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Impact of mode of birth and perinatal antibiotics on infant gut microbiota and health: a systematic review and meta-analysis

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ABSTRACT

Objective To evaluate how the mode of birth and perinatal antibiotic exposure, independently and together, influence infant gut-microbiota composition, diversity and early health outcomes.

Design Systematic review and meta-analysis conducted in accordance with Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2020 and prospectively registered with PROSPERO (CRD42024536785).

Data sources MEDLINE, Embase, Web of Science and Cochrane CENTRAL from inception to October 2024.

Eligibility criteria Randomised controlled trials, cohort or case–control studies of healthy term infants comparing vaginal versus caesarean birth and/or perinatal antibiotic exposure, with microbiota analysed by sequencing within 12 months post-delivery.

Results Eleven studies (n=5309 infants) were included, comprising ten prospective cohort studies and one randomised controlled trial across Europe, North America, Africa and Asia. Synthesis of six studies showed no statistically significant difference in bacterial abundance between vaginally delivered and caesarean-born infants (mean difference 3.44%, 95% CI −2.00 to 8.89; I^2 = 99%; very low certainty). Among antibiotic-exposed infants, the mean difference was −0.31% (95% CI −3.52 to 2.89), while among antibiotic-unexposed infants an exploratory trend towards higher bacterial abundance following vaginal delivery was observed. Narrative synthesis indicated consistent reductions in microbial diversity and depletion of Bacteroides and Bifidobacterium following caesarean birth or perinatal antibiotic exposure. Overall, caesarean delivery and perinatal antibiotic exposure were associated with differences in gut microbiota composition and diversity. Exclusive breastfeeding emerged as a modifying factor associated with partial restoration of microbial balance.

Conclusions This review, the first to integrate both delivery mode and perinatal antibiotic exposure within a single analysis, suggests a consistent directional pattern of association between these exposures and early microbial assembly, with exclusive breastfeeding mitigating some potential negative effects. Due to imprecision in estimates and inherent limitations of observational data, pooled differences were not statistically significant, and overall certainty of evidence was very low. Long-term clinical consequences remain uncertain, highlighting the need for further study.

PROSPERO registration number CRD42024536785.

WHAT IS ALREADY KNOWN ON THIS TOPIC

- ⇒ Early-life gut microbiota development is crucial for immune and metabolic health, with caesarean delivery and antibiotic exposure linked to altered microbiota composition.
- ⇒ Previous studies showed reduced microbial diversity and depletion of beneficial taxa like Bacteroides and Bifidobacterium but did not evaluate these factors together or consider breastfeeding's role.

WHAT THIS STUDY ADDS

- ⇒ This systematic review and meta-analysis synthesise evidence from 11 studies involving 5309 infants, revealing consistent reductions in microbial diversity and beneficial taxa due to caesarean birth and antibiotic exposure.
- ⇒ Exclusive breastfeeding is identified as a protective factor that aids microbial recovery, highlighting its importance for infant health.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- ⇒ Findings advocate for promoting exclusive breastfeeding and careful antibiotic use in perinatal care, stressing the need to integrate microbiome considerations into clinical guidelines.
- ⇒ Further research is essential to explore the long-term health implications of altered gut microbiota, as current evidence is of very low certainty.

INTRODUCTION

The human gut microbiota plays a vital role in nutrient metabolism, immune development and resistance to infection. Colonisation begins at birth and evolves rapidly in the first year of life, shaped by delivery mode, maternal microbiota, perinatal antibiotic exposure and feeding practices.[1–4] Early life represents a critical window for microbial and immune programming, influencing later risks for allergic, metabolic and inflammatory diseases.[3 4]

Birth via caesarean delivery (CD) bypasses exposure to maternal vaginal and intestinal microbiota, producing altered microbial profiles dominated by skin and environmental taxa such as *Staphylococcus*, *Clostridium*, *Enterococcus* and *Klebsiella*.[5 6] These profiles show reduced abundance of *Bacteroides* and *Bifidobacterium*, taxa fundamental for immune maturation and gut-barrier integrity.[3 7] Caesarean rates now exceed 30% in many countries and are projected to approach 29% globally by 2030,[8] raising concerns about population-level implications for microbial transmission and infant-health trajectories.

Perinatal antibiotic exposure, most commonly intrapartum antibiotic prophylaxis (IAP) for *group B Streptococcus*, can further disrupt early microbial assembly. Antibiotics may suppress maternal reservoirs and delay colonisation by obligate anaerobes, lowering diversity and favouring opportunistic or resistant species.[9 10] These perturbations can persist for months, particularly among infants who are not exclusively breastfed for three to 6 months.[11–13] While these interventions remain clinically necessary, their ubiquity means most infants experience at least one potential disruption at or around birth.

Two recent systematic reviews illustrate the continuing interest and complexity of this field.[14] The synthesised 17 studies focused exclusively on antibiotic exposure, while[15] the analysed 12 studies explored delivery mode alone. Both reviews confirmed reduced microbial diversity and depletion of *Bacteroides* and *Bifidobacterium* but each examined a single exposure in isolation. By contrast, the present review evaluates both mode of birth and perinatal antibiotics together, enabling assessment of their independent and combined effects and of breastfeeding as a modifying factor. This analysis includes 11 studies (n=5309 infants).

Disrupted early-life microbiota has been associated with asthma, obesity, atopy, inflammatory bowel disease and metabolic disorders.[16–18] Reduced early diversity and delayed colonisation by *Bacteroides* and *Bifidobacterium* may alter immune tolerance, mucosal integrity and host–microbe signalling pathways implicated in these conditions.[3 19–21] However, causality remains uncertain and evidence beyond infancy is sparse.

Some longitudinal cohorts report that microbial differences by delivery mode narrow after 6–12 months[22 23] whereas others show persistent divergence into early childhood.[24 25] The extent of recovery depends on breastfeeding duration and exclusivity, environmental exposures and maternal diet. Understanding these interactions is essential for guiding perinatal care and developing interventions that preserve microbial diversity.

The WHO and the National Institute for Health and Care Excellence both advocate exclusive breastfeeding for at least 6 months and judicious antibiotic use during the peripartum period.[26–28] Integrating microbiome awareness into these frameworks could enhance perinatal decision-making and support antimicrobial stewardship.

This systematic review and meta-analysis pull together evidence on how mode of birth and perinatal antibiotic exposure independently and jointly affect infant-gut microbiota composition and diversity within the first year of life. It also examines breastfeeding as a potential protective factor and summarises available data on early health outcomes. By unifying these exposures within a single analysis the review provides an updated and comprehensive overview of current evidence and identifies priorities for future longitudinal and mechanistic research.

METHODS

Study design and registration

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines[29] and was prospectively registered on PROSPERO (CRD42024536785). Ethical approval was not required because only published anonymised data were analysed. Two parent and public representatives contributed at protocol stage to ensure clinical relevance and accessible interpretation of outcomes.

Eligibility criteria

Eligible studies included randomised controlled trials, cohort and case–control designs involving healthy term infants (≥37 weeks' gestation) that compared vaginal and caesarean birth and/or examined perinatal antibiotic exposure (maternal use within 2 weeks before delivery or during labour or infant exposure within the first 6 weeks of life). Outcomes had to include gut-microbiota composition, relative abundance, or diversity indices assessed by molecular sequencing (eg, 16S rRNA, metagenomics) within the first year of life. Studies focusing exclusively on preterm populations, probiotic or microbial-seeding interventions, or culture-only methods were excluded. Non-English papers and conference abstracts without primary data were also excluded.

Outcomes

Primary outcomes included microbial composition and diversity (α- and β-diversity indices, richness, Shannon and Simpson metrics) as well as the relative abundance of dominant taxa, particularly Bacteroides, Bifidobacterium, Clostridium and Enterococcus, stratified by delivery mode and antibiotic exposure. Breastfeeding was considered a modifying factor affecting these primary outcomes. Additional outcomes encompassed reported clinical outcomes in infants, such as infection, allergy, necrotising enterocolitis and growth during the first year of life.

Information sources and search strategy

Four databases, namely MEDLINE (Ovid), Embase, Web of Science and Cochrane CENTRAL, were searched from inception to October 2024. Search strings combined

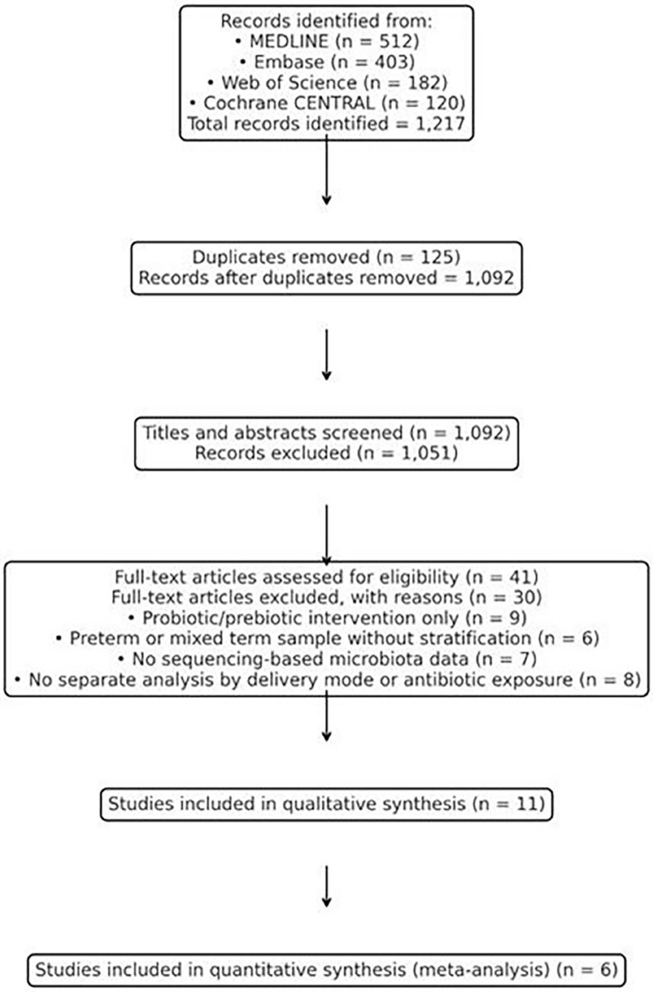


Figure 1 Preferred Reporting Items for Systematic reviews and Meta-Analyses 2020 Flow Diagram.

controlled vocabulary and free-text terms relating to delivery mode, antibiotic exposure, microbiota and infancy: (“caesarean section” OR “caesarean delivery” OR “vaginal birth” OR “mode of delivery”) AND (“antibiotic” OR “antimicrobial prophylaxis” OR “intrapartum antibiotics” OR “perioperative antibiotics”) AND (“microbiota” OR “microbiome” OR “gut flora”) AND (“infant” OR “newborn” OR “neonate”).

No date limits were applied. Reference lists of included papers and related reviews were hand-searched to ensure completeness.

Study selection

Titles, abstracts and full texts were screened independently by two reviewers, with disagreements resolved through discussion or consultation with a third reviewer. Inclusion decisions were recorded in a PRISMA flow diagram (figure 1), and reasons for exclusion were logged in accordance with PRISMA transparency standards.

Data extraction

Data were extracted directly from the papers by two reviewers, independently using a pre-tested template that captured study design, country, sample size, infant age at sampling, exposure definitions, sequencing platform, breastfeeding variables and key quantitative results. Extracted data were cross-checked by a senior reviewer for accuracy. Any uncertainties were discussed within the multidisciplinary team, comprising neonatologists, microbiologists and epidemiologists, to maintain methodological rigour. Alpha-diversity outcomes were extracted as reported in the included studies. Raw sequencing data were not reanalysed. Mean abundance values are reported as mean relative abundance (%) defined as the proportion of classified sequencing reads assigned to the named taxon within the respective processed gut-microbiota dataset of each study. Values were extracted from published articles or supplementary material after the specific preprocessing and taxonomic-classification pipeline of each study, that is, raw reads were not reprocessed using a common pipeline. Since sequencing regions, bioinformatic methods, taxonomic resolution and sampling ages varied across studies, these values should be interpreted as study-specific estimates.

Risk of bias assessment

Randomised trials were appraised using the Cochrane Risk of Bias 2.0 tool (RoB 2)[29]; observational studies were assessed with the risk of bias in non-randomised studies of exposures (ROBINS-E) instrument.[30] Domains included confounding, participant selection, exposure measurement, missing data and outcome assessment. Judgements of low risk, some concerns or high risk were assigned (figure 2).

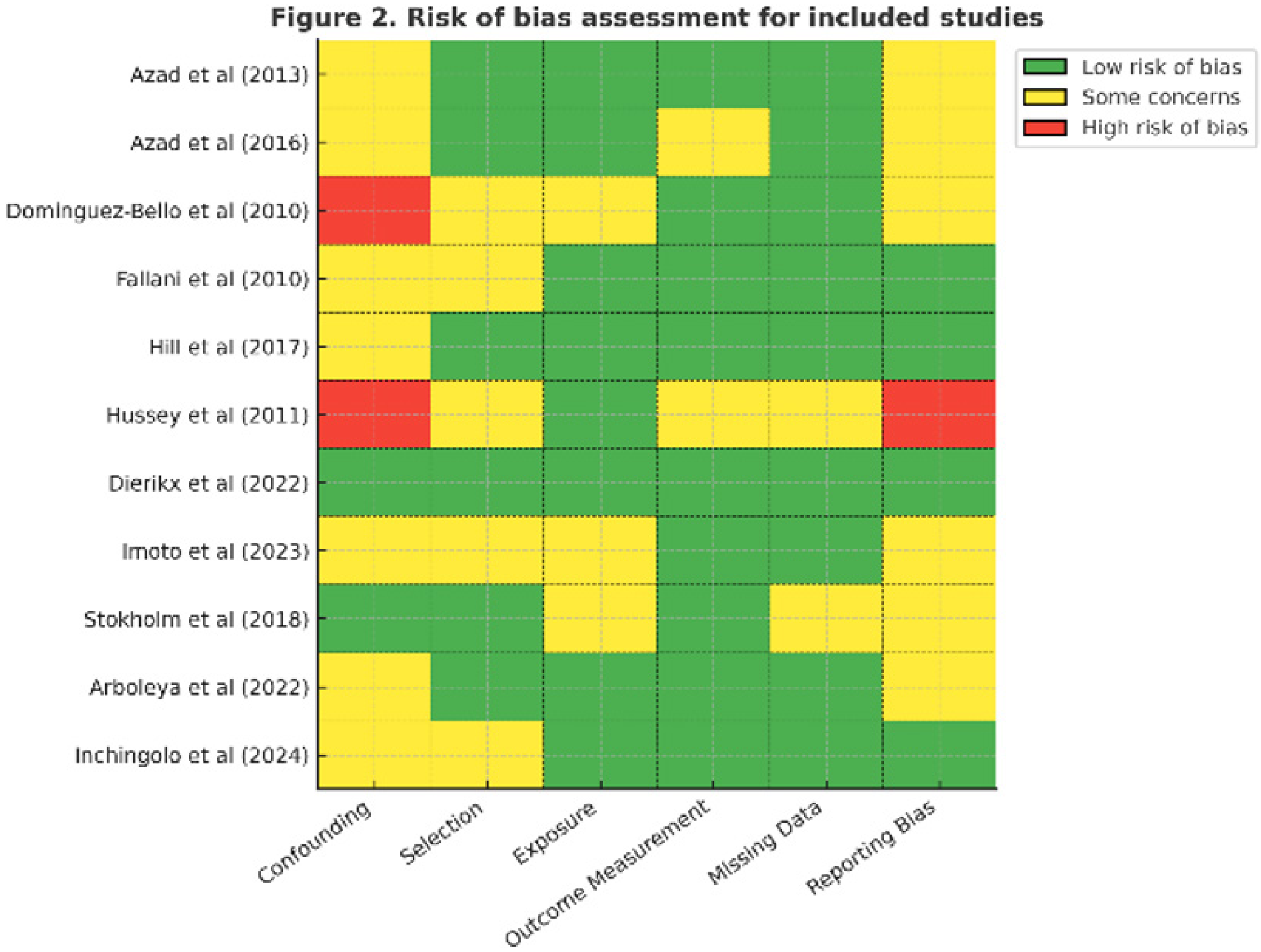
Certainty of evidence

Certainty of evidence for each primary outcome was rated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.[31] Criteria considered study design limitations, inconsistency, indirectness, imprecision and publication bias. Evidence was graded as high, moderate, low or very low certainty.

Statistical analysis

Where data permitted, quantitative synthesis was performed using Review Manager (RevMan V. 5.4, Cochrane Collaboration). Quantitative pooling was performed only when at least three studies reported the same outcome using a comparable metric and a comparable sampling window; otherwise findings were synthesised narratively following the Synthesis Without Meta-analysis (SWiM) guidance.[27] Alpha-diversity indices (e.g. Shannon, Simpson observed OTUs/ASVs) were extracted from each study that reported them. Formal meta-analysis of diversity was not performed owing to heterogeneous index types and incomplete dispersion reporting across studies, and diversity findings are therefore synthesised narratively.[27]

Mean differences with 95% CIs were calculated for continuous outcomes using random-effects models,



	Confounding	Selection	Exposure	Outcome Measurement	Missing Data	Reporting Bias
Azad et al (2013)	🟨	🟩	🟩	🟩	🟩	🟨
Azad et al (2016)	🟨	🟩	🟩	🟨	🟩	🟨
Dominguez-Bello et al (2010)	🟥	🟨	🟨	🟩	🟩	🟨
Fallani et al (2010)	🟨	🟨	🟩	🟩	🟩	🟩
Hill et al (2017)	🟨	🟩	🟩	🟩	🟩	🟩
Hussey et al (2011)	🟥	🟨	🟩	🟨	🟨	🟥
Dierikx et al (2022)	🟩	🟩	🟩	🟩	🟩	🟩
Imoto et al (2023)	🟨	🟨	🟨	🟩	🟩	🟨
Stokholm et al (2018)	🟩	🟩	🟨	🟩	🟨	🟨
Arboleya et al (2022)	🟨	🟩	🟩	🟩	🟩	🟨
Inchingolo et al (2024)	🟨	🟨	🟩	🟩	🟩	🟩

Figure 2 Risk of bias assessment for included studies. Summary of risk-of-bias assessment using ROBINS-E for observational studies and RoB 2.0 for the randomised trial. Colours indicate domain-level judgments (green, low risk; yellow, some concerns; red, high risk).

with between-study variance (τ^2) estimated using the DerSimonian–Laird method, which is implemented by default in RevMan 5.4. Effect sizes were derived from reported means, SD and sample sizes. Where studies reported medians with IQRs, means and SD these were approximated using the Wan *et al* method,[28] and where only standard errors or 95% CIs were reported, SD were back-calculated (SD=SE × $\sqrt{n}$, or using the known 95% CI width). Studies without an extractable variance were restricted to the narrative synthesis. Heterogeneity was assessed using the I^2 statistic, with 25%, 50% and 75% representing low, moderate and high heterogeneity, respectively. The I^2 statistic was used to quantify the proportion of total variability in effect estimates deriving from between-study heterogeneity as opposed to within-study sampling error, where again 25%, 50% and 75% was interpreted as low, moderate and high heterogeneity.

Subgroup analyses explored intrapartum antibiotic exposure (yes/no) and breastfeeding exclusivity (exclusive, partial and formula-fed). An a priori power calculation was not conducted as pooled precision was planned to be determined by the studies identified through the prespecified search rather than by a target sample size.

Joint exposure to delivery mode and perinatal antibiotics was prespecified to be examined through a 2×2 analysis of the four exposure combinations (caesarean vs vaginal crossed with antibiotic-exposed vs unexposed). A formal interaction or ratio-of-ratios analysis could not be undertaken because the included studies did not report relative-abundance outcomes for all four exposure cells, and no study provided sufficiently granular individual participant data. Although both delivery mode and perinatal antibiotic exposure were considered within a single analytical framework, the available data did not permit formal interaction modelling across combined exposure categories. Accordingly, analyses reflect subgroup-based and descriptive associations rather than true joint or interaction effects. The joint effect was therefore approached in two ways: (i) antibiotic exposure was treated as a subgroup modifier of the delivery-mode effect in the random-effects meta-analysis and (ii) the narrative synthesis was described for each included study, which of the four exposure combinations were present, and the direction of effect was observed.

Narrative synthesis

When quantitative pooling was inappropriate due to heterogeneity, findings were summarised narratively following established guidance for narrative synthesis in systematic reviews. Direction and magnitude of effects were tabulated to capture clinically meaningful trends.

Quality assurance and reproducibility

All stages of searching, screening, extraction and analysis were conducted in duplicates and recorded in an electronic decision log to ensure reproducibility and transparency. This approach meets or exceeds minimum PRISMA standards through independent verification, explicit cross-validation and parent involvement in defining outcomes.

RESULTS

Study identification and selection

Database searches identified 1217 records. After removing duplicates and screening titles and abstracts, 41 full-text articles were reviewed for eligibility. Eleven studies met the inclusion criteria. Together they included 5309 infants from Europe, North America, Asia, Africa and South America.[22–25 29–35] These comprised ten prospective cohort studies and one randomised controlled trial. Reasons for exclusion at full-text stage included preterm populations, non-comparative design, probiotic or microbial-seeding interventions or culture-based analyses only.

Characteristics of included studies

All included studies (table 1) examined the association between delivery mode and/or perinatal antibiotic exposure and infant gut microbiota within the first year of life. Sample sizes ranged from 10 to 2412 participants. Most studies used 16S rRNA gene sequencing of stool samples collected between birth and 6 months, with some extending to 12 months. Seven studies assessed intrapartum or neonatal antibiotic exposure, most often prophylaxis for *group B. streptococcus*. Five studies recorded feeding type or breastfeeding exclusivity. Across studies, 23–33% of infants were delivered by caesarean section, and 35–60% were exposed to maternal or infant antibiotics.

Consistent trends were observed across geographical settings despite methodological variation. Caesarean birth was associated with reduced *Bacteroides* and *Bifidobacterium* abundance and an increased prevalence of facultative anaerobes such as *Clostridium*, *Enterococcus* and *Staphylococcus*. Early antibiotic exposure produced similar compositional changes, a pattern consistent with shared compositional effects on the early gut microbiota.

Quantitative synthesis

In relation to the outcome of bacterial abundance, six studies provided sufficient quantitative data for meta-analysis (online supplemental figure S1). The pooled random-effects analysis (table 2) showed no statistically significant difference in bacterial abundance between vaginally delivered and caesarean-born infants (mean difference 3.44%, 95% CI −2.00 to 8.89; $I^2 = 99\%$). Among antibiotic-exposed infants, the pooled mean difference was −0.31% (95% CI −3.52 to 2.89), indicating no meaningful difference between delivery modes. In antibiotic-unexposed infants, a trend toward higher bacterial abundance following vaginal delivery was observed (mean difference 11.89%, 95% CI −4.34 to 28.13; $I^2 = 100\%$). This subgroup estimate should be interpreted as exploratory only, as it was based on three studies. In this context, the very high I^2 likely reflects small within-study standard errors combined with modest between-study differences rather than clinically meaningful heterogeneity, and the pooled estimate should not be interpreted as a reliable effect size. Across analyses, pooled estimates should be interpreted cautiously due to heterogeneity in sequencing platforms, bioinformatic pipelines and sampling time points. Although none of the pooled effects reached statistical significance, the direction of effect was broadly consistent across cohorts. Certainty of evidence for all comparisons was rated as very low due to study design limitations, heterogeneity and wide CIs.

Taxonomic and diversity patterns

Narrative synthesis across the eleven studies revealed consistent patterns of reduced microbial diversity and lower relative abundance of *Bacteroides* and *Bifidobacterium* in infants born by caesarean section or exposed to perinatal antibiotics. Vaginally delivered infants demonstrated higher α-diversity and earlier colonisation by obligate anaerobes. Caesarean-born infants showed delayed colonisation and increased abundance of skin- and environment-associated taxa including *Staphylococcus*, *Corynebacterium* and *Enterobacter*.

Several studies quantified these differences. Azad *et al*[11] and Imoto *et al*[34] reported significantly lower *Bifidobacterium* abundance in antibiotic-exposed infants at 1 and 3 months ($p<0.05$). Hussey *et al*[33] found reduced *Bifidobacterium* detection and diversity among neonates who received parenteral antibiotics. Dierickx *et al*[30] demonstrated that prophylactic antibiotics administered before cord clamping reduced *Bacteroides* colonisation at 1 month. Functional analyses reported decreased short-chain fatty acid production and delayed metabolic pathway maturation in antibiotic-exposed or caesarean-born infants.[21 34]

Influence of breastfeeding

Seven studies evaluated breastfeeding practices, with five collecting data concurrently around the 6-week mark. Additional data were collected at various time points, including 3 months and 12 months, allowing for observations on how feeding practices may change over time. This variation is significant because it suggests that feeding practices after 6 months could impact gut microbiota composition. While exclusive breastfeeding

Table 1 Characteristics of included studies

Study (year)	Country / Region	Design	Sample	Infant age	Exposure(s)	Outcomes	Main findings
Arboleya *et al*[18] (2022)	Spain	Prospective cohort	145	1, 3, 6 months	Maternal intrapartum antibiotics, delivery mode	Gut microbiota composition (16S rRNA)	Antibiotic exposure reduced Bifidobacterium and Bacteroides; diversity partly restored by breastfeeding.
Azad *et al*[36] (2013)	Canada	Prospective cohort	173	4 months	Delivery mode (VD vs CD), feeding mode	Gut microbiota composition (16S rRNA)	CD associated with reduced Bacteroides and Bifidobacterium.
Azad *et al*[11] (2016)	Canada	Prospective cohort	1984	3, 12 months	Delivery mode, intrapartum antibiotics, feeding mode	Gut microbiota composition (16S rRNA)	IAP and CD reduced Bifidobacterium; breastfeeding mitigated effects.
Dierikx *et al*[30] (2020)	Belgium	Randomised controlled trial	89	Birth, 1 month	Timing of maternal IAP (before vs after cord clamping)	Gut microbiota composition (16S rRNA)	Early IAP reduced Bacteroides colonisation.
Dominguez-Bello *et al*[5] (2010)	Venezuela / USA	Observational cohort	10	Birth	Delivery mode	Skin, oral, nasal and gut microbiota (16S rRNA)	VD infants had maternal vaginal-like microbiota; CD infants showed increased Staphylococcus colonisation.
Fallani *et al*[37] (2010)	Europe (multicentre)	Prospective cohort	117	6 weeks	Delivery mode, feeding, antibiotics	Gut microbiota composition (16S rRNA)	CD and antibiotic exposure reduced Bacteroides and Bifidobacterium.
Hill *et al*[32] (2017)	Ireland	Prospective cohort	192	Birth – 24 weeks	Delivery mode, feeding mode	Gut microbiota composition (16S rRNA)	Breastfeeding partially normalised CD-associated microbiota differences 8 weeks.
Hussey *et al*[38] (2011)	South Africa	Observational cohort	30	Days 0–21	Neonatal parenteral antibiotics	Gut microbiota composition (culture, 16S rRNA)	Antibiotics reduced Bifidobacterium detection and diversity.
Imoto *et al*[39] (2023)	Japan	Prospective cohort	165	1, 3 months	Delivery mode, maternal β-lactam antibiotics	Gut microbiota composition (16S rRNA)	Antibiotic exposure and CD reduced Bifidobacterium and Bacteroides.
Inchingolo *et al*[21] (2024)	Italy	Prospective cohort	198	1, 6 months	Delivery mode	Gut microbiota diversity and taxonomic composition	CD associated with lower diversity and delayed Bacteroides colonisation; differences persisted to 6 months.
Stokholm *et al*[40] (2018)	Denmark	Prospective cohort	2412	1 week, 1 month	Delivery mode, intrapartum antibiotics	Gut microbiota composition (16S rRNA)	CD and IAP reduced Bacteroides and Bifidobacterium.

CD, caesarean delivery; IAP, intrapartum antibiotic prophylaxis; VD, vaginal delivery.

Table 2 Summary of pooled results

Comparison	n studies	Pooled mean difference (95% CI)	I² (%)	Certainty (GRADE)
All infants	6	3.44 (–2.00 to 8.89)	99%	Very low
Antibiotic exposed	5	–0.31 (–3.52 to 2.89)	96%	Very low
Antibiotic unexposed	3	11.89 (–4.34 to 28.13)	100%	Very low

was associated with higher levels of beneficial bacteria, particularly Bifidobacterium, the extent of its impact on microbial recovery varied among studies. Some evidence suggested that caesarean-born infants who were exclusively breastfed showed trends toward microbiota profiles like those of vaginally delivered infants over time, highlighting the potential of breastfeeding to influence gut microbiota development.

Exclusive breastfeeding consistently supported microbial recovery, increasing *Bifidobacterium* abundance and restoring diversity. Hill *et al*[32] reported that caesarean-born infants who were exclusively breastfed exhibited partial microbial convergence toward vaginally delivered profiles by 8 weeks and near-complete convergence by 24 weeks. Formula-fed infants, by contrast, showed persistently lower diversity and higher proportions of facultative anaerobes such as *Enterobacteriaceae*. Across studies, breastfed infants demonstrated mean *Bifidobacterium* levels of approximately 40%, compared with 15–20% among formula-fed infants.[33] Extended exclusive breastfeeding beyond 12 weeks was the strongest predictor of microbial recovery.

Infant clinical outcomes

Only one study followed participants beyond the first year of life.[11] At 3 years, no significant differences were reported in infection, allergy or growth outcomes between delivery groups. None of the studies provided data on necrotising enterocolitis, hospitalisation, respiratory illness or neurodevelopmental outcomes. The absence of longitudinal outcome data highlights a persistent evidence gap linking early microbiota disruption with later childhood and long-term health.

Risk of bias and certainty assessment

Risk-of-bias assessment using ROBINS-E and RoB 2 indicated low risk for exposure classification and outcome measurement but moderate risk for confounding in most observational studies. The randomised trial was assessed as low risk across all domains. Variation in definitions of antibiotic exposure, timing of sampling and feeding data quality introduced inconsistency.

Certainty of evidence, evaluated using the GRADE framework, was rated as very low to low for all pooled outcomes because of observational designs, heterogeneity and imprecision. Nevertheless, the consistent direction of effect across studies is consistent with an association between caesarean birth, perinatal antibiotic exposure and reduced early microbial diversity and *Bifidobacterium* abundance.

Summary of key findings

*Consistent directional effects indicating microbial depletion after caesarean delivery and antibiotic exposure but no statistically significant pooled differences in bacterial abundance.

*Universally lower α-diversity in caesarean-born and perinatally antibiotic-exposed infants.

*Reduced *Bacteroides* and *Bifidobacterium* with relative enrichment of *Clostridium*, *Enterococcus* and *Staphylococcus*.

*Exclusive breastfeeding associated with partial microbial recovery and diversity restoration.

*Certainty of evidence very low due to heterogeneity, yet consistent across continents and study designs.

DISCUSSION

This systematic review and meta-analysis pull together current evidence on how mode of delivery and perinatal antibiotic exposure relate to early gut-microbiota development, with particular emphasis on interpretation of patterns and overall implications of the results. Across 11 studies involving more than five thousand infants, both exposures were consistently associated with reduced microbial diversity and depletion of key anaerobes such as *Bacteroides* and *Bifidobacterium*. Although pooled quantitative results did not reach statistical significance, the direction of effect was uniform, indicating biologically plausible alterations in early microbial colonisation.

Principal findings

Our findings are consistent with a pattern in which both caesarean birth and antibiotic exposure are associated with differences in the composition and diversity of the early gut microbiota, although pooled differences did not reach statistical significance and the overall certainty of evidence was very low. Vaginally delivered infants generally show more rapid colonisation by *Bacteroides* and *Bifidobacterium*, while caesarean-born infants exhibit delayed acquisition and increased abundance of facultative anaerobes including *Enterococcus*, *Clostridium* and *Staphylococcus*.[22–25 29–35] These taxa differences mirror previous reports of delayed microbial maturation following operative delivery or antibiotic exposure.[14 15]

The review extends existing literature by examining both exposures together and identifying breastfeeding as a critical modifier that supports microbial recovery. Exclusive breastfeeding supported microbial recovery, consistent with mechanisms whereby human milk oligosaccharides selectively promote *Bifidobacterium* growth.[33 34] Formula-fed infants, conversely, showed persistently lower diversity and reduced *Bifidobacterium* abundance. However, breastfeeding is not always an easy solution for all parents; modern-day stressors, such as workplace challenges and societal pressures, have increased obstacles to breastfeeding. Support from midwives, health visitors and wider society is essential to provide the support mothers may need including necessary workplace adjustments, such as flexible hours and designated breastfeeding areas. Taken together, these patterns suggest that infant feeding practices may influence the extent and timing of microbial recovery following early perturbation.

Comparison with other reviews

Two prior systematic reviews addressed each exposure independently: one on antibiotic exposure[15] and another on delivery mode.[14] Both confirmed disrupted early colonisation, but neither analysed interactions between exposures. By contrast, the present review integrates delivery mode and perinatal antibiotic exposure within a single analytical framework while also considering breastfeeding as a modifying factor. The inclusion of two additional eligible studies and transparent clarification of exclusion criteria strengthened the comprehensiveness and reproducibility of the evidence base.

Clinical and public-health implications

Understanding the combined influence of caesarean birth and antibiotics on microbiota composition is increasingly relevant as both interventions are common in modern maternity practice. Caesarean delivery rates exceeding 30% and high levels of intrapartum antibiotic prophylaxis mean that most infants experience at least one microbial disruption at or around birth.[8–10] Given the very low certainty of evidence, these findings warrant further study to confirm the impact (if any) of caesarean delivery or intrapartum antibiotic exposure on infant gut microbial diversity and health. Clinicians should remain mindful that while these interventions may often be clinically necessary, they can have unintended effects on microbial development.

Evidence linking early microbial disturbance to later disease remains largely associative. However, longitudinal studies have suggested connections between reduced early diversity and risks of asthma, obesity, atopy and inflammatory disease.[16–18] Continued long-term cohort follow-up is needed to clarify causal pathways and identify windows for intervention.

Given the very low certainty of evidence, these findings should not be used to alter clinical indications for caesarean delivery or intrapartum antibiotic prophylaxis. Rather, they support existing guidance emphasising prudent antibiotic use and promotion of exclusive breastfeeding, which may offer a low-risk strategy to support early microbial recovery without compromising maternal or neonatal safety.

Strengths and limitations

This review has several strengths. It was conducted in accordance with PRISMA 2020 guidelines, registered prospectively on PROSPERO, and applied duplicate screening, extraction and bias assessment to minimise error. Inclusion criteria were carefully defined and justified, ensuring reproducibility. The updated search, including manual reference checks, identified all relevant studies published to October 2024, confirming that the dataset is complete and current.

Limitations include heterogeneity in sequencing methods, exposure definitions and sampling times across studies, including the use of different sequencing platforms and bioinformatic pipelines reflecting methodological evolution over time, which precluded more extensive meta-analysis. Most included studies were observational, limiting causal inference and leaving potential for residual confounding. Reporting of feeding variables and antibiotic timing was inconsistent.

Included study sample sizes ranged from 10 to 2412 infants. Although inverse-variance weighting in random-effects meta-analysis limits the influence of very small studies, this imbalance contributed to imprecision in pooled estimates, which should therefore be interpreted with caution. Alpha-diversity indices were extracted where reported but could not be quantitatively pooled because of heterogeneous indices and incomplete dispersion reporting, and diversity findings are therefore presented narratively. Differences in pooled relative abundance describe compositional and diversity patterns rather than establishing disrupted maternal–infant microbial transmission, which would require strain-level tracking or functional analyses not available in the included studies.

CONCLUSIONS AND FUTURE RESEARCH

Both caesarean delivery and perinatal antibiotic exposure show a consistent directional association with reduced infant gut-microbiota diversity and lower relative abundance of *Bacteroides* and *Bifidobacterium* in the first year of life, though pooled estimates were not statistically significant, and certainty of evidence was very low. Exclusive breastfeeding appears to promote partial microbial recovery. While evidence quality remains low, the biological plausibility and consistency of findings support consideration of microbiome-conscious practices in perinatal care.

Future studies should integrate longitudinal microbiome, metabolomic and clinical data to determine how early perturbations translate into later health outcomes. Standardisation of sequencing and reporting methods, alongside detailed recording of antibiotic regimens and feeding practices, will enhance comparability across studies and enhance evidence synthesis and relevant clinical implications. Interventions to restore or protect microbial diversity, such as maternal or neonatal probiotic strategies, warrant cautious but systematic evaluation within ethically approved frameworks.

Contributors MK conceived the review. MK, HS, AM, CL, RM, SC-C and HB designed the protocol and methods. RM led the literature search and data extraction, with HS as second reviewer. AM and HS drafted the introduction, and CL conducted the meta-analysis. HS performed the narrative synthesis and drafted the discussion and conclusions. All authors reviewed and approved the final manuscript including responses to reviewers. HS is the guarantor. An AI language model (ChatGPT, OpenAI) was used to assist with language editing and formatting. The authors maintained full control over the content, analysis and interpretation of data, and are responsible for all conclusions.

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