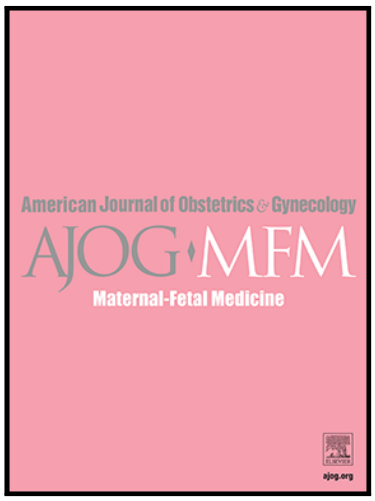

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In-utero antibiotic exposure and subsequent infections in infancy: A register-based cohort study with sibling analysis

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Disclosure

AON and HK are employees and LP is a former employee of the Centre for Pharmacoepidemiology at Karolinska Institutet which receives grants from different entities including regulatory authorities, pharmaceutical companies and contract research organizations to conduct drug safety and drug utilization studies, unrelated to this work. The other authors report no conflict of interest.

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Presentations

Preliminary results of the study were presented orally at the 13th Nordic PharmacoEpidemiology Network (NorPEN) Conference, Stockholm, Sweden, held 11-12th November 2021. The final results were presented orally at the 38th International Conference on Pharmacoepidemiology & Therapeutic Risk Management (ICPE), Copenhagen, Denmark, held 24-28th August 2022.

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Condensation

This population-based cohort study observed minor associations between in-utero antibiotic exposure and infections during infancy; these were partly explained by shared familial factors.

Short title

In-utero antibiotic exposure and infections in infancy

AJOG-MFM at a Glance

- Though antibiotics are frequently used during pregnancy, their associations with infections in the offspring have not been comprehensively explored. Using Swedish population-based registers, we performed a cohort study including sibling analyses and estimated hazard ratios and incidence rate ratios of infection-indicative events in the first year of life.

- Infants exposed to antibiotics in-utero had slightly higher rates of filling antimicrobial prescriptions and of infections diagnosed in specialist care across antibiotic classes, when compared with unexposed. These associations were attenuated in sibling analyses. Exposure to antibiotics was not associated with infection-related infant mortality, when accounting for shared familial factors.
- The associations between in-utero antibiotic exposure and infections during infancy were minor and partly explained by shared familial factors. No differential associations were observed across commonly used antibiotic classes.

Abstract

Background: Prenatal antibiotic use, the ensuing maternal dysbiosis and subsequent acquisition of altered microbiota in early life have been linked to the offsprings' increased susceptibility to childhood infections. However, infection risks during the first year of life associated with in-utero antibiotic exposure, have not been comprehensively explored.

Objective: To investigate the associations between exposure to antibiotics in-utero and subsequent infections during infancy, and if such associations differ by antibiotic class.

Study design: All data were retrieved from Swedish population-based registers. Singletons live-born between 2006 and 2018 were followed from birth until their first birthday. Exposure was maternal filling of at least one antibiotic prescription between the last menstrual period and delivery. Outcomes were the infants' antimicrobial prescription fills, incident infections diagnosed in specialist care and deaths with infections indicated as underlying or contributing causes ("infection-related deaths"). Birth year, birth season, maternal age, place of residence, parity, co-morbidity indicator, body mass index, proxies for general health status, education level and smoking were considered as covariates. Poisson regression was used to estimate crude and adjusted incidence rate ratios (aIRRs) with 95% confidence intervals (95% CIs) for the number of antimicrobial prescriptions filled to the infant. Cox regression was used to estimate crude and adjusted hazard ratios (aHRs) with 95% CIs for incident infections diagnosed in specialist care and at death. Sibling analyses was used to account for shared familial factors. Sensitivity of the results to exposure definition and perinatal factors prognostic for the outcomes were assessed in supplementary analyses.

Results: Of 1,347,018 infants in the full cohort, 294,657 (21.9%) were exposed to antibiotics in-utero. There were 677,430 antimicrobial prescriptions filled (1.38 per 1000 person-days), 423,705 incident infections diagnosed in specialist care (0.87 per 1000 person-days) and 2,800 infection-related deaths (0.006 deaths per 1000 person-days) during follow-up. Compared to unexposed, infants exposed in-utero had higher rates of antimicrobial prescription fills (aIRR 1.34; 95% CI 1.33–1.34); incident infections diagnosed in specialist care (aHR 1.28; 95% CI 1.27–1.29); and infection-related mortality (aHR 1.15; 95% CI 1.05–1.25). For antimicrobial prescriptions and infections diagnosed in specialist care, associations were consistent across most antibiotic classes but were attenuated in the sibling analyses: aIRR 1.05 (95% CI 1.04–1.06) and aHR 1.05 (95% CI 1.03-1.07), respectively. No associations with infant mortality were found in the sibling cohort (aHR 0.93; 95% CI 0.81–1.08).

Conclusion: The minor associations between in-utero antibiotic exposure and infections during infancy were partly explained by shared familial factors, and did not differ across frequently used antibiotic classes.

Key words

Pregnancy, antibiotics, infant, siblings, infections, deaths, pharmacoepidemiology, cohort study, population-based registers

Introduction

In western countries about 20-40% of pregnant women are prescribed antibiotics,[1-7] and increasing trends have been reported.[1] Although often warranted and largely considered safe,[8] increased risks of childhood infections such as otitis media, infection-related hospitalizations and filling antibiotic prescriptions, have been reported among offsprings exposed in-utero to antibiotics.[9-12] Antibiotics inadvertently alter microbiota resulting in dysbiosis,[13] and the acquisition of dysbiotic maternal microbiota by the offspring during pregnancy, birth and postnatally has been suggested to explain the increased susceptibility to childhood infections.[9-12] However, previous studies were limited by incomplete information on antibiotic exposures, smaller sample sizes and familial confounding. Considering the huge burden of childhood infections globally and related deaths that mostly occur in the first year of life,[14,15] antibiotic prescribing for pregnant women and women of reproductive age should be evidence-informed.

The present study was conducted to investigate the associations between exposure to antibiotics in-utero and infections during infancy, and whether such associations differed by antibiotic class.

Materials and Methods

Study design and data sources

In this population-based cohort study, we analyzed data from Swedish population and health registers: the Medical birth register (MBR),[16] Prescribed drug register (PDR),[17] National patient register (NPR),[18] Cause of death register (CoDR)[15] and Total population

register (TPR);[19] and the Longitudinal integrated database for health insurance and labour market studies (LISA).[20] The low fees and accessible healthcare in Sweden coupled with mandatory reporting by healthcare providers to the registers ensures high coverage.[19] Data linkages between registers are enabled by unique individual identifiers assigned to residents in Sweden at birth or immigration.[21] The Regional Ethical Review Board in Stockholm approved the study. Informed consent for participation in register-based studies is not required.[22]

The MBR contains perinatal information on up to 99% of births in Sweden since 1973.[23] The PDR contains records of all prescribed drugs dispensed at pharmacies in Sweden, including Anatomical therapeutic chemical (ATC) codes and dispensing dates.[17] ATC codes are unique alphanumeric keys developed and assigned by the World Health Organization to drugs in accordance with their anatomical, therapeutic and chemical properties.[24] The NPR contains information on diagnoses as International Classification of Diseases 10th revision (ICD-10) codes recorded during hospitalization and at specialist outpatient visits,[18] whereas the CoDR contains data on underlying and multiple contributing causes of death with ICD-10 codes as indicated in death certificates issued by physicians.[15] The TPR contains individual-level information on demographic, civil and emigration status of all Swedish residents with records on nearly all births and deaths; 95% immigrations and 91% of emigrations.[25] The LISA database covers education, income and occupation among other information on the Swedish population aged at least 16 years.[20]

Study population

Information concerning all singletons, live-born in Sweden from 1 July 2006 to 31 December 2018 were obtained from the MBR. The study period ensured full coverage of prescription data for all pregnancies in the study including a three-month lookback before the last menstrual period (LMP).

Exposure

Infants were categorized as exposed to antibiotics in-utero or unexposed on the basis of their mothers' filling of at least one antibiotic prescription, as identified from the PDR, in the period from the LMP to delivery. As almost all pregnancies are routinely ultrasound-dated during antenatal care in Sweden, the date of LMP was computed from the ultrasound-estimated gestational age of the infant at birth. Observations with missing information on gestational age at birth were not included. The exposure comprised of antibacterials for systemic use as well as gynecological and intestinal antibiotics; categorized into antibiotic classes by ATC pharmacological subgroup, except for J01X which was done at ATC chemical subgroup level (Supplemental Table 1). Gynecological and intestinal preparations were categorized into the corresponding pharmacological subgroups for antibacterials for systemic use (Supplemental Table 1).

Outcomes

The primary outcome of the study was infant infections which were established from three infection-indicative events in the offspring during the first year of life: number of

antimicrobial prescription fills (i.e. all antibacterial, antiviral and antifungal preparations, Supplemental Table 2); incident infections diagnosed in specialist care (i.e. specialist outpatient care or during hospitalization); and infection-related deaths, defined as deaths where infection was indicated as underlying or contributing cause (Supplemental Table 3).

Covariates

Covariates were identified from existing literature and directed acyclic graphs.[1,2,4,7,26] Birth year, birth season, maternal age, place of residence, parity, summary indicator for co-morbidities of relevance (asthma, diabetes, chronic renal disease, immunodeficiency disorders), body mass index (BMI), general health status, education level and smoking during pregnancy were included in the final regression models. As proxies for general health status before pregnancy we considered the total number of prescriptions filled within 90 days prior to LMP, as well as the number of outpatient visits and hospitalizations in the one-year period before LMP. Maternal smoking was identified mainly in early pregnancy when women are enrolled in antenatal care. Maternal education was the highest level of education attained by the delivery year. Perinatal and maternal characteristics were all retrieved from the MBR, NPR and PDR. The LISA database provided individual-level data on education, and information on maternal place of residence were obtained from the TPR.

Statistical analyses

Following univariate descriptive analyses, we assessed the association between in-utero antibiotic exposure and number of antimicrobial prescription fills during infancy. Using

Poisson regression, we estimated the crude and adjusted incidence rate ratios (aIRRs) with 95% confidence intervals (CIs). The offset was included to scale the modelling of the mean number of prescriptions filled with respect to the time at risk in days, i.e. the follow-up time of each infant. Similarly, crude and adjusted hazard ratios (aHRs) and 95% CIs were estimated using Cox proportional-hazards regression models to assess the association between in-utero antibiotic exposure and incident infection diagnoses at specialist care or at death, with age at outcome in days as the time-to-event variable. Crude models included only the exposure while adjusted models included the identified covariates. For all regression models, follow-up was censored on the day before their first birthday, at emigration, death or 31 December 2019, which ever came first. The infants' emigration status was determined from the TPR, and deaths from the CoDR. Cluster-robust standard errors were computed to account for interdependency of infants born by the same mother. All statistical analyses were performed using R.[27]

In the sibling analyses, the study population was restricted to siblings born by the same mother. Those subsequently considered in the regression models were discordant for both the primary exposure and each of the three outcomes independently to emulate a matched case-control study.[28] Conditional Poisson and stratified Cox regression analyses were performed to estimate IRRs and HRs while controlling for familial confounding.[28,29]

Supplementary analyses

Regression models were repeated for all outcomes with a subpopulation that excluded infants with severe co-morbidities, which are risk factors for the outcomes: extreme prematurity (<28 weeks of gestation), extremely low birth weight (<1000g), congenital

infections (ICD-10 codes P35-37), neonatal hospital admissions of at least 7 days and major congenital anomalies as adapted from the European surveillance of congenital anomalies (EUROCAT).[30]

To assess the sensitivity of the results to exposure definition, we considered two additional data sources i.e. MBR for self-reported antibiotic use and NPR for parenteral antibiotics administered in specialist care. Prenatal drug information in the MBR is self-reported by pregnant women and recorded by midwives or physicians with ATC codes, brand or generic names in standardized medical forms at antenatal visits during early and later pregnancy.[16] The NPR contains, for selected drugs, ATC codes of those mainly administered in inpatient care, alongside procedure codes for administration.[18]

Results

In the full cohort of 1,347,018 infants born by 846,714 mothers, 294,657 (21.9%) were exposed to antibiotics in-utero (Table 1). Mothers of exposed infants were more likely than unexposed to be younger, multiparous, smoke during pregnancy and have a lower education level. Co-morbidities and higher BMI were more prevalent among mothers of exposed infants. Additionally, mothers of exposed infants had more filled prescriptions and specialist outpatient or inpatient visits prior to pregnancy; and more often resided in counties with a higher density of physicians. Overall, 3611 emigrations and 2800 deaths occurred during follow-up.

A total of 677,430 antimicrobial prescriptions were filled to 383,866 infants covering more than 488.9 million person-days of follow-up, with an overall incidence rate (IR) of 1.38 prescriptions filled per 1000 person-days. The majority (68.2%) of prescriptions filled were

for systemic antibiotics. Antimicrobial prescription fill rates were higher among exposed than unexposed infants: 1.8 vs 1.3 per 1000 person-days (Table 2). Compared to unexposed, infants exposed to any antibiotics in-utero had higher antimicrobial prescription fill rates (aIRR 1.34; 95% CI 1.33–1.34) and this association was comparable across antibiotic classes.

There were 423,705 incident infections diagnosed in specialist care over 394.6 million person-days (IR 1.07 per 1000 person-days), of which upper respiratory tract infections were most common (13.6%). The IR of incident infections for exposed infants was higher than for unexposed: 1.36 vs 1.00. In-utero exposure with any antibiotic was associated with a higher rate of incident infections during infancy (aHR 1.28; 95% CI 1.27–1.29) and associations were similar for in-utero exposures to all antibiotics classes, except aminoglycosides (aIRR 0.37; 95% CI 0.17–0.80) (Table 3).

During 488.9 million person-days of follow-up 2,800 infants died from infections, resulting in an overall infection-related infant mortality rate of 0.006 per 1000 person-days. All deaths had lower respiratory and serious bacterial infections as underlying or contributing causes. The majority of deaths (1,768, 63%) occurred within the first 28 days of life and of these 1,305 deaths had occurred within the first week of life. Infection-related mortality rate was higher among exposed (IR 1.39) than unexposed infants (IR 1.22) (Table 4). The aHR comparing infants exposed to any antibiotics in-utero to unexposed was 1.15 (95% CI 1.05–1.25).

Sibling analyses

Of 909,048 siblings identified from the full cohort, 198,477 (21.8%) were exposed (Table 1). During follow-up, 466,817 antimicrobial prescriptions were filled to infants with siblings (IR 1.42 per 1000 person-days), while 294,702 incident infections (IR 0.89 per 1000 person-days) and 2220 infection-related deaths occurred (IR 0.007 per 1000 person-days). Regression analyses comparing exposed to unexposed siblings yielded an aIRR of 1.05 (95% CI 1.04–1.06) for antimicrobial prescription fills, an aHR of 1.05 (95% CI 1.03–1.07) for incident infections diagnosed in specialist care and an aHR of 0.93 (95% CI 0.81–1.08) for infection-related deaths (Tables 2-4).

Supplementary analyses

The IRR and HR estimates remained similar for all outcomes in sensitivity analyses where exposure was defined by maternal self-reported use, filled prescriptions or administrations of antibiotics in specialist care; and for a subpopulation of infants without severe comorbidities (Tables 2–4).

Comment

Principal findings

This population-based cohort study found minor associations between in-utero antibiotic exposure and infections during the first year of life. Infants exposed to any antibiotics in-utero had slightly higher rates of filling antimicrobial prescriptions, incident infections diagnosed in specialist care and infection-related infant mortality overall. For both prescriptions fills and incident infections, the associations were similar across antibiotic

classes. All associations remained in supplementary analyses, performed to account for exposure misclassification and perinatal factors prognostic of the outcomes, but were substantially attenuated in the sibling analyses, diminishing to the null for infection-related infant mortality.

Results in the context of what is known

Previous studies have reported similarly minor risks of childhood infections with in-utero antibiotic exposures.[9-12] The odds of filling antibiotic prescriptions were higher for infants born in Norway if their mothers had also filled antibiotic prescriptions during pregnancy.[12] Our study found an increased rate of antimicrobial prescription fills to infants exposed in-utero, of which almost 70% were systemic antibiotics. In a Danish study, the risk of otitis media and ventilation tube insertions were 30% higher among children born to mothers who filled antibiotic prescriptions,[10] which was comparable with our results on infections diagnosed in specialist care. In a population-based cohort study in Denmark, HRs of febrile seizures during 5 years of follow-up were similarly slightly higher (aHR 1.08) among singletons exposed to any systemic antibiotics in-utero.[9] This agreement albeit the longer follow-up time could be due to the fact that the first year of life accounts for the largest proportion of infections experienced during childhood.[31] A further Danish population-based cohort study also associated maternal antibiotic use during pregnancy with higher rates of infection-related hospitalizations in the first year of life.[11] Two of these studies explored the role of familial factors and demonstrated associations between maternal pre-pregnancy[11] and postnatal[10] antibiotic use and childhood infections. Maternal infections during pregnancy and infant infections are heterogenous, but as in these previous studies

discerning the effect of antibiotics from infections in our study was complicated by the unavailability of indications for which antibiotics were prescribed.[9-12]

The present study differed from others by considering current antibiotic regimens used during pregnancy, and investigating broader exposure-outcome associations including mortality and conducting sibling analyses. The exposure included locally-acting intestinal and gynecological preparations in addition to systemic antibiotics, accounting for the major colonization during vaginal birth when the offspring acquires maternal vaginal and gut microbiota. Furthermore, the secondary exposure included self-reported use and also aimed to include specialist care administrations of antibiotics. Our reasonably powered sibling analyses are arguably more robust in accounting for factors shared within families compared to previous approaches,[32] and is of particular interest as both prenatal antibiotic use and childhood infections recur within families.[33,34]

Clinical and research implications

Our findings of slight increases in infection rates for infants exposed to commonly used antibiotics in-utero is reassuring, particularly as the impact on infant mortality in the presence of superseding risk factors like extreme prematurity and low birth weight appeared minimal. These findings could be substantiated by future studies that account for peripartum antibiotic use with estimation of cumulative risks, and from settings beyond Scandinavia where infectious disease burden and antibiotic use vary. Sweden in particular has a long history of nationwide programmes against antibiotic resistance that has maintained relatively low levels of antibiotic use.[35]

Our findings downplay the dysbiosis hypothesis. Although perturbed microbiota have been isolated from infants exposed to antibiotics in-utero with varying effects on immunity,[36-38,39] no apparent proportionate or differential associations between antibiotic classes have been demonstrated by epidemiological studies specifically looking at infections.[9,11] Multiple testing may explain the relatively higher rate of antimicrobial prescriptions filled to the infants exceptionally associated with in-utero exposure to "other beta-lactamases" and not with other broad-spectrum antibiotics. Infants born by caesarean section are unlikely to be affected by in-utero antibiotic exposure should the dysbiosis hypothesis hold, because they are colonized by flora from the maternal skin and healthcare setting.[40] Follow-up studies aimed at profiling microbiota according to infection susceptibility and assessing the potential mediating role of mode of delivery may therefore clarify underlying dysbiosis-related mechanisms.

Strengths and limitations

The use of Swedish national registers provided a large cohort generalizable to the current Swedish population and other similar populations such as those with comparable maternal and infant characteristics in the United States.[41] Because register data are prospectively and systematically collected for routine healthcare purposes, selection bias and differential misclassification were mitigated. We looked into a continuum of infant infectious disease morbidity and mortality alongside important confounders, all sourced from registers validated to have good agreement with medical and death records.[15,18]

There were some limitations. Non-adherence to dispensed antibiotics could have led to non-differential exposure misclassification and biased our results towards the null. However, non-adherence to and delaying intake of antibiotics is low among pregnant women in Sweden as they are often indicated for acute illnesses and prescribed when warranted.[42] For the same reason, potential carry-over effects in the sibling analyses, such as the recurrence of prenatal antibiotic use or disuse in subsequent pregnancies owing to consequences of use or disuse in prior pregnancies, are likely to be minimal and compounded by other maternal factors that we accounted for in the analyses.[34] Consistent confounding adjustment and the minimal cross-over effects mitigated biases that would have been otherwise amplified by the selected sampling of the sibling cohorts.[28] Prescription data were also supplemented with self-reported use and hospital administrations to obtain the best possible estimate of exposure,[43] and further tackle misclassification. However, antibiotic administrations during hospitalization including prophylaxis against group B streptococcus that is given intrapartum were ultimately inadequately captured, introducing biases in the estimates for infants exposed to parenteral antibiotics such as aminoglycosides. Estimates for infrequently used antibiotics classified as glycopeptide, steroid and other antibacterials were also less certain. Early life antibiotic exposures and co-existing morbidities may in theory have skewed our findings, but seems unlikely as a subpopulation analysis excluding these infants yielded estimates similar to the overall analyses. We lacked information on some confounders and risk factors such as maternal diet including alcohol intake, the infants' vaccination status and feeding. This was partly addressed in the sibling analyses which controlled for several shared familial factors ranging from genetic, environmental to parental behaviors that affect both maternal and infant infection risks, although we did not distinguish between half- and full siblings. In the

main analyses, the presence of older siblings in the home who are likely to impact infection transmission and hence antibiotic use in later pregnancies and newborns was accounted for by adjusting for parity.[44]

Conclusions

In this large population-based cohort, associations between prenatal antibiotic exposure and infections during infancy were minor and partly explained by shared familial factors. No differential associations were observed across antibiotic classes commonly used during pregnancy.

Author contributions Credit

Aya Olivia Nakitanda (AON): Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Validation, Visualization, Writing - original draft. **Helle Kieler (HK)**: Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Writing - review and editing. **Ingvild Odsbu (IO)**: Conceptualization, Investigation, Methodology, Supervision, Writing - review and editing. **Samuel Rhedin (SR)**: Conceptualization; Writing - review and editing. **Catarina Almqvist (CA)**: Conceptualization, Writing - review and editing. **Björn Pasternak (BP)**: Conceptualization, Methodology, Supervision, Writing - review and editing. **Laura Pazzagli (LP)**: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Supervision, Validation, Writing - review and editing.

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Table 1: Characteristics of infants in the full and sibling cohorts, according to in-utero exposure to antibiotics

Characteristics	All			Siblings		
	Total	Unexposed	Exposed	Total	Unexposed	Exposed
	N (%)	n (%)	n (%)	N (%)	n (%)	n (%)
Total	1,347,018	1,052,361 (71.8)	294,657 (21.9)	909,048	710,571	198,477
Sex						
Female	654,070 (48.6)	511,001 (48.6)	143,069 (48.6)	440,856 (48.5)	344,496 (48.5)	96,360 (48.5)
Male	692,945 (51.4)	541,357 (51.4)	151,588 (51.4)	468,190 (51.5)	366,073 (51.5)	102,117 (51.5)
Missing	3 (<0.1)	3 (<0.1)	0 (0)	2 (<0.1)	2 (<0.1)	0 (0)
Gestational age at birth, weeks						
<37	62,517 (4.6)	46,657 (4.4)	15,860 (5.4)	39,121 (4.3)	29,205 (4.1)	9,916 (5.0)
37-40+	944,154 (70.1)	735,213 (69.9)	208,941 (70.9)	644,564 (70.9)	502,334 (70.7)	142,230 (71.7)
≥41	340,347 (25.3)	270,491 (25.7)	69,856 (23.7)	225,363 (24.8)	179,032 (25.2)	46,331 (23.3)
Birth weight, grams						
<2500	38,285 (2.8)	29,011 (2.8)	9,274 (3.1)	22,824 (2.5)	17,226 (2.4)	5,598 (2.8)
2500 - 3999	1,052,097 (78.1)	823,212 (78.2)	228,885 (77.7)	707,454 (77.8)	553,380 (77.9)	154,074 (77.6)
≥4000	255,114 (18.9)	198,982 (18.9)	56,132 (19.0)	177,763 (19.6)	139,202 (19.6)	38,561 (19.4)
Missing	1,522 (0.1)	1,156 (0.1)	366 (0.1)	1,007 (0.1)	763 (0.1)	244 (0.1)
Mode of delivery						

Table 1 cont.

Vaginal	1,121,028 (83.2)	881,445 (83.8)	239,583 (81.3)	772,933 (85.0)	607,834 (85.5)	165,099 (83.2)
Caesarean section	225,990 (16.8)	170,916 (16.2)	55,074 (18.7)	136,115 (15.0)	102,737 (14.5)	33,378 (16.8)
Birth year						
2006 – 2010	468,492 (34.8)	357,061 (33.9)	111,431 (37.8)	294,018 (32.3)	226,695 (31.9)	67,323 (33.9)
2011 – 2014	431,806 (32.1)	337,691 (32.1)	94,115 (31.9)	343,223 (37.8)	268,291 (37.8)	74,932 (37.8)
2015 – 2018	446,720 (33.2)	357,609 (34)	89,111 (30.2)	271,807 (29.9)	215,585 (30.3)	56,222 (28.3)
Birth season						
Spring	342,678 (25.4)	265,440 (25.2)	77,238 (26.2)	236,048 (26.0)	182,962 (25.7)	53,086 (26.7)
Summer	363,711 (27.0)	282,528 (26.8)	81,183 (27.6)	244,663 (26.9)	190,005 (26.7)	54,658 (27.5)
Autumn	333,263 (24.7)	262,482 (24.9)	70,781 (24.0)	221,307 (24.3)	174,563 (24.6)	46,744 (23.6)
Winter	307,366 (22.8)	241,911 (23.0)	65,455 (22.2)	207,030 (22.8)	163,041 (22.9)	43,989 (22.2)
Maternal age at birth, years						
<20	17,732 (1.3)	12,378 (1.2)	5,354 (1.8)	11,278 (1.2)	7,821 (1.1)	3,457 (1.7)
20-24	168,074 (12.5)	126,340 (12.0)	41,734 (14.2)	120,291 (13.2)	90,179 (12.7)	30,112 (15.2)
25-29	406,656 (30.2)	320,965 (30.5)	85,691 (29.1)	293,379 (32.3)	230,943 (32.5)	62,436 (31.5)
30-34	460,126 (34.2)	363,910 (34.6)	96,216 (32.7)	317,534 (34.9)	251,828 (35.4)	65,706 (33.1)
35-39	240,388 (17.8)	187,269 (17.8)	53,119 (18.0)	142,551 (15.7)	111,395 (15.7)	31,156 (15.7)
40-44	51,280 (3.8)	39,364 (3.7)	11,916 (4.0)	23,071 (2.5)	17,690 (2.5)	5,381 (2.7)
≥45	2,760 (0.2)	2,133 (0.2)	627 (0.2)	944 (0.1)	715 (0.1)	229 (0.1)
Parity						

Table 1 cont.

0	591,776 (43.9)	474,580 (45.1)	117,196 (39.8)	344,770 (37.9)	276,149 (38.9)	68,621 (34.6)
1+	755,242 (56.1)	577,781 (54.9)	177,461 (60.2)	564,278 (62.1)	434,422 (61.1)	129,856 (65.4)
Maternal comorbidities						
Asthma[a]	33,036 (2.5)	22,956 (2.2)	10,080 (3.4)	21,845 (2.4)	15,210 (2.1)	6,635 (3.3)
Pre-existing diabetes[b]	9,180 (0.7)	6,075 (0.6)	3,105 (1.1)	5,865 (0.6)	3,915 (0.6)	1,950 (1)
Chronic renal disease[c]	335 (0)	197 (0)	138 (0)	221 (<0.1)	138 (<0.1)	83 (<0.1)
Gestational diabetes[d]	9,769 (0.7)	6,947 (0.7)	2,822 (1.0)	5,829 (0.6)	4,114 (0.6)	1,715 (0.9)
Immunodeficiency disorders[e]	3,616 (0.3)	2,454 (0.2)	1,162 (0.4)	2,279 (0.3)	1,528 (0.2)	751 (0.4)
Co-morbidity indicator[f]	54,949 (4.1)	38,065 (3.6)	16,884 (5.7)	35,486 (3.9)	24,595 (3.5)	10,891 (5.5)
Maternal body mass index						
<18.5	31,550 (2.3)	24,435 (2.3)	7,115 (2.4)	499,627 (55)	395,851 (55.7)	103,776 (52.3)
18.5 – 24.9	729,058 (54.1)	577,146 (54.8)	151,912 (51.6)	21,350 (2.3)	16,442 (2.3)	4,908 (2.5)
25.0 – 29.9	318,333 (23.6)	247,133 (23.5)	71,200 (24.2)	212,400 (23.4)	164,784 (23.2)	47,616 (24)
30.0 – 34.9	114,126 (8.5)	86,225 (8.2)	27,901 (9.5)	75,523 (8.3)	57,002 (8.0)	18,521 (9.3)
>34.9	63,126 (4.7)	46,956 (4.5)	16,170 (5.5)	41,560 (4.6)	30,952 (4.4)	10,608 (5.3)
Missing	90,825 (6.7)	70,466 (6.7)	20,359 (6.9)	58,588 (6.4)	45,540 (6.4)	13,048 (6.6)
Maternal general health status before pregnancy						
Prescriptions, N ± SD	1.0 ± 2.3	0.9 ± 2.0	1.4 ± 2.9	0.9 (2.1)	0.8 (1.9)	1.3 (2.7)
Outpatient visits, N ± SD	3.0 ± 6.0	2.8 ± 5.6	4.0 ± 7.2	2.9 (5.8)	2.7 (5.3)	3.9 (7.0)
Hospitalizations, N ± SD	0.5 ± 1.7	0.5 ± 1.6	0.7 ± 2.0	0.6 (1.8)	0.6 (1.7)	0.8 (2.2)

Table 1 cont.

Maternal smoking during pregnancy						
No	1,219,935 (90.6)	960,085 (91.2)	259,850 (88.2)	828,156 (91.1)	651,948 (91.7)	176,208 (88.8)
Yes	83,710 (6.2)	58,490 (5.6)	25,220 (8.6)	52,565 (5.8)	36,471 (5.1)	16,094 (8.1)
Missing	43,373 (3.2)	33,786 (3.2)	9,587 (3.3)	28,327 (3.1)	22,152 (3.1)	6,175 (3.1)
Maternal education						
Compulsory, 9 years	146,986 (10.9)	107,010 (10.2)	39,976 (13.6)	99,152 (10.9)	71,790 (10.1)	27,362 (13.8)
Pre-university, 12 years	657,779 (48.8)	508,600 (48.3)	149,179 (50.6)	433,542 (47.7)	335,741 (47.2)	97,801 (49.3)
University	499,257 (37.1)	401,937 (38.2)	97,320 (33.0)	349,857 (38.5)	281,956 (39.7)	67,901 (34.2)
Postgraduate	12,763 (0.9)	10,381 (1.0)	2,382 (0.8)	8,219 (0.9)	6,696 (0.9)	1,523 (0.8)
Missing	30,233 (2.2)	24,433 (2.3)	5,800 (2.0)	18,278 (2.0)	14,388 (2.0)	3,890 (2.0)
Maternal county of residence at birth						
> 3.8 doctors per 1000 inhabitants	662,899 (49.2)	509,491 (48.4)	153,408 (52.1)	444,915 (48.9)	341,823 (48.1)	103,092 (51.9)
< 3.8 doctors per 1000 inhabitants	681,928 (50.6)	541,014 (51.4)	140,914 (47.8)	463,385 (51.0)	368,116 (51.8)	95,269 (48.0)
Missing	2,191 (0.2)	1,856 (0.2)	335 (0.1)	748 (0.1)	632 (0.1)	116 (0.1)

SD, Standard deviation

[a] *ICD-10 codes J45-46, or ATC codes R03BA, R03DC, R03AK or R03AC*

[b] *ICD-10 codes E10/O24.0 (Type I), E11/O24.1(Type II), E13, E14; or ATC codes A10 without concomitant diagnoses N97 and/or E28.2*

[c] *ICD-10 codes N18*

[d] *ICD-10 codes ICD-10 codes 024.4 OR ICD-10 codes E10/O24.0 (Type I), E11/O24.1(Type II), E13, E14; or ATC codes A10. Additionally, women did not have diabetes diagnoses in the year before LMP or filled prescriptions within 3 months before LMP.*

[e] *ICD-10 codes D70-D71, D80-D84, D89; or ATC codes L01, L04*

[f] *Any history of asthma, pre-existing diabetes, gestational diabetes, chronic renal disease or immunodeficiency disorder*

Table 2: Associations between in-utero antibiotic exposure and the number of antimicrobial prescriptions filled in the first year of life

Exposure status	N	Events, n	Person-time, days	IR, n per 1000 person-days	Crude IRR (95% CI)	Adjusted IRR[a] (95% CI)
Full cohort						
Unexposed	1,052,361	484,300	381,954,832	1.27	1.00 Ref	1.00 Ref
Any antibiotics	294,657	193,130	106,940,962	1.81	1.42 (1.42 - 1.43)	1.34 (1.33 - 1.34)
Tetracyclines	7,510	5,174	2,725,493	1.90	1.50 (1.46 - 1.54)	1.40 (1.37 - 1.44)
Penicillins	217,047	146,672	78,788,939	1.86	1.47 (1.46 - 1.48)	1.36 (1.35 - 1.37)
Other beta-lactamases	24,897	18,332	9,035,141	2.03	1.60 (1.58 - 1.62)	1.49 (1.46 - 1.51)
Sulfonamides and trimethoprim	3,530	2,343	1,281,749	1.83	1.44 (1.38 - 1.50)	1.35 (1.29 - 1.40)
Macrolides, lincosamides and streptogramins	26,580	17,857	9,635,627	1.85	1.46 (1.44 - 1.48)	1.37 (1.35 - 1.39)
Aminoglycosides[b]	26	12	9,464	1.27	1.00 (0.57 - 1.76)	0.54 (0.30 - 0.94)
Quinolone antibacterials	3,401	2,184	1,233,430	1.77	1.40 (1.34 - 1.46)	1.30 (1.25 - 1.36)
Glycopeptide antibacterials[b]	52	33	18,928	1.74	1.37 (0.98 - 1.93)	1.14 (0.81 - 1.61)
Steroid antibacterials[b]	19	17	6,916	2.46	1.93 (1.20 - 3.11)	1.53 (0.95 - 2.45)
Imidazole derivatives	4,295	2,859	1,559,590	1.83	1.44 (1.39 - 1.50)	1.38 (1.33 - 1.43)
Nitrofuran derivatives	64,160	41,198	23,283,020	1.77	1.40 (1.38 - 1.41)	1.33 (1.32 - 1.34)
Other antibacterials[b]	13	17	4,732	3.59	2.83 (1.76 - 4.55)	2.24 (1.39 - 3.60)

Supplementary analysis with extended exposure definition[c]						
Unexposed	1,050,032	483,218	381,109,472	1.27	1.00 Ref	1.00 Ref
Any antibiotic	296,986	194,212	107,786,322	1.80	1.42 (1.41 – 1.43)	1.33 (1.33 – 1.34)
Subpopulation analysis with exclusion of serious comorbidities[d]						
Unexposed	984,262	429,976	357,567,110	1.20	1.00 Ref	1.00 Ref
Any antibiotic	276,641	172,509	100,513,474	1.72	1.43 (1.42 – 1.43)	1.34 (1.33 – 1.35)
Sibling analysis[e]						
Unexposed	89,749	87,853	32,565,583	2.70	1.00 Ref	1.00 Ref
Any antibiotics	77,707	84,743	28,213,455	3.00	1.08 (1.06 - 1.09)	1.05 (1.04 - 1.06)

IR, Incidence rate; IRR, Incidence rate ratio; CI, Confidence interval; Ref, Reference group

[a] *Adjusted for maternal age, parity, general health status before pregnancy, co-morbidity indicator, body mass index, education level, smoking, place of residence, birth year and season.*

[b] *Strata with extremely few observations excluded from interpretations*

[c] *Based on maternal prescriptions filled and self-reported use.*

[d] *Excluding infants who were extremely preterm (< 28 completed weeks of gestation), extremely low birth weight (<1000g), with at least one major congenital or chromosomal anomaly, congenital infections and hospital admission for at least 7 days as a neonate.*

[e] *Only siblings discordant on both antibiotic exposure and number of antimicrobial prescriptions filled (Supplemental Table 4)*

Table 3: Associations between in-utero antibiotic exposure and incident infections diagnosed in specialist care in the first year of life

Exposure status	N	Events, n	Person-time, days	IR, n per 1000 person-days	Crude HR (95% CI)	Adjusted HR[a] (95% CI)
Full cohort						
Unexposed	1,052,361	312,300	312,843,505	1.00	1.00 Ref	1.00 Ref
Any antibiotic	294,657	111,405	81,728,392	1.36	1.35 (1.34 - 1.36)	1.28 (1.27 - 1.29)
Tetracyclines	7,510	2,857	2,073,736	1.38	1.36 (1.31 - 1.42)	1.28 (1.23 - 1.33)
Penicillins	217,047	82,954	60,002,283	1.38	1.37 (1.36 - 1.38)	1.29 (1.28 - 1.30)
Other beta-lactamases	24,897	9,760	6,850,118	1.42	1.41 (1.38 - 1.44)	1.31 (1.28 - 1.34)
Sulfonamides and trimethoprim	3530	1,309	985,551	1.33	1.32 (1.25 - 1.39)	1.22 (1.15 - 1.29)
Macrolides, lincosamides and streptogramins	26,580	10,659	7,193,715	1.48	1.46 (1.44 - 1.49)	1.36 (1.34 - 1.39)
Aminoglycosides[b]	26	6	8,044	0.75	0.75 (0.35 - 1.63)	0.37 (0.17 - 0.80)
Quinolone antibacterials	3,401	1,325	925,435	1.43	1.42 (1.34 - 1.50)	1.30 (1.23 - 1.38)
Glycopeptide antibacterials[b]	52	26	13,194	1.97	1.93 (1.32 - 2.82)	1.51 (1.01 - 2.26)
Steroid antibacterials[b]	19	8	5,016	1.59	1.56 (0.78 - 3.14)	1.33 (0.66 - 2.69)
Imidazole derivatives	4,295	1,758	1,155,087	1.52	1.50 (1.43 - 1.57)	1.41 (1.35 - 1.48)
Nitrofuran derivatives	64,160	24,544	17,690,309	1.39	1.37 (1.36 - 1.39)	1.29 (1.28 - 1.31)

Other antibacterials[b]	13	5	3,503	1.43	1.41 (0.58 - 3.47)	1.31 (0.53 - 3.28)
Supplementary analysis with extended exposure definition[c]						
Unexposed	1,050,032	311,532	312,163,682	1.00	1.00 Ref	1.00 Ref
Any antibiotic	296,986	112,173	82,408,215	1.36	1.35 (1.34 – 1.36)	1.28 (1.27 – 1.29)
Subpopulation analysis with exclusion of serious comorbidities[d]						
Unexposed	984,262	284,313	294,939,773	0.96	1.00 Ref	1.00 Ref
Any antibiotic	276,641	102,090	77,529,806	1.32	1.35 (1.34 – 1.36)	1.28 (1.27 – 1.29)
Sibling analysis[e]						
Unexposed	79,847	37,218	20,603,935	1.81	1.00 Ref	1.00 Ref
Any antibiotic	68,094	33,940	17,076,915	1.99	1.06 (1.05 - 1.08)	1.05 (1.03 - 1.07)

IR, Incidence rate; HR, Hazard ratio; CI, Confidence interval; Ref, Reference group

[a] *Adjusted for maternal age, parity, general health status before pregnancy, co-morbidity indicator, body mass index, education level, smoking, place of residence, birth year and season.*

[b] *Strata with extremely few observations excluded from interpretations*

[c] *Based on maternal prescriptions filled and self-reported use.*

[d] *Excluding infants who were extremely preterm (< 28 completed weeks of gestation), extremely low birth weight (<1000g), with at least one major congenital or chromosomal anomaly, congenital infections and hospital admission for at least 7 days as a neonate.*

[e] *Only siblings discordant on both antibiotic exposure and incident infection diagnosed in specialist care (Supplemental Table 5)*

Table 4: Associations between in-utero antibiotic exposure and infection-related death in the first year of life

Exposure status	N	Events, n	Person-time, days	IR, n per 1000 person-days	Crude HR (95% CI)	Adjusted HR[a] (95% CI)
Full cohort						
Unexposed	1,052,361	2091	381,954,832	0.005	1.00 Ref	1.00 Ref
Any antibiotic	294,657	709	106,940,962	0.007	1.21 (1.11 – 1.32)	1.15 (1.05 – 1.25)
Supplementary analysis with extended exposure definition[b]						
Unexposed	1,050,032	2,087	381,109,472	0.005	1.00 Ref	1.00 Ref
Any antibiotic	296,986	713	107,786,322	0.007	1.21 (1.11 – 1.32)	1.15 (1.05 – 1.25)
Subpopulation analysis with exclusion of serious comorbidities[c]						
Unexposed	984,262	888	357,567,110	0.002	1.00 Ref	1.00 Ref
Any antibiotic	276,641	307	100,513,474	0.003	1.23 (1.08 – 1.40)	1.15 (1.01 – 1.31)
Sibling analysis[d]						
Unexposed	1,662	589	417,233	1.39	1.00 Ref	1.00 Ref
Any antibiotic	1,304	420	344,502	1.22	0.85 (0.75 – 0.97)	0.93 (0.81 – 1.08)

IR, Incidence rate; HR, Hazard ratio; CI, Confidence interval; Ref, Reference group

[a] *Adjusted for maternal age, parity, general health status before pregnancy, co-morbidity indicator, body mass index, education level, smoking, place of residence, birth year and season.*

[b] *Based on maternal prescriptions filled and self-reported use.*

[c] *Excluding infants who were extremely preterm (< 28 completed weeks of gestation), extremely low birth weight (<1000g), with at least one major congenital or chromosomal anomaly, congenital infections and hospital admission for at least 7 days as a neonate.*

[d] *Only siblings discordant on both antibiotic exposure and infection-related death (Supplemental Table 6)*