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Title: Breastfeeding and childhood hospitalizations for infections

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ABSTRACT

Background: Infectious disease is a leading cause of morbidity and hospitalization for infants and children. During infancy, breastfeeding protects against infectious diseases, particularly respiratory infections, gastrointestinal infections, and otitis media. Little is known about the longer-term impact of breastfeeding on infectious disease in children.

Methods: We investigated the relationship between infant feeding and childhood hospitalizations from respiratory and gastrointestinal infections in a population-based birth cohort of 8327 children born in 1997 and followed for 8 years. The main outcomes were public hospital admissions for respiratory infections, gastrointestinal infections, and all infectious diseases. Cox regression was used to assess time to first hospitalization.

Results: Exclusive breastfeeding for 3 or more months was associated with a lower risk of hospital admission for respiratory infections (hazard ratio = 0.64 [95% confidence interval = 0.42 – 0.97]), gastrointestinal infections (0.51 [0.25 – 1.05]), and any infections (0.61 [0.44 – 0.85]) in the first 6 months of life, adjusted for sex, type of hospital at birth, and household income. Partial breastfeeding for any length of time or exclusive breastfeeding for less than 3 months also reduced hospitalizations from infections but with smaller effect sizes. There was no association between breastfeeding and hospitalization for infectious disease beyond 6 months of age.

Conclusions: Exclusive breastfeeding for 3 or more months substantially reduced hospital admissions for many infectious diseases in the first 6 months of life, when children are most vulnerable.

Infectious diseases are a leading cause of morbidity and hospitalization in infants and children.[1] Breastfeeding offers substantial protection against infectious diseases in infancy,[2-4] including respiratory infections,[3 5-8] gastrointestinal infections (GI),[9-12] and otitis media.[6 11 13] Breastfeeding reduces outpatient treatment for respiratory, GI, and febrile illnesses up to 18 months of age and reduces hospitalization for respiratory illnesses up to 9 months of age.[8] However, most of these studies from western developed countries are subject to possible bias by uncontrolled or uncontrollable confounding by socio-economic position.

Furthermore, few studies, have examined the impact of breastfeeding on infectious disease beyond the first few years of life. A longer duration of breastfeeding has been found to protect against pneumonia in children of 1 to 2 years of age[6] and otitis media in children until 3 years of age.[14-17] Breastfeeding has also been shown to reduce the risk of respiratory illness in children up to 7 years of age[18] and to protect against *Haemophilus influenzae* type b (Hib) infection up to 10 years of age.[19] The majority of the studies on the benefits of breastfeeding in older children have methodological limitations including retrospective design,[9 15 19] failure to adjust adequately for known confounders,[20] small sample size,[18] and failure to stratify children by age group to differentiate the effects of breastfeeding on infants and older children.[21-23] The distinction between the effect of breastfeeding in infancy and in childhood is important in understanding the biological mechanism of breastfeeding—whether it confers passive immunity in infancy alone or if it promotes maturation of infants' active immunity and protection beyond infancy.[24]

In contrast to long-term developed countries, where breastfeeding mothers tend to be better educated,[25] educated Hong-Kong-born mothers tend to cease breastfeeding relatively early whereas less educated or migrant mothers tend to continue breastfeeding.[26] Moreover, some common infectious diseases, such as influenza, have different socioeconomic patterns in Hong

Kong than in other countries.[27] Hence, economically-developed Hong Kong offers a useful non-western setting in which to examine the long-term effects of breastfeeding.

We prospectively examined whether breastfeeding was associated with hospitalizations for infectious diseases until 8 years of age in a large, population-based birth cohort of Hong Kong children. Our primary hypothesis was that breastfeeding would protect children against hospital admission for respiratory and gastrointestinal infections up to 8 years of age. We also specifically examined whether breastfeeding was protective beyond the immediate period of breastfeeding.

METHODS

Sources of Data

The basis of this study is a large, prospective population-based birth cohort "Children of 1997," which had initially been recruited through all 49 publicly-funded maternal and child health centers of the Hong Kong Department of Health in 1997.[28] The sampling frame consisted of all infants born in April and May 1997 and brought to one of the health centers for their first postnatal visit. For the index year, 92% of infants born in Hong Kong went at least once to one of these clinics, which provide free-of-charge preventive care and immunizations. The "Children of 1997" birth cohort recruited 8327 mother-infant pairs, covering 88% of all births during the recruitment period. At their first (baseline) visit, mothers provided information on infant feeding history, household smoking patterns, socioeconomic position (parental education, employment status and type of housing) and birth characteristics (mode of delivery, gestational age, maternal age and parity) through a standardized self-administered questionnaire in Chinese. Infant feeding was ascertained by asking questions about the initiation (ever/never), duration (months), and exclusivity of breastfeeding. According to the World Health Organization definitions, infants are considered exclusively breastfed if they receive no solids, no non-breast milk substitutes, or no water or other liquids (other than vitamins or medications).[29] Follow-up questionnaires were administered at subsequent well-child visits at 3, 9 and 18 months after birth to update

information on infant feeding status, health-care utilization, and household smoking patterns. Infants participating in the birth cohort were similar to the general population on several sociodemographic characteristics, such as parental education and type of housing, with relatively small Cohen Kappa (P<0.17).

In 2005-2006, more detailed information on socioeconomic position was abstracted manually from the original hard-copy clinic records, and hospital discharges were obtained by record linkage from the Hospital Authority. The Hospital Authority manages all public hospitals in Hong Kong, and these hospitals account for 89% of acute bed-days and 87% of all hospital admissions for children under eight years old in Hong Kong.[30] Information contained in the Hospital Authority discharge records includes the date of each hospital admission and discharge, name of hospital, principal and secondary reasons for admission, and principal medical procedures.

Exposure: Breastfeeding

Information on breastfeeding was obtained from self-administered questionnaires in Chinese completed by the primary caregiver (most commonly mothers), with help as necessary, at the first post-natal (baseline) visit to the maternal and child health centres and at subsequent routine visits when the infants were about 3, 9 and 18 months of age. At the baseline visit the primary caregiver was asked "How is the infant currently fed?," specified as "Exclusively breastfed," "Partially breastfed" and "Only formula-fed." At follow-up visits the primary care giver was asked "How has the infant been fed from birth until now?," specified as one of the three original options or an additional option applying to the initially exclusively breastfed of "Initially breastfed, but now formula-fed," with the care giver also asked to recall the age in months when breastfeeding terminated. As always with studies with repeated measurements, follow-up information was sometimes missing and answers were sometimes contradictory. In such cases,

we gave precedence to the most contemporaneous and hence most likely accurate response (e.g. for early feeding patterns, information that was reported at 3 months rather than 18 months).

Infants were initially classified as "exclusively breastfed," "partially breastfed" and "never breastfed." Infants were classified as "exclusively breastfed" if they were exclusively breastfed at the baseline interview or, if that information was missing; they were reported at the next available follow-up as having been exclusively breastfed. Infants were classified as "partially breastfed" if they were partially breastfed either at the baseline interview or, if that information was missing, at the next available follow-up. Infants were also classified as "partially breastfed" if they were formula-fed at the baseline interview but with some breastfeeding at 3 months (breastfeeding may have been established after the baseline interview). Infants were classified as "never breastfed" if they were formula-fed at the baseline interview and with no breastfeeding either at 3 months or, if that information was missing, at the next available follow-up.

Breastfeeding is usually of limited duration in Hong Kong. Maternity leave in Hong Kong is 10 weeks, which the mother usually starts about 2 to 4 weeks before the due date. In this cohort, only 7% of infants were still given some breast milk supplemented with formula after 3 months. Additionally, few mothers continued breastfeeding beyond 3 months; at 6 months 3% of infants were exclusively breastfed, at 9 months 2% were still breastfed and at 18 months 1% were still breastfed. Therefore, for analysis we categorized infants into three groups: (1) exclusively breastfed for 3 or more months, (2) partially breastfed for any length of time or exclusively breastfed for less than 3 months, and (3) never breastfed. Infants were considered to have been exclusively breastfed for 3 or more months if at 3 months (or the next available follow-up) they were reported as exclusively breastfed or if exclusive breastfeeding terminated at 3 months or older. However, we do not have the age of starting complementary feeding, so exclusive breastfeeding for 3 or more months may also include the introduction of non-milk liquids or solid foods but not artificial formula or other milk replacements. For more than half of the

exclusively-breastfed infants, breastfeeding terminated at 1 or 2 months, making breastfeeding for less than 3 months and partial breastfeeding physiologically similar; these two groups were combined to reduce misclassification.

Outcome: Hospital Use

Hospital utilization was assessed from birth up to 8 years of age. We also considered hospital utilization in various age-groups so as to clarify the association beyond infancy. These age-groups were chosen to reflect diet transitions, motor development and increasing social contact (i.e., 0 up to 6 months, 6 up to 24 months, 2 up to 5 years and 5 up to 8 years), as well as to distinguish the primary period of breastfeeding in our cohort (0 up to 6 months) from the rest of the follow-up period. Admissions are coded at discharge according to the *International Classification of Diseases, Ninth Version Clinical Modification* (ICD-9CM). Admissions with a principal diagnosis of ICD-9CM 33, 34.0, 381-2, 460-6, 477, 480-7, 477, 490 or 493 were classified as respiratory (and related) infections; ICD-9CM 001-009, 535.00, 535.50, 558.9, 538, 535.40 or 787.91 were classified as gastrointestinal infections; ICD-9CM 10-32, 34.1-139, 320-1, 370, 372.0-372.3, 390-2, 540-2, 590, 595, 599.0, 680-6, 771, 780.3, or 780.6 were classified as other infections; and ICD-9CM 800-999 or E800-E999 were classified as accidents. Admissions for accidents (ICD-9CM 800-999 or E800-E999) were used as a control to examine possible residual confounding by socioeconomic position. (With adequate control for socioeconomic position, there should be no relation between breastfeeding and admissions for accidents.) We included both day-patient and in-patient admissions. Children with no record of hospital admission were assumed to have none.

The average hospital stay for infants delivered by caesarean section was 7.9 days, while that by natural birth was 3.0 days.[31] Thus, the inclusion of hospitalizations in the immediate neonatal period could have introduced bias. For this reason, admissions occurring within the first 8 days of life were excluded.

Statistical Analysis

We used multivariable regression analyses to assess the association between breastfeeding and hospitalization for various causes during the first 8 years of life. For the primary analysis, we used Cox regression to assess the adjusted association between breastfeeding and time to first hospitalization, from which we reported the hazard ratio (HRs) of admission for all the causes considered (respiratory infections, gastrointestinal infections, other infections, all infections, and accidents) with associated 95% confidence intervals (CIs). Children who died were censored at the date of death. The proportional-hazards assumption was checked by visual inspection of plots of log (- log (S)) against time, where S was the estimated survival function. Children with an admission in an earlier age-group might be more susceptible to admission when older; however, in age-stratified analysis results were similar with and without adjustment for admission at an earlier age.

Finally, because the data were over-dispersed for a Poisson model, we used negative binomial regression to assess the adjusted association between breastfeeding and the number of hospitalizations and days of hospitalization. A zero-inflated negative binomial model produced a similar pattern of results, and so for parsimony was not used. For the multivariable analyses, we added potential confounders in turn (categorized as presented below), and we retained confounders based on subject-matter relevance and a change-in-estimate criteria for the association of breastfeeding with earlier admission for any infection.[32] On this basis we included sex, type of hospital at birth and household per capita income (quintiles) as confounders. We did not include highest parental education or maternal and infant characteristics, as these had minimal additional impact on the estimates.

Potential effect modification of the effect of breastfeeding on hospitalization by sex and small-for-gestational age (SGA) status was assessed by statistical significance of interaction terms and heterogeneity of effect across strata. SGA status was defined as birth weight below the 10th

percentile by sex and gestational age using the Williams curve,[23] for which the cut-offs were derived from 1.3 million non-Hispanic white middle class infants from 1970-1976 birth cohorts in California. In addition, as there is increasing evidence that premature birth is associated with poorer health across many domains,[34 35] we also examined possible differential effects of breastfeeding in premature (<37 weeks gestation) and low-birth-weight babies (<2500 grams). We assessed the significance of interaction terms in models with and without the interaction term, examining the statistical significance of the likelihood ratio test of the difference between the two models on the relevant chi-square distribution.

Ethical approval was obtained from the Institutional Review Board of The Hong Kong West Cluster and the Li Ka-Shing Faculty of Medicine, University of Hong Kong. All analyses were conducted using Stata version 9.2 statistical software (Stata Corp, College Station, Tx).

RESULTS

There are 8327 mother-infant pairs in the birth cohort. We excluded 546 with missing breastfeeding status or type of hospital at birth, leaving 7781 (93%) birth-cohort members in this analysis. Among these 7781 children, half (n = 3881; 50%) were admitted to a public hospital (day-patient or in-patient) for any illness at least once before the end of December 2005 (eTable 1, http://links.lww.com). Of these, 1966 (51%) were admitted for respiratory infections, 894 (23%) for gastrointestinal infections, and 863 (22%) for other infections.

Table 1 shows the baseline characteristics of the mothers and children by breastfeeding status. Only 43% (n = 3342) of birth-cohort mothers initiated breastfeeding, with 37% (n = 2851) partial breastfeeding for any length of time or exclusive breastfeeding for less than 3 months and 6% (n = 491) exclusively breastfeeding for at least 3 months. Higher education and higher income were positively associated with breastfeeding initiation, although less educated and lower income women were more likely to exclusively breastfeed for at least 3 months.

Women with caesarean delivery and secondhand smoke exposure during pregnancy or post partum were less likely to breastfeed.

Table 2 shows the hazard ratios for time to first hospital admission by breastfeeding status for each outcome by age at admission within each age range, adjusted for sex, type of birth hospital and household per capita income. Breastfeeding was associated with a lower risk of hospitalization in the first six months of life for respiratory infections, gastrointestinal infections and any infections, with a clear dose-response. Breastfeeding of any duration was not associated with a lower risk of hospitalization for infections beyond 6 months of age.

The associations of breastfeeding with the number of hospital admissions and with the number of hospital admission days for infectious diseases were similar (eTable 2 and 3, http://links.lww.com). Breastfeeding was associated with a lower risk of ever-admission, a lower number of admissions, and fewer bed-days in the first 6 months of life, with clear-dose response relationships. However, there were no similar associations in the older age groups or for the overall period from birth to 8 years. There was no association between breastfeeding and hospital admission for accidents in any analysis. Finally there was little evidence that the association of breastfeeding with time to first admission varied with sex, SGA status, low-birth-weight status, or prematurity status (data not shown).

DISCUSSION

Consistent with previous studies,[3 8 36] we found that, even in a highly developed region, breastfeeding provides substantial protection from hospitalization for infectious disease in infancy. Even a short duration of breastfeeding reduced hospitalization for respiratory and possibly non-gastrointestinal infections. Nonetheless, we were unable to show that breastfeeding provided any protection from hospitalization for infections beyond infancy up until 8 years of age. Our findings concerning infancy are similar to other studies from developing and developed locations, but our findings at older ages differ from most previous studies, which have found protective

effects of breastfeeding against infectious disease in older children. Most previous studies have come from low- and middle-income countries,[9 21-23] or from marginalized populations,[37] where patterns of infectious disease are different from developed countries.[4] Of the studies from developed countries that found breastfeeding protective in older children, one was an ecological study,[20] another used parent-reported respiratory symptoms (including wheeze) as the outcome,[18] and others were limited to specific diseases, such as otitis media[15] or haemophilus influenzae.[19] Most studies that considered overall infections did not identify age at illness, i.e. whether during the typical period of breastfeeding or later.[15 18 38] Thus, it is not clear whether the protection against serious infection illnesses occurred during breastfeeding or after the cessation of breastfeeding.

In our prospective birth cohort, breastfeeding data were collected prospectively before the onset of health outcomes of interest, thus minimizing reporting bias. Unlike previous studies examining illnesses and hospitalizations,[8 36] case ascertainment was based on doctor diagnosis and public-hospital discharge records rather than self-report, thereby eliminating parental recall bias and misclassification. Furthermore, we used a number of regression models to make full use of the hospitalization data, and we considered hospital admissions in terms of four different outcomes. These different models all produced similar results. Additionally, we considered the effect on the estimates of a range of confounders, including several measures of socio-economic position. We considered whether our findings could be due to residual confounding by examining whether breastfeeding status was associated with admission for accidents. In the age range from 0 to 6 months, where breastfeeding for 3 months or more was associated with reduced risk of hospitalization for infections, there was no association between breastfeeding and hospital admission for accidents, suggesting adequate control for social position.

Our study also had inevitable limitations. We were not able to account for admissions to private hospitals in this analysis. Admissions to private hospitals are most likely to occur among

children from more socioeconomically advantaged families, possibly resulting in an overestimation of the protective effect of breastfeeding on infectious disease hospitalization. However, we adjusted for indicators of private hospital use (birth in a private hospital and household income), as well as other markers of socioeconomic position.

In our data, protection against infectious disease from breastfeeding was dose-dependent, with longer durations of exclusive breastfeeding conferring greater benefits.[39] The low rate of breastfeeding beyond 6 months may not be suitable for studying the effect of long-term breastfeeding; however, it is ideal for studying the long-term effects of breastfeeding during early infancy, a critical period of development.[40-42]

As with all observational research we are unable to rule out a reverse causality bias in that early hospitalization may have resulted in a shorter duration of breastfeeding. Additionally, because we do not have data on when complementary foods were introduced, infants categorized as exclusively breastfed for three months or more could also have been given weaning foods and non-milk liquids, which is not completely consistent with WHO classifications.

Finally, hospital admission data may not be sensitive enough to capture a protective effect of breastfeeding against infectious disease in older children. Health services utilization data (i.e., outpatient and doctor visits) may be more representative of the overall burden of infectious disease in older children. Hospitalizations, however, reflect more severe diseases, with substantially greater costs than outpatient care. Even in this population with a high hospital admission rate, there was no evidence of protective effect of breastfeeding after infancy up to 8 years of age. This conclusion is consistent with a cohort study conducted in the United Kingdom, which found that the protective effect of breastfeeding in infants wears off soon after the discontinuation of breastfeeding.[36] Whether there might be beneficial effects of breastfeeding on children's health in later years remains to be answered.

The reduction in infectious-disease hospitalizations in infants observed in this study is consistent with a biological effect of breast milk directly stimulating the recipient's immune system via the transfer of anti-idiotypic antibodies and lymphocytes, resulting in a better-functioning immune system.[43] In formula-fed infants, infection can also result from contamination of the formula itself or of the bottles and plastic nipples used to deliver the formula.[44] In older children, it has been hypothesized that an improvement in immune function with early breastfeeding could produce long-term protection against infections and allergies.[45] Results from this study, however, indicate that breastfeeding does not reduce the risk of hospitalization from infectious disease beyond infancy, suggesting that breastfeeding provides no long-term benefits in the development of the immune system.

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Table

Table 1: Characteristics by breastfeeding status for 7781 children from Hong Kong's "Children of 1997" birth cohort

Characteristics		No.	Breastfeeding status: Never breastfed (n = 4439) %	Partially breastfed for any length of time or exclusively breastfed for <3 months (n = 2851) %	Exclusively breastfed for 3+ months (n = 491) %
Sex					
	Female	3685	47	47	54
	Male	4096	53	53	46
Birth weight (grams)					
	<2500	395	5	5	4
	2500-2999	1870	24	25	23
	3000-3499	3650	47	47	48
	3500-3999	1602	20	21	23
	≥4000	263	4	3	3
Gestational age (weeks)					
	≤36	408	5	5	4
	37	608	9	7	8
	38	1665	22	21	18
	39	2228	29	29	28
	40	1832	23	25	26
	41	816	10	11	11
	≥42	215	3	2	5
Small-for-gestational age status					
	Non-SGA	7042	90	92	89
	SGA	729	10	8	11
Mother's age at delivery (years)					
	≤24	948	13	11	13

	25-29	2393	32	30	35
	30-34	2913	37	40	33
	≥35	1384	18	18	19
Mode of delivery					
	Natural labor	4327	54	58	71.0
	Assisted natural labor	1268	16	19	14
	Caesarean	2045	30	24	16
Birth order					
	1st	3615	44	53	41
	2nd	3179	44	38	43
	≥3rd	853	12	9	16
Mother's pre- and post-natal secondhand smoke exposure					
	No pre-natal and no post-natal	2091	27	29	32
	Occasional non-parental pre-natal	2393	30	36	26
	Daily non-parental pre-natal	276	4	4	3
	Father occasional smoker	745	10	9	12
	Father daily smoker	1507	21	17	24
	Non-parental post-natal only	139	2	2	2
	Mother smoked during pregnancy or post partum	389	7	3	2
Highest parental education (grade)					
	9	2326	33	24	42
	10-11	3272	47	39	36
	12	2052	21	37	22
Type of hospital during delivery					
	Public	5573	70	70	93
	Private	2208	30	30	8
Highest parental occupation					
	I (professional)	1684	20	32	18
	II (managerial)	1096	16	17	14
	IIINM (non-manual skilled)	2010	32	27	20

	IIIM (manual skilled)	1177	19	13	24
	VI (semi-skilled)	710	11	9	15
	V (unskilled)	237	3	3	8
Household income per capita in quintiles (mean ± SD) (HK$)[a]					
	1st ($1749±420)	1418	18	16	30
	2nd ($2851±325)	1427	19	16	26
	3rd ($4366±557)	1402	20	16	14
	4th ($6829±884)	1392	18	19	9
	5th ($14958±15724)	1420	15	25	10

[a](US$1=HK$7.8)

Table 2: Association of breastfeeding status with first hospitalisation by age group and cause

		Respiratory infections		Gastro-intestinal infections		Other infections		Any infections		Accidents	
Age group	Breastfeeding	HR	(95% CI)[a]	HR	(95% CI)[a]	HR	(95% CI)[a]	HR	(95% CI)[a]	HR	(95% CI)[a]
0-8 years	Never breastfed	1.00		1.00		1.00		1.00		1.00	
	Some breastfeeding	1.03	(0.94 - 1.13)	1.07	(0.93 - 1.23)	0.97	(0.84 - 1.12)	0.98	(0.91 - 1.06)	1.01	(0.85 - 1.21)
	Exclusively breastfed for 3+ mths	0.96	(0.81 - 1.15)	1.10	(0.85 - 1.41)	1.02	(0.78 - 1.33)	0.96	(0.83 - 1.12)	0.96	(0.69 - 1.34)
0-5.9 months	Never breastfed	1.00		1.00		1.00		1.00		1.00	
	Some breastfeeding	0.79	(0.64 - 0.97)	0.83	(0.61 - 1.15)	0.89	(0.67 - 1.18)	0.80	(0.69 - 0.94)	0.96	(0.47 - 1.94)
	Exclusively breastfed for 3+ mths	0.64	(0.42 - 0.97)	0.51	(0.25 - 1.05)	0.58	(0.30 - 1.10)	0.61	(0.44 - 0.85)	2.15	(0.79 - 5.81)
6-23.9 months	Never breastfed	1.00		1.00		1.00		1.00		1.00	
	Some breastfeeding	1.12	(0.97 - 1.28)	1.09	(0.89 - 1.35)	0.89	(0.72 - 1.11)	1.05	(0.95 - 1.17)	0.97	(0.70 - 1.36)
	Exclusively breastfed for 3+ mths	0.98	(0.76 - 1.28)	1.14	(0.78 - 1.67)	1.00	(0.67 - 1.50)	0.98	(0.80 - 1.20)	0.96	(0.52 - 1.76)
2-4.9 years	Never breastfed	1.00		1.00		1.00		1.00		1.00	
	Some breastfeeding	1.10	(0.95 - 1.27)	1.12	(0.88 - 1.43)	1.15	(0.90 - 1.47)	1.10	(0.98 - 1.24)	0.87	(0.66 - 1.16)
	Exclusively breastfed for 3+ mths	1.00	(0.75 - 1.31)	1.22	(0.79 - 1.87)	1.20	(0.77 - 1.86)	1.06	(0.85 - 1.32)	0.70	(0.39 - 1.23)

5-8 years	Never breastfed	1.00			1.00			1.00			1.00		1.00		
	Some breastfeeding	1.01	(0.77	- 1.34)	1.06	(0.69	- 1.63)	0.77	(0.48	- 1.22)	1.01	(0.82 - 1.25)	1.27	(0.91 - 1.75)
	Exclusively breastfed for 3+ mths	1.04	(0.62	- 1.76)	1.45	(0.71	- 2.97)	1.77	(0.92	- 3.42)	1.33	(0.93 - 1.91)	1.09	(0.58 - 2.05)

[a] adjusted for sex, type of hospital at birth and household income per capita (quintiles)

[b] Reference category

[c]Partially breastfed for any length of time or exclusively breastfed for <3 months