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ORIGINAL ARTICLE

Formula feeding increases the risk of antibiotic prescriptions in children up to 2 years: results from a cohort study

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Abstract

Association between the use of infant formula and risks for infants' health is seldom studied in western countries. We set up a historical cohort based on record linkage analysis, combining the data from administrative databases providing individual data. Infants receiving the second dose of pediatric immunization between 2015 and 2017 were included. The main outcome measure was antibiotic prescriptions from enrolment up to 24 months of age, by infant feeding category at enrolment. The extended Cox regression technique was used to account for recurrent events. The infants' cohort included 40,258 5-month-old infants; during the study period, 60,932 antibiotic prescriptions were filled. Compared with infants fully breastfed, children fed with both maternal milk and formula received 106 more antibiotic prescriptions per 1000 children/year, whereas infants receiving formula only had 138 excess prescriptions per 1000 children/year. The association with infant feeding was statistically significant and remained unchanged after adjustment for common confounders (adjusted hazard ratio, HR, for complementary feeding vs full breastfeeding 1.09; 95%CI 1.05 to 1.12; formula only versus full breastfeeding adj. HR 1.12; 95%CI 1.08 to 1.16).

Conclusion: In our cohort, we observed a positive association between infant formula use considered a proxy of infections antibiotic prescription rate, considered a proxy of infections. The association followed a gradient.

What is Known:
- *Formula feeding is associated with increased morbidity and mortality even in western countries, but still, it is common.*
- *Information on formula are seldom unbiased; thus, public perception of risks is distorted.*

What is New:
- *In a large Italian cohort of infants, formula feeding at 5 months of age results to be associated with an increased rate of antibiotic prescription (considered to be a proxy of infection) up to 24 months of age: the association follows a dose-response relationship.*
- *Record linkage analysis using administrative databases provides useful information at a limited cost.*

Keywords Breastfeeding · Infections · Record linkage analysis · Italy

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Abbreviations

BF	Breastfeeding
BMI	Body mass index
DRG	Diagnosis-related group
95%CI	95% confidence interval
HR	Hazard ratio
ICD-IX	International Classification of Diseases, 9th edition

Introduction

Formula feeding is an alternative to breastfeeding for informed mothers who have no possibility or desire to breastfeed. It is difficult to quantify the proportion of infants that need formula: clinical conditions contraindicating breastfeeding occur rarely [24]. However, in many countries, formula is largely used: in Italy, the rate of formula feeding is roughly 20% at hospital discharge, 45% at 3 months of age, and 60% at 5 months of age. As formula use is related, among others, to both health professionals' and mothers' knowledge [17, 25], a complete and balanced information on risks associated with formula feeding is needed.

Independent studies have consistently shown that formula feeding is associated with increased risk of morbidity and mortality, even in western industrialized countries [8, 14, 22, 33]; nevertheless, data on the association between formula feeding and risk of infections in western countries are sparse [13, 19, 32, 36].

The aim of this study was to determine the possible association between use of infant formula and risk of receiving an antibiotic prescription (considered as a proxy of infections) in the first 2 years of life in a large population of Italian children.

Method

This is a historical cohort study based on record linkage analysis of regional administrative databases providing individual data of the population of Emilia-Romagna, a region of Northeast Italy with four and a half million inhabitants.

The study population was represented by 5-month-old infants, included in the regional immunization database (years 2015 to 2017), and receiving the second dose of pediatric immunization during the infant feeding surveys.

Data on infant nutrition were retrieved from the regional immunization database [11]. In addition to vaccination data, the database contains information on infant nutrition. This information is collected in all infants receiving a vaccination during specific time periods: in 2015 from March 16 to June 30, and thereafter, in 2016 and 2017, from March 16 to November 30. Exposition at 5 months of age was classified, according to the World Health Organization [41], as fully breastfed (reference group, infants receiving breastmilk, without formula), complementary fed (infants receiving both breastmilk and formula), not breastfed (infants receiving exclusively formula).

The rate of all antibiotics for systemic use (J01 according to Anatomical Therapeutic Chemical classification from the World Health Organization) [40], prescribed to infants between 5 and 24 months of age or up to the end of May 2018—censor date—whichever came first, represented the primary outcome measure. Data on antibiotic prescriptions were derived from the regional administrative database for drugs reimbursement, containing information on individual prescriptions, but not diagnosis, for all children living in Emilia-Romagna region [12]. Each infant included in the regional databases is assigned an anonymous unique patient identifier that can be used for record linkage across databases. Crude antibiotic prescription rates per 1000 children per year were calculated for each exposition level. Variables considered for adjustment were underlying morbidity of the child, defined according to data extracted from the hospital discharge regional database (list of ICD-IX codes used to define underlying morbidity of the child in additional on-line material), maternal characteristics, type of pregnancy, and mode of delivery based on data extracted from the regional medical birth database and, finally, anti-pneumococcal immunization status, defined according to the regional immunization database. The final multivariate model included all variables found to be significantly associated with the outcome of interest (p value < 0.05) and confounders. Crude and adjusted hazard ratio were estimated using the extended Cox regression technique according to Andersen-Gill (option robust standard error), to account for recurrent events [2]. Statistical analyses were carried out using the Stata statistical software package version 14.2.

Results

In the observation period—spanning the three infant feeding surveys from 2015 to 2017—40,258 5-months-old infants received the second dose of pediatric immunization. Infant feeding information was available for 38,055 (94.5%): of these infants, 15,019 (39.5%) were fully breastfed, 11,943 (31.4%) received both breastmilk and formula, and 11,093 (29.1%) were given formula only.

The cohort infants received 60,932 antibiotic prescriptions between 5 and 24 months of age or censoring (overall antibiotic prescription rate, 1183 per 1000 children/year; 95%CI 1174 to 1193); 23,628 infants (58.7% of the cohort) had at least one antibiotic prescription. In detail, 9273 infants (23% of the cohort) received one prescription during the study period, 5642 infants (14%) received two prescriptions, 3444

(8.6%) three prescriptions, and the rest (13.1%) received more than three prescriptions.

Most of the infants (31,514 out of 40,258, 78.3%) at hospital discharge received a code corresponding to normal, healthy baby (diagnosis-related group, DRG 391) and had no hospital admission during the follow-up. In 1746 cases (4.3% of the cohort), infants received a code of possible severe condition (DRG 385, 386, or 387) at hospital discharge and/or were subsequently admitted in hospital for a relevant condition. In 6998 cases (17.4% of the cohort), infants were discharged from hospital exclusively with a code associated to a probably mild condition (DRG 388, 389, or 390) without further subsequent hospital admissions. In 1338 cases, there was a coexistence of possible severe and probably mild condition codes: these were considered, in the analysis, as infant with a possible severe condition.

Almost all infants included in the survey received an antipneumococcal vaccine (40,012 infants, 99.4% of the cohort): numbers of doses received depending on the infants' age at the end of May 2018, when the immunization status was checked for.

Principal background characteristics for the infants' study population by exposition level (including those with unknown infant feeding status) are shown in Table 1. Infant characteristics associated with a higher risk of full formula feeding at 5 months were male sex, low birth weight, low gestational age, twins, no siblings, and severe condition at birth. The following maternal characteristics were associated with higher risk of full formula feeding at 5 months of age: age 35+, Italian nationality, low educational level, in employment, obesity, cigarette smoking, at-risk pregnancy, not attending an antenatal course, cesarean delivery.

Compared with infants fully breastfed (antibiotic prescription rate, 1110/1000 infants/year; 95%CI 1095, 1125), children fed with both maternal milk and formula received 106 more antibiotic prescriptions per 1000 children/year (rate 1216; 95%CI 1199, 1233), whereas infants receiving formula only had a 138 excess prescriptions per 1000 children/year (rate 1248; 95%CI 1229, 1266), while infants with unknown feeding status had 47 excess prescriptions per 1000 children/year (rate 1157; 95%CI 1120, 1196). The crude hazard ratio of antibiotic prescription, which was calculated according to the method of infant feeding, showed a positive dose-response relationship: infants in complementary breastfeeding and infants fully formula fed showed a trend of increasing risk of antibiotics prescription (Table 2). The association remained unchanged after controlling for variables found to be associated with the outcome of interest in the univariate analysis (severe condition at birth or in the subsequent 24 months based on DRG, cesarean section, single born, male sex, presence of other siblings, maternal age < 35 years, maternal overweight/obesity, mother of Italian nationality, mother employed) (Table 2).

Discussion

Our study, based on record linkage analysis of administrative databases of an Italian region, shows that increasing levels of formula feeding (reference being infants fully breastfed) are associated with a 5 to 16% increase in antibiotic prescriptions in children up to 24 months of age. The association is not influenced by other variables controlled for. Our interpretation is that the use of formula at the age of 5 months is associated with increased frequency of infections in the first 2 years of age, antibiotic prescription being a proxy of infections. Although Italian children in general are exposed to a high level of antibiotic prescriptions [10], this is no longer so in Emilia-Romagna, where a long-lasting project on the prudent and appropriate use of antibiotics has produced good results [12], similarly to other experiences [1, 35]. Therefore, we can be confident that in our region, antibiotic prescription is likely related to bacterial infection and can be used as a proxy of infection. On the other hand, the regional rate of breastfeeding falls short of internationally recommended targets, even if activities to improve protection, promotion, and support of breastfeeding have been implemented and an increase in breastfeeding rates has been detected [11]. Studies suggest a range of possible reasons for low breastfeeding initiation rates and short duration of breastfeeding, both in term and preterm infants [7, 34]: some of these are non-modifiable (like maternal education, nationality, and parity), some are inherent to the health system (processes and organization of the assistance to pregnant women and new mothers and families) and/or require specific additional funds to be changed, but some can be influenced by providing unbiased and complete information to both parents and health professionals, as knowledge is reported to impact on attitude and behavior [4, 20, 43]. As formula companies are the main source of information on breastmilk substitutes [21, 38], messages can be biased focusing the attention on the advantages of formula feeding and seldom discussing the risks [16, 28]: this is of concern for health decision-makers, health professionals, and breastfeeding support groups [5, 9, 29].

Previous studies investigated infant feeding and frequency of infections leading to hospital admissions and found an association, mainly limited to the first 12 months of life [32, 36]. Nevertheless, restricting the analysis to infections leading to hospital admission can underestimate risks of formula, as in at-term infants only a limited proportion of infections results in hospitalization. However, family life can be influenced also by mild infections, often associated with lost school and working days [30]. In addition, since antibiotics are frequently prescribed for common pediatric infections, with a well-established impact on antimicrobial resistance [42] and other

Table 1 Study population characteristics (number and proportion, unless otherwise specified) by infant feeding categories, Emilia-Romagna 2015–2017

Variables	Categories	Full BF[a] (*N* = 15,019) *n* (%)		Complementary feeding (*N* = 11,943) *n* (%)		Formula feeding only (*N* = 11,093) *n* (%)		Unknown (*N* = 2203) *n* (%)		Total (*N* = 40,258) *n* (%)	
Maternal age	< 18	18	(0.1)	16	(0.1)	28	(0.3)	4	(0.2)	66	(0.2)
	18–35	10,044	(66.9)	7802	(65.3)	6835	(61.6)	1296	(58.8)	25,977	(64.5)
	> 35	3602	(24.0)	3109	(26.0)	3082	(27.8)	497	(22.6)	10,290	(25.6)
	Missing	1355	(9.0)	1016	(8.5)	1148	(10.3)	406	(18.4)	3925	(9.7)
Maternal nationality	Italian	8978	(59.8)	6844	(57.3)	7631	(68.8)	1225	(55.6)	24,678	(61.3)
	Not Italian	4689	(31.2)	4094	(34.3)	2334	(21.0)	572	(26.0)	11,689	(29.0)
	Missing	1352	(9.0)	1005	(8.4)	1128	(10.2)	406	(18.4)	3891	(9.7)
Maternal education[b]	8	3064	(20.4)	2916	(24.4)	2584	(23.3)	450	(20.4)	9014	(22.4)
	13	5478	(36.5)	4593	(38.5)	4771	(43.0)	756	(34.3)	15,598	(38.7)
	> 13	5125	(34.1)	3429	(28.7)	2610	(23.5)	591	(26.8)	11,755	(29.2)
	Missing	1352	(9.0)	1005	(8.4)	1128	(10.2)	406	(18.4)	3891	(9.7)
Maternal employment	No	4915	(32.7)	4152	(34.8)	3196	(28.8)	629	(28.6)	12,892	(32.0)
	Yes	8670	(57.7)	6716	(56.2)	6681	(60.2)	1153	(52.3)	23,220	(57.7)
	Missing	1434	(9.5)	1075	(9.0)	1216	(11.0)	421	(19.1)	4146	(10.3)
Maternal BMI[c]	Underweight	1049	(7.0)	734	(6.1)	754	(6.8)	140	(6.4)	2677	(6.6)
	Normal	9165	(61.0)	6931	(58.0)	5978	(53.9)	1124	(51.0)	23,198	(57.6)
	Overweight	2303	(15.3)	2173	(18.2)	1902	(17.1)	342	(15.5)	6720	(16.7)
	Obese	918	(6.1)	945	(7.9)	1123	(10.1)	158	(7.2)	3144	(7.8)
	Missing	1584	(10.5)	1160	(9.7)	1336	(12.0)	439	(19.9)	4519	(11.2)
Maternal smoking	No	11,742	(78.2)	9254	(77.5)	7812	(70.4)	1477	(67.0)	30,285	(75.2)
	Stopped while pregnant	1256	(8.4)	1002	(8.4)	1097	(9.9)	181	(8.2)	3536	(8.8)
	Yes	523	(3.5)	587	(4.9)	948	(8.5)	127	(5.8)	2185	(5.4)
	Missing	1498	(10.0)	1100	(9.2)	1236	(11.1)	418	(19.0)	4252	(10.6)
Pregnancy	Low risk	11,011	(73.3)	8306	(69.5)	7328	(66.1)	1237	(56.2)	27,882	(69.3)
	At risk	1668	(11.1)	1607	(13.5)	1727	(15.6)	273	(12.4)	5275	(13.1)
	Missing	2340	(15.6)	2030	(17.0)	2038	(18.4)	693	(31.5)	7101	(17.6)
Antenatal course	No	6567	(43.7)	5865	(49.1)	5332	(48.1)	972	(44.1)	18,736	(46.5)
	No, already done	2002	(13.3)	1308	(11.0)	1236	(11.1)	206	(9.4)	4752	(11.8)
	Yes	4936	(32.9)	3657	(30.6)	3255	(29.3)	609	(27.6)	12,457	(30.9)
	Missing	1514	(10.1)	1113	(9.3)	1270	(11.4)	416	(18.9)	4313	(10.7)
Delivery	Vaginal	10,707	(71.3)	8044	(67.4)	6529	(58.9)	1304	(59.2)	26,584	(66.0)
	Cesarean section	2960	(19.7)	2894	(24.2)	3436	(31.0)	493	(22.4)	9783	(24.3)
	Missing	1352	(9.0)	1005	(8.4)	1128	(10.2)	406	(18.4)	3891	(9.7)
Infant sex	Male	7613	(50.7)	6130	(51.3)	5768	(52.0)	1131	(51.3)	20,642	(51.3)
	Female	7406	(49.3)	5813	(48.7)	5325	(48.0)	1072	(48.7)	19,616	(48.7)
Birth weight	< 2500	422	(2.8)	629	(5.3)	1037	(9.3)	105	(4.8)	2193	(5.4)
	2500–4000	12,307	(81.9)	9604	(80.4)	8445	(76.1)	1582	(71.8)	31,938	(79.3)
	> 4000	998	(6.6)	771	(6.5)	547	(4.9)	120	(5.4)	2436	(6.1)
	Missing	1292	(8.6)	939	(7.9)	1064	(9.6)	396	(18.0)	3691	(9.2)
Gestational age	< 37	526	(3.5)	662	(5.5)	1064	(9.6)	117	(5.3)	2369	(5.9)
	37–42	13,109	(87.3)	10,255	(85.9)	8881	(80.1)	1671	(75.9)	33,916	(84.2)
	>42	32	(0.2)	21	(0.2)	20	(0.2)	9	(0.4)	82	(0.2)
	Missing	1352	(9.0)	1005	(8.4)	1128	(10.2)	406	(18.4)	3891	(9.7)
Twins	No	13,563	(90.3)	10,611	(88.8)	9328	(84.1)	1746	(79.3)	35,248	(87.6)
	Yes	104	(0.7)	327	(2.7)	637	(5.7)	51	(2.3)	1119	(2.8)
	Missing	1352	(9.0)	1005	(8.4)	1128	(10.2)	406	(18.4)	3891	(9.7)
Siblings	No	6910	(46.0)	5718	(47.9)	5738	(51.7)	942	(42.8)	19,308	(48.0)
	Yes	6755	(45.0)	5220	(43.7)	4227	(38.1)	855	(38.8)	17,057	(42.4)
	Missing	1354	(9.0)	1005	(8.4)	1128	(10.2)	406	(18.4)	3893	(9.7)
Disease	None	12,294	(81.9)	9345	(78.2)	8130	(73.3)	1745	(79.2)	31,514	(78.3)
	Mild	2326	(15.5)	2120	(17.8)	2198	(19.8)	354	(16.1)	6998	(17.4)
	Severe	399	(2.7)	478	(4.0)	765	(6.9)	104	(4.7)	1746	(4.3)

[a] *BF* breastfeeding

[b] Maternal education level at the year of birth, categorized into 8 years or less (lower secondary school or less), 9–13 years (upper secondary school), and more than 13 (graduated)

[c] Pregnancy BMI categorized as underweight (BMI < 18.5), normal (BMI 18.5–24.9), overweight (BMI 25.0–29.9), and obese (BMI ≥ 30.0)

adverse effects [15, 26], reducing the incidence of common infection is crucial. Thus, focusing our investigation on a wider spectrum of bacterial infections seemed to be more relevant for families, health professionals, and public health. It is

Table 2 Crude and adjusted hazard ratio of antibiotic prescription by study covariate, immunization cohort 2015–2017

	N	HR (95%CI)	
		Crude	Adjusted*
Infant feeding	38,055		
Full breastfeeding		1	1
Complementary feeding		1.08 (1.05, 1.12)	1.09 (1.05, 1.12)
Formula only		1.11 (1.08, 1.15)	1.12 (1.08, 1.16)
Severe disease	40,258	1.29 (1.21, 1.37)	1.29 (1.20, 1.38)
Male sex	40,258	1.15 (1.12, 1.18)	1.15 (1.12, 1.19)
Single fetus	36,367	1.23 (1.13, 1.33)	1.35 (1.24, 1.48)
Siblings	36,365	1.32 (1.28, 1.35)	1.35 (1.31, 1.39)
Maternal overweight/obesity	35,739	1.11 (1.08, 1.15)	1.08 (1.05, 1.11)
Italian mother	36,367	1.05 (1.02, 1.09)	1.04 (1.01, 1.08)
Maternal age 18–35	36,333	1.02 (1.00, 1.05)	1.08 (1.05, 1.12)
Mother employed	36,112	1.15 (1.12, 1.19)	1.21 (1.17, 1.25)
Cesarean section	36,367	1.05 (1.02, 1.08)	1.04 (1.01, 1.07)

*The final model included 33,723 subjects, due to missing value for included variables

possible that the association between formula feeding and risk of infections is even larger, as we were not able to assess the impact on viral infections that do not require an antibiotic treatment but still cause family discomfort.

In addition, with rare interesting exceptions [37], most of the trials on breastfeeding have a short follow-up, limited to the first year of life [13, 32, 36]. This can be due to the assumption that in the first year of life, the magnitude of the association is more evident, but it can also be caused by the difficulties in conducting large prospective cohort with long follow-up [37]. Using record linkage analysis allowed us to extend the follow-up to 24 months of age, thus showing a sustained detrimental effect of formula on children health.

Previous studies have already shown the association of some of the variables considered in our analysis and increased risk of infections, like male sex [27], presence of siblings [3], and maternal overweight/obesity [39]. Being born with a malformation or other severe conditions requiring NICU admission is associated with an increased risk of antibiotic use [18, 31]. To the best of our knowledge, other associations are described for the first time in our study sample: Italian nationality of the mother, maternal age less than 35 years, maternal employment, and being single born. It is possible that some of these are not risk factors per se but are a proxy of an attitude and behavior that favors higher demand for antibiotics either for lack of experience or for urgent need to return to work. These hypotheses should be addressed in future studies. The finding on cesarean section is interesting: while the association between cesarean section and lower breastfeeding rate is widely reported, our study detects a direct association between mode of delivery and antibiotic prescription rate independently from the feeding modality. We found a Danish study describing an association between cesarean delivery and higher rate of respiratory syncytial virus infection [23], and an Australian study based on record linkage analysis of data spanning 10 years (from 2001 and 2011) that found an association between mode of delivery, gestational age at birth, feeding modality, and hospital admission for gastroenteritis up to 1 year of age [6]. The authors explain that microbioma of vaginally born infants is more similar to the maternal one and is more able to fight infections; instead, in the case of cesarean delivery, the infant microbioma is not colonized by healthy maternal bacteria and the child risk of developing infections increases.

Strengths of our study are the large number of observations collected and the length of follow up; in absence of databases linkable on a single patient base, it would have been difficult to conduct such a time and resource consuming ad hoc study. On the other hand, considering the large sample size, some of the observed associations that happened to be statistically significant could have minor clinical relevance. Another strength is the quality and completeness of the administrative databases used: Emilia-Romagna has a long tradition of administrative databases and is one of the Italian regions with the largest number of good quality databases, routinely used for regional surveillance activity and health care planning. There are other advantages in using our breastfeeding monitoring system that have been already described [11]: almost the entire infant population is included, irrespective of nationality of the mother and socioeconomic characteristics; thus, selection biases are unlikely to occur. Less than 3% of our infant population has parents that refuse the immunization, in most cases under the influence of antivaccination movements, and therefore are not included in our survey. However, these parents are believed to be more prone to breastfeed and to have low propensity to antibiotic use. Therefore, the exclusion of this marginal part

of the population may have led to an underestimation of the association between formula use and antibiotic prescriptions, which however is strong and significant.

One limitation of our study is that the outcome considered, antibiotic prescription, is only a proxy of the frequency of infections; however, we could have not been more accurate, as our drugs database does not include diagnosis. Nevertheless, antibiotic use can be considered a good proxy of infant infections as it is strictly related to bacterial infections and, if any, the error will be on the side of underestimation of infections, as antibiotics are not usually prescribed for viral infections. Lastly, because of the increase in appropriateness of antibiotic prescription in Emilia-Romagna region in the last years [12], we can be confident about the relevance of using antibiotic prescription as a proxy of bacterial infectious episodes in children.

Another limitation of our study is that, being based on administrative data, the analysis can only be controlled for data included in our databases. It is possible that other information, like daycare attendance, could be of interest when assessing the occurrence of infections in infants and children. Nevertheless, it is reasonable that other variables systematically recorded in our databases, like maternal education, age, marital status, and employment status, can be assumed to be a proxy of daycare utilization.

Despite these limitations, we are confident that the results of our study can contribute a more detailed understanding of the association between infant feeding and infant and child morbidity in western countries with a prevalence of formula use similar to the one of Emilia-Romagna region; moreover, we have shown that record linkage analysis using administrative database is a practicable way to produce evidence and to identify trends: further analysis with ad hoc research and data collection can enrich and expand these findings.

Providing evidence-based and unbiased information on infant feeding can contribute to modifying attitude and practice regarding the use of formula and favor the implementation of activities to protect, promote, and support breastfeeding, to ensure that all mothers and babies can enjoy their right to health through appropriate feeding.

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Compliance with ethical statements

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

References

1. Achten NB, Dorigo-Zetsma JW, van der Linden PD, van Brakel M, Plötz FB (2018) Sepsis calculator implementation reduces empiric antibiotics for suspected early-onset sepsis. Eur J Pediatr 177:741-746. https://doi.org/10.1007/s00431-018-3113-2
2. Amorim LDAF, Cai J (2015) Modelling recurrent events: a tutorial for analysis in epidemiology. Int J Epidemiol 44:324-333. https://doi.org/10.1093/ije/dyu222.324-333
3. Anderson H, Vuillermin P, Jachno K, Allen KJ, Tang ML, Collier F, Kemp A, Ponsonby AL, Burgner D, Barwon Infant Study Investigator Group (2017) Prevalence and determinants of antibiotic exposure in infants: a population-derived Australian birth cohort study. J Paediatr Child Health 53:942-949. https://doi.org/10.1111/jpc.13616
4. Balogun OO, Dagvadorj A, Yourkavitch J, da Silva Lopes K, Suto M, Takemoto Y, Mori R, Rayco-Solon P, Ota E (2017) Health facility staff training for improving breastfeeding outcome: a systematic review for step 2 of the Baby-Friendly Hospital Initiative. Breastfeed Med 12:537-546. https://doi.org/10.1089/bfm.2017.0040
5. Beasley A, Amir LH (2007) Policy on infant formula industry funding, support or sponsorship of articles submitted for publication. Int Breastfeed J 2:5. https://doi.org/10.1186/1746-4358-2-5
6. Bentley JP, Simpson JM, Bowen JR, Morris JM, Roberts CL, Nassar N (2016) Gestational age, mode of birth and breastmilk feeding all influence acute early childhood gastroenteritis: a record-linkage cohort study. BMC Pediatr 16:55. https://doi.org/10.1186/s12887-016-0591-0

7. Bonnet C, Blondel B, Piedvache A, Wilson E, Bonamy AE, Gortner L, Rodrigues C, van Heijst A, Draper ES, Cuttini M, Zeitlin J, EPICE Research Group (2018) Low breastfeeding continuation to 6 months for very preterm infants: a European multiregional cohort study. Matern Child Nutr 15:e12657. https://doi.org/10.1111/mcn.12657
8. Bowatte G, Tham R, Dai X (2015) Breastfeeding and childhood acute otitis media: a systematic review and meta-analysis. Acta Paediatr 104:85-95. https://doi.org/10.1111/apa.13151
9. Brady JP, Brady JP (2012) Marketing breast milk substitutes: problems and perils throughout the world. Arch Dis Child 97:529-532. https://doi.org/10.1136/archdischild-2011-301299
10. Clavenna A, Bonati M (2011) Differences in antibiotic prescribing in paediatric outpatients. Arch Dis Child 96:590-595. https://doi.org/10.1136/adc.2010.183541
11. Di Mario S, Borsari S, Verdini E, Battaglia S, Cisbani L, Sforza S, Cuoghi C, Basevi V (2017) Regular monitoring of breast-feeding rates: feasible and sustainable. The Emilia-Romagna experience. Public Health Nutr 20:1895-1902. https://doi.org/10.1017/S136898001700074X
12. Di Mario S, Gagliotti C, Buttazzi R, Cisbani L, Di Girolamo C, Brambilla A, Moro ML, regional working group "Progetto ProBA-Progetto Bambini e Antibiotici-2014" (2018) Observational pre-post study showed that a quality improvement project reduced paediatric antibiotic prescribing rates in primary care. Acta Paediatr 107:1805-1809. https://doi.org/10.1111/apa.14381
13. Duijts L, Jaddoe VWV, Hofman A, Moll HA (2010) Prolonged and exclusive breastfeeding reduces the risk of infectious diseases in infancy. Pediatrics 126:e18-e25. https://doi.org/10.1542/peds.2008-3256
14. Eidelman AI, Schanler RJ, American Acedemy of Pediatrics (2012) Breastfeeding and the use of human milk. Pediatrics 129:e827-e841. https://doi.org/10.1542/peds.2011-3552
15. Esaiassen E, Fjalstad JW, Juvet LK, van den Anker JN, Klingenberg C (2017) Antibiotic exposure in neonates and early adverse outcomes: a systematic review and meta-analysis. J Antimicrob Chemother 72:1858-1870. https://doi.org/10.1093/jac/dkx08836
16. Fabbri A, Holland TJ, Bero LA (2018) Food industry sponsorship of academic research: investigating commercial bias in the research agenda. Public Health Nutr 21:3422-3430. https://doi.org/10.1017/S1368980018002100
17. Feldman-Winter L, Szucs K, Milano A, Gottschlich E, Sisk B, Schanler RJ (2017) National trends in pediatricians' practices and attitudes about breastfeeding: 1995 to 2014. Pediatrics 140:e20171229. https://doi.org/10.1542/peds.2017-1229
18. Hartz LE, Bradshaw W, Brandon DH (2015) Potential NICU environmental influences on the neonate's microbiome: a systematic review. Adv Neonatal Care 15:324-335. https://doi.org/10.1097/ANC.0000000000000022042.
19. Hawkins SS, Griffiths LJ, Dezateux C, Law C, Millennium Cohort Study Child Health Group (2007) The impact of maternal employment on breast-feeding duration in the UK Millennium Cohort Study. Public Health Nutr 10:891-896. https://doi.org/10.1017/S1368980007226096
20. Hernandez Perez M, feminine C, Diaz-Gomez NM, Romero Manzano AM, Díaz Gómez JM, Rodríguez Pérez V, Jiménez Sosa A (2018) Effectiveness of an intervention to improve breastfeeding knowledge and attitudes among adolescents. Rev Esp Salud Publica 92:e201806033
21. Howard CR, Howard FM, Weitzman ML (1994) Infant formula distribution and advertising in pregnancy: a hospital survey. Birth 21:14-19
22. Ip S, Chung M, Raman G, Chew P, Magula N, DeVine D, Trikalinos T, Lau J (2007) Breastfeeding and maternal and infant health outcomes in developed countries. Evid Rep Technol Assess (Full Rep) 1-186
23. Kristensen K, Fisker N, Haerskjold A, Ravn H, Simões EA, Stensballe L (2015) Caesarean section and hospitalization for respiratory syncytial virus infection: a population-based study. Pediatr Infect Dis J 34:145-148. https://doi.org/10.1097/INF.0000000000000552
24. Lawrence RM (2013) Circumstances when breastfeeding is contraindicated. Pediatr Clin NA 60:295-318. https://doi.org/10.1016/j.pcl.2012.09.012
25. Li R, Rock VJ, Grummer-Strawn L (2007) Changes in public attitudes toward breastfeeding in the United States, 1999-2003. J Am Diet Assoc 107:122-127. https://doi.org/10.1016/j.jada.2006.10.002
26. Lovegrove MC, Geller AI, Fleming-Dutra KE, Shehab N, Sapiano MRP, Budnitz DS (2018) US emergency department visits for adverse drug events from antibiotics in children, 2011-2015. J Pediatric Infect Dis Soc. https://doi.org/10.1093/jpids/piy066
27. Muenchhoff M, Goulder PJR (2014) Sex differences in pediatric infectious diseases. J Infect Dis 209:s120-s126. https://doi.org/10.1093/infdis/jiu232
28. Mugambi MN, Musekiwa A, Lombard M, Young T, Blaauw R (2013) Association between funding source, methodological quality and research outcomes in randomized controlled trials of synbiotics, probiotics and prebiotics added to infant formula: a systematic review. BMC Med Res Methodol 13:137. https://doi.org/10.1186/1471-2288-13-137
29. Nestle M (2001) Commentary food company sponsorship of nutrition research and professional activities: a conflict of interest? Public Health Nutr 4:1015-1022. https://doi.org/10.1079/PHN2001253
30. Neuzil KM, Hohlbein C, Zhu Y (2002) Illness among schoolchildren during influenza season: effect on school absenteeism, parental absenteeism from work, and secondary illness in families. Arch Pediatr Adolesc Med 156:986-991
31. O'Grady NP, Alexander M, Burns LA, Dellinger EP, Garland J, Heard SO, Lipsett PA, Masur H, Mermel LA, Pearson ML, Raad II, Randolph AG, Rupp ME, Saint S, Healthcare Infection Control Practices Advisory Committee (HICPAC) (2011) Guidelines for the prevention of intravascular catheter-related infections. Clin Infect Dis 52:e162-e193. https://doi.org/10.1093/cid/cir257
32. Quigley M, Kelly Y, Sacker A (2009) Infant feeding, solid foods and hospitalisation in the first 8 months after birth. Arch Dis Child 94:148-150. https://doi.org/10.1136/adc.2008.146126
33. Robinson S, Fall C (2012) Infant nutrition and later health: a review of current evidence. Nutrients 4:859-874. https://doi.org/10.3390/nu4080859
34. Rosenthal A, Oliveira SB, Madubuko U, Tanuos H, Schwab J, Monteiro IM (2019) Effects of immigration on infant feeding practices in an inner city, low socioeconomic community. J Natl Med Assoc 111:153-157. https://doi.org/10.1016/j.jnma.2018.07.006
35. Schrier L, Hadjipanayis A, Del Torso S, Stiris T, Emonts M, Dornbusch HJ (2018) European Antibiotic Awareness Day 2017: training the next generation of health care professionals in antibiotic stewardship. Eur J Pediatr 177:279-283. https://doi.org/10.1007/s00431-017-3055-0
36. Størdal K, Lundeby KM, Brantsæter AL, Haugen M, Nakstad B, Lund-Blix NA, Stene LC (2017) Breastfeeding and infant hospitalisation for infections: large cohort- and sibling analysis. J Pediatr Gastroenterol Nutr 65:225-231. https://doi.org/10.1097/MPG.0000000000001539
37. Tromp I, Kiefte-de Jong J, Raat H, Jaddoe V, Franco O, Hofman A, de Jongste J, Moll H (2017) Breastfeeding and the risk of respiratory tract infections after infancy: the Generation R Study. PLoS One 12:e0172763. https://doi.org/10.1371/journal.pone.0172763

38. van Tulleken C (2018) Overdiagnosis and industry influence: how cow's milk protein allergy is extending the reach of infant formula manufacturers. BMJ 363:k5056. https://doi.org/10.1136/bmj.k5056
39. Videholm S, Silfverdal SA, Reniers G (2019) Maternal weight and infections in early childhood: a cohort study. Arch Dis Child 104: 58-63. https://doi.org/10.1136/archdischild-2017-314628
40. WHO Collaborating Centre for Drug Statistics Methodology (2012) Guidelines for ATC classification and DDD assignment 2013. Oslo. https://www.whocc.no/filearchive/publications/1_2013guidelines.pdf. Accessed 13 March 2019
41. World Health Organization/UNICEF (2008) Indicators for assessing infant and young child feeding practices. Geneva. https://apps.who.int/iris/bitstream/handle/10665/43895/9789241596664_eng.pdf;jsessionid=2BCEEB67C03460CC225761AAC98EFB78?sequence=1. Accessed 13 March 2019
42. Yonts AB, Kronman MP, Hamdy RF (2018) The burden and impact of antibiotic prescribing in ambulatory pediatrics. Curr Probl Pediatr Adolesc Health Care 48:272-288. https://doi.org/10.1016/j.cppeds.2018.09.002
43. Zhang Z, Zhu Y, Zhang L, Wan H (2018) What factors influence exclusive breastfeeding based on the theory of planned behaviour. Midwifery 62:177-182. https://doi.org/10.1016/j.midw.2018.04.006

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