis for the Global Burden of Disease Study 2015. The Lancet infectious diseases. 2017 Sep; 17(9): 909-48.
- [10] Schuck-Paim C, Taylor RJ, Alonso WJ, Weinberger DM, Simonsen L. Effect of pneumococcal conjugate vaccine introduction on childhood pneumonia mortality in Brazil: a retrospective observational study. The Lancet Global Health. 2019 Feb; 7(2): e249-56. doi: 10.1016/S2214-109X(18)30455-8
- [11] Ujunwa FA and Ezeonu CT. Risk factors for acute respiratory tract infections in under-five children in enugu Southeast Nigeria. Annals of medical and health sciences research. 2014; 4(1): 95-9. doi: 10.4103/2141-9248.126610
- [12] National Institute of Population Studies (NIPS) [Pakistan] and ICF. Pakistan demographic and health survey 2017-18. Pakistan demographic and health survey 2017-18. 2019 Jan.
- [13] Dadonaite B, Ritchie H, Roser M. Diarrheal diseases. Our World in Data. 2018 Nov 1.
- [14] WHO. IMCI Chart Booklet. 2014 [cited 2019 Feb 21]. Available from: <u>https://www.who.int/</u> <u>maternal_child_adolescent/documents/IMCI_chart</u> <u>booklet/en/</u>
- [15] Prameela KK and Vijaya LR. The importance of breastfeeding in rotaviral diarrhoeas. Malaysian journal of nutrition. 2012 Mar; 18(1).
- [16] UNICEF, G.o.P., National Nutrition Survey 2018 Key Findings Report. 2018
- [17] de Deus N, Chilaúle JJ, Cassocera M, Bambo M, Langa JS, Sitoe E, et al. Early impact of rotavirus vaccination in children less than five years of age in Mozambique. Vaccine. 2018 Nov; 36(47): 7205-9. doi: 10.1016/j.vaccine.2017.10.060
- [18] Shati AA, Khalil SN, Asiri KA, Alshehri AA, Deajim YA, Al-Amer MS, et al. Occurrence of diarrhea and feeding practices among children below two years of age in southwestern Saudi Arabia. International journal of environmental research and public health. 2020 Feb; 17(3): 722. doi: 10.3390/ijerph17030722
- [19] Das S, Sahoo GC, Das P, Singh UK, Jaiswal AK, Singh P, et al. Evaluating the impact of breastfeeding on rotavirus antigenemia and disease severity in Indian

children. PLoS One. 2016 Feb; 11(2): e0146243. doi: 10. 1371/journal.pone.0146243

- [20] Shen J, Zhang BM, Zhu SG, Chen JJ. No direct correlation between rotavirus diarrhea and breast feeding: A meta-analysis. Pediatrics & Neonatology. 2018 Apr; 59(2): 129-35. doi: 10.1016/j.pedneo.2017. 06.002
- [21] Madhusudhan K, Sreenivasaiah B, Kalivela S, Nadavapalli SS, Babu RT, Jampana VR. Clinical and bacterial profile of pneumonia in 2 months to 5 years age children: A prospective study done in a tertiary care hospital. International Journal of Contemporary Paediatrics. 2017 Jan; 4(1): 90–5. doi:
- [22] Lamberti LM, Zakarija-Grković I, Fischer Walker CL, Theodoratou E, Nair H, et al. Breastfeeding for reducing the risk of pneumonia morbidity and mortality in children under two: a systematic literature review and meta-analysis. BMC public health. 2013 Sep; 13: 1-8. doi: 10.1186/1471-2458-13-S3-S18
- [23] Boccolini CS, Carvalho ML, Oliveira MI, Boccolini PD. Breastfeeding can prevent hospitalization for pneumonia among children under 1 year old. Jornal de pediatria. 2011; 87: 399-404. doi: 10.2223/JPED.2136
- [24] Ásbjörnsdóttir KH, Slyker JA, Weiss NS, Mbori-Ngacha D, Maleche-Obimbo E, Wamalwa D, et al. Breastfeeding is associated with decreased pneumonia incidence among HIV-exposed, uninfected Kenyan infants. AIDS (London, England). 2013 Nov; 27(17): 2809. doi: 10.1097/01.aids.000043 2540.59786.6d
- [25] Fathima P, Blyth CC, Lehmann D, Lim FJ, Abdalla T, De Klerk N, et al. The impact of pneumococcal vaccination on bacterial and viral pneumonia in Western Australian children: record linkage cohort study of 469589 births, 1996–2012. Clinical Infectious Diseases. 2018 Mar; 66(7): 1075-85. doi: 10.1093/ cid/cix923
- [26] Mackenzie GA, Hill PC, Sahito SM, Jeffries DJ, Hossain I, Bottomley C, et al. Impact of the introduction of pneumococcal conjugate vaccination on pneumonia in The Gambia: population-based surveillance and case-control studies. The Lancet infectious diseases. 2017 Sep; 17(9): 965-73. doi: 10.1016/S1473-3099(17)30321-3