

Long-term impact of pre-incision antibiotics on children born by caesarean section: a longitudinal study based on UK electronic health records

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Declared competing interests of authors: Krishnarajah Nirantharakumar reports grants from the Medical Research Council (MRC) (London, UK), National Institute for Health and Care Research (NIHR), Health Data Research UK (London, UK), AstraZeneca (Cambridge, UK), Vifor Pharma (Glattbrugg, Switzerland) and Action Against AMD (London, UK); grants and personal fees from Boehringer Ingelheim (Bracknell, UK); and personal fees from Sanofi SA (Paris, France) and Merck Sharp & Dohme (London, UK). He is also the director of OpenClinical.net and a trustee of the Network for Improving Critical care Systems and Training (Colombo, Sri Lanka) outside the submitted work. Magdalena Skrybant received grants from the NIHR Applied Research Collaboration West Midlands (Coventry, UK) during the conduct of the study. Jonathan J Deeks reports grants from the NIHR Health Technology Assessment (HTA) programme, during the conduct of the study. He is a former member of the HTA Medical Tests Methods Group, Pre-Exposure Prophylaxis Impact Review Panel, HTA Post-Funding Committee teleconference (POC members to attend), HTA Funding Committee Policy Group (formerly CSG), HTA Commissioning Committee, HTA Efficient Study Designs – 2, HTA Commissioning Committee and HTA End of Life Care and Add-on Studies. Peter Brocklehurst is a member of a Clinical Trials Unit funded by NIHR, a former member of HTA Efficient Study Designs – 2, the former chairperson of the HTA Maternal, Neonatal and Child Health Panel, an emeritus senior NIHR investigator and the former chairperson of MRC/NIHR Methodology Research Programme panel. He has received research grants as chief investigator from the NIHR HTA programme, the NIHR Efficacy and Mechanism Evaluation programme and the Wellcome Trust (London, UK), and consultancy fees from Biotest AG (Dreieich, Germany).

Published June 2022
DOI: 10.3310/ZYZC8514

Scientific summary

Impact of pre-incision antibiotics for caesarean section

Health Technology Assessment 2022; Vol. 26: No. 30

DOI: 10.3310/ZYZC8514

NIHR Journals Library www.journalslibrary.nihr.ac.uk

Scientific summary

Background

In the UK, a caesarean section (CS) is a common surgical procedure, with around one-third of babies being delivered this way. The risk of developing an infection in the post-partum period is considerably higher following CS than vaginal delivery (VD). National Institute for Health and Care Excellence (NICE) Clinical Guideline 132 on CS recommends offering prophylactic antibiotics to women undergoing a CS to reduce the risk of post-partum infections (NICE. *Caesarean Birth*. NICE Guideline NG192. London: NICE; 2021).

Before 2011, this clinical guideline recommended providing intravenous prophylactic antibiotics after cord clamping to prevent the baby from being exposed to the maternal antibiotics. In 2011, the recommendation was changed to offering antibiotics to women before skin incision. This change in recommendation was based on evidence that earlier administration reduces the risk of maternal infections, although most of the infections are mild and respond well to treatment.

Pre-operative antibiotics can cross the placenta, resulting in babies being exposed to them at the time of birth. During birth, the intestines are colonised by microbes and there is a growing body of evidence that intestinal microbe composition in infants plays a key role in the development of their immune system. This intestinal microbiota can be altered by exposure to antibiotics, and disruptions to intestinal microbiota are associated with susceptibility to asthma, eczema, allergies and other immune-related diseases later in childhood.

This study aimed to examine the effect, if any, that changing national guidelines from recommending prophylactic antibiotics after cord clamping to pre-incision antibiotics has had on the incidence of allergic and other related health conditions in children born by CS.

Objectives

- To investigate if in-utero exposure to pre-incision antibiotics immediately prior to birth compared with no pre-incisional antibiotic exposure increases the risk of (1) asthma and (2) eczema in children born by CS.
- To investigate the effect of pre-incision antibiotics in children born by CS on (1) other allergic and allergy-related diseases, (2) autoimmune diseases, (3) infections and inflammation, (4) other immune system-related conditions, (5) neurodevelopmental conditions and (6) less specific measures of child health (i.e. colic and failure to thrive).
- To investigate the effect of pre-incision antibiotics in children born by CS on health service use (defined as overall consultation frequency in primary care and hospital admissions).
- To investigate if the effects of reducing post-partum maternal infectious morbidity, as shown in randomised controlled trials outside the UK, can be replicated in the UK using routine health-care data.

Methods

A controlled interrupted time series study was undertaken using data from two routine primary care databases, The Health Improvement Network (THIN) and the Clinical Practice Research Datalink (CPRD), and one secondary care database, Hospital Episode Statistics (HES).

Both THIN and the CPRD contain anonymised patient records from general practices across the UK. Previously published algorithms were adapted to identify those general practices that were contributing to both databases to ensure that the study database did not include duplicate records and to link mother and baby records in THIN.

In the UK health-care system, hospital records relating to delivery and those relating to the baby are separate clinical records and do not have linkage identifiers. This means that, in observational studies, it is difficult to obtain the unique identifiers of children, attribute clinical variables of their delivery to their identifiers and then map future health events back to these variables. Previously validated deterministic and probabilistic linkage strategies were used to link mother and baby records in HES.

All live-born children between 2006 and 2018 were included in the study if their mode of delivery could be determined and if their record could be linked with that of their mother in the databases. The follow-up of children was until the age of 5 years.

The outcomes of the study were defined based on previous literature and refined following two research engagement sessions with parents and parents-to-be from diverse backgrounds and a wider public and clinician consultation. For outcomes recorded in primary care, the study data set containing records of diagnoses in THIN and CPRD was used. For outcomes resulting in hospital admission, the anonymised HES data set was analysed.

The timing of prophylactic antibiotic administration is not recorded in the above databases, and we used information from our national survey of maternity care providers to determine the year when the national guidance was adopted in each unit undertaking CSs.

We compared rates of diagnosis of asthma, eczema and other outcomes over the study period in children delivered by CS. Outcomes were compared according to whether or not the mother of each child received antibiotics before skin incision. In the primary analysis, for primary care data, national policy uptake rates in the year of delivery were used as a basis for estimating the probability that each mother had received pre-incisional antibiotics. For secondary care data, each hospital's response indicating the year of local policy implementation was used.

Children born vaginally were used as a comparator, as these children would have been subject to all the same temporal changes as children delivered by CS, but would not have routinely received prophylactic antibiotics at the time of birth. To investigate the validity of the study model, we also examined changes over time in the case mix covariates to assess any differential changes over the study period in relation to delivery mode.

Data were analysed using a Poisson regression model, with an offset for follow-up duration and adjustment for calendar year of delivery, child's year of life, their interaction, delivery type (vaginal or caesarean) and the probability of exposure to pre-incision prophylactic antibiotics.

Results

The primary care data set included records of 515,945 mother-baby pairs [144,861 (28.1%) of which were CS deliveries] and the main secondary care data set included records of 3,945,351 mother-baby pairs [1,001,598 (25.4%) of which were CS deliveries] linked to the survey data on pre-incision antibiotics.

Pre-incision antibiotics were not associated with a significantly higher risk of asthma diagnosis in children born by CS [incidence rate ratio (IRR) 0.91, 95% confidence interval (CI) 0.78 to 1.05] and asthma resulting in hospital admission (IRR 1.05, 95% CI 0.99 to 1.11). There was also no evidence of

increased risk of eczema (IRR 0.98, 95% CI 0.94 to 1.03), including for hospital admissions (IRR 0.96, 95% CI 0.71 to 1.29). The results of subgroup analyses by the type of CS (i.e. emergency or elective) and by the type of antibiotic regimen administered (i.e. cefuroxime alone, cefuroxime and metronidazole, co-amoxiclav alone) did not alter these findings.

There were no significantly increased risks associated with exposure to pre-incision antibiotics for any of the other allergic and allergy-related conditions in this study, that is allergic rhinitis and conjunctivitis (IRR 0.98, 95% CI 0.83 to 1.16), food allergy and intolerance (IRR 1.02, 95% CI 0.89 to 1.17), having two or more of the above allergic and allergy-related conditions (IRR 0.99, 95% CI 0.88 to 1.12), penicillin allergy (IRR 0.68, 95% CI 0.42 to 1.08), being at high risk of anaphylactic reaction (IRR 0.81, 95% CI 0.60 to 1.09) and anaphylaxis (IRR 1.07, 95% CI 0.43 to 2.67 and IRR 1.01, 95% CI 0.82 to 1.25 based on diagnosis recorded in primary care and hospital admission, respectively).

We did not find evidence for significantly increased risk in relation to the change to pre-incision antibiotic administration for any of the autoimmune diseases in this study, that is type 1 diabetes diagnosis recorded in primary care (IRR 0.57, 95% CI 0.20 to 1.67) and hospital admissions (IRR 0.99, 95% CI 0.82 to 1.20), coeliac disease diagnosis recorded in primary care (IRR 0.54, 95% CI 0.21 to 1.39), hospital admissions for juvenile idiopathic arthritis (IRR 0.97, 95% CI 0.54 to 1.74), hospital admissions for autoimmune (idiopathic) thrombocytopenic purpura (IRR 1.11, 95% CI 0.88 to 1.39) and childhood vitiligo diagnosis recorded in primary care (IRR 1.13, 95% CI 0.36 to 3.52). The rates of autoimmune conditions in children aged < 5 years, however, were low and there is a high level of uncertainty around the estimates. The number of children with diagnoses of systemic sclerosis and scleroderma, inflammatory myopathies, systemic lupus erythematosus and juvenile pernicious (megaloblastic) anaemia were very small in this age group and meaningful risk estimates could not be calculated.

There was a relative decrease in the risk of neonatal sepsis in children whose mothers gave birth after the introduction of the pre-incision antibiotic policy, with an IRR of 0.75 (95% CI 0.65 to 0.87) for early-onset sepsis and an IRR of 0.88 (95% CI 0.80 to 0.97) for late-onset neonatal sepsis. There was no evidence of differential risk for hospital admissions for sepsis in older children (IRR 0.98, 95% CI 0.91 to 1.04), recording of wheeze in primary care (IRR 1.00, 95% CI 0.93 to 1.06), upper respiratory tract infections (IRR 0.99, 95% CI 0.97 to 1.02), lower respiratory tract infections (IRR 1.04, 95% CI 0.99 to 1.10, for diagnoses in primary care and IRR 0.99, 95% CI 0.9 to 1.01, for hospital admissions), bronchiolitis (IRR 1.05, 95% CI 0.98 to 1.12, for diagnoses in primary care and IRR 1.01, 95% CI 0.98 to 1.03, for hospital admissions), urinary tract infections (IRR 1.00, 95% CI 0.90 to 1.11, for diagnoses in primary care and IRR 1.00, 95% CI 0.95 to 1.04) and gastroenteritis for diagnoses recorded in primary care (IRR 1.03, 95% CI 0.97 to 1.10). The point estimate for gastroenteritis resulting in a hospital admission (IRR 1.02, 95% CI 1.00 to 1.05) was lower than that for all gastroenteritis recorded in primary care; however, because of the much larger size of the secondary data set, the CI was narrower. There was also a very small relative increase in the likelihood of being prescribed antibiotics in early childhood (IRR 1.03, 95% CI 1.00 to 1.06).

Changes in necrotising enterocolitis (IRR 1.16, 95% CI 0.95 to 1.42) and leukaemia (IRR 0.97, 95% CI 0.74 to 1.29) had considerable uncertainty. The number of children with a diagnosis of neurodevelopmental conditions was also small in this study, resulting in estimates with a very wide range of compatible values and, consequently, preventing us from drawing conclusions regarding association with pre-incision antibiotics. The IRR for cerebral palsy was 1.65 (95% CI 0.79 to 3.45) and the IRR for autism spectrum disorder was 1.14 (95% CI 0.77 to 1.67). For attention deficit hyperactivity disorder, the IRR decreased from 2.53 (95% CI 1.05 to 6.12) in the main analysis to 1.24 (95% CI 0.66 to 2.34) in the sensitivity analysis comparing years with > 50% uptake of pre-incision antibiotics (2013–18) with years with very low uptake of pre-incision antibiotics.

We also did not find a convincing increase in risk for colic (IRR 1.06, 95% CI 0.96 to 1.16) and failure to thrive (IRR 1.08, 85% CI 0.87 to 1.34). There was a very small relative increase in the total number of consultations recorded in primary care (IRR 1.02, 95% CI 1.01 to 1.02) and the risk of having a hospital admission for any reason (IRR 1.01, 95% CI 1.01 to 1.02).

Pre-incision antibiotics were associated with a decreased risk of composite maternal infectious morbidity in the unadjusted analysis in primary care (IRR 0.67, 95% CI 0.56 to 0.79), but not in secondary care (IRR 0.98, 95% CI 0.94 to 1.02). In the analysis that controlled for rates in the VD group (as overall rates of recorded maternal sepsis diagnoses in routine health-care records have increased markedly over the study period), the composite risk estimate was significantly decreased for maternal infectious morbidity recorded in both primary care (IRR 0.70, 95% CI 0.63 to 0.77) and secondary care (IRR 0.84, 95% CI 0.81 to 0.87). These estimates are in line with the evidence from randomised controlled trials and the evidence forming the NICE recommendation to give prophylactic antibiotics for CS before skin incision. When controlling for rates in the VD group, we did not find evidence of significantly reduced risk of urinary tract infections (IRR 1.01, 95% CI 0.87 to 1.17 in primary care and IRR 1.04, 95% CI 0.96 to 1.13 in secondary care), but women who gave birth after the pre-incision antibiotic policy was introduced were less likely to be prescribed antibiotics in primary care in the post-partum period (IRR 0.89, 95% CI 0.85 to 0.92) and the length of hospital stay was also slightly reduced (mean difference of -0.23 days, 95% CI -0.24 to -0.21 days).

Conclusions

Change in the recommendation to pre-incision antibiotics for CS, aiming to further reduce maternal post-partum infectious mortality, was not associated with an increased risk of asthma, eczema and other allergic and allergy-related conditions in young children. It may have reduced the relative risk of neonatal sepsis, although these results should be interpreted with caution, as the study relied on recording of diagnoses in routine health-care records, which have increased for neonatal sepsis over time because of changing thresholds for prevention and treatment of suspected sepsis. There was no convincing evidence for reduced or increased risk in autoimmune and other child health outcomes in this study because of considerable uncertainty around the estimates, and further research in other populations and older children may be warranted.

Study registration

This study is registered as [researchregistry3736](https://www.researchregistry.com/record/3736).

Funding

This project was funded by the National Institute for Health and Care Research (NIHR) Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 26, No. 30. See the NIHR Journals Library website for further project information.

Health Technology Assessment

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 4.014

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The research reported in this issue of the journal was funded by the HTA programme as project number 16/150/01. The contractual start date was in April 2018. The draft report began editorial review in December 2020 and was accepted for publication in June 2021. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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