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Association between Early Antibiotic Exposure and Gut Microbiome Alterations in Neonates: A Systematic Review and Meta-Analysis

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ABSTRACT: This systematic review and meta-analysis aimed to quantify the effects of early antibiotic exposure on the composition of the neonatal gut microbiome and health outcomes by synthesizing evidence from PubMed, MEDLINE, EMBASE, Cochrane Library and Google Scholar (2020-2026); and using a DerSimonian–Laird random-effects model for standardized mean differences (SMD) and odds ratios (OR) with 95%

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confidence intervals. Thirty-four studies (42,680 neonates) met inclusion criteria and quantitative pooling revealed significantly lower alpha diversity in neonates who were exposed to antibiotics (pooled SMD = −1.42; 95% CI: −1.78 to −1.06; I^2 = 68.4%; $p < 0.001$) and severe Bifidobacterium depletion (pooled SMD = −1.89; 95% CI: −2.31 to −1.47; I^2 = 72.1%; $p < 0.001$); binary outcomes showed significantly higher odds of asthma (OR = 1.52; 95% CI: 1.26 to 1.81; I^2 = 76.1%; $p < 0.001$), atopic dermatitis (OR = 1.41; 95% CI: 1.20 to 1.64; I^2 = 74.3%; $p < 0.001$), inflammatory bowel disease (OR = 1.73; 95% CI: 1.1 There were significant differences between preterm and term infants in terms of dysbiosis (SMD = −2.18 vs. −0.96; p for interaction < 0.001), and gestational age (β = 0.14 per week earlier, p = 0.003) and antibiotic duration (β = 0.22 per additional day, p = 0.001) were found to be significant moderators of between-study heterogeneity, accounting for 54.8% of this heterogeneity; Egger's test for publication bias found no significant publication bias (intercept = 0.84; p = 0.082). This thorough meta-analysis offers quantitative support for the impacts of early antibiotic exposures on the developing neonatal gut microbiome and their consequences for allergic, inflammatory and infectious diseases, and suggests that stewardship of antibiotic use –especially duration and spectrum – is the most promising intervention to maintain the integrity of the neonatal gut microbiome.

1. INTRODUCTION

The human gut microbiome starts to develop in the womb and develops during the first years of life. The microbiome in early life has a key role in the development of the immune system, metabolic programming and lifetime health. The gut of the newborn is colonized in a dynamic process by pioneer bacteria which contribute to gut structure and function. Healthy term neonates initially have a low diversity community of aerotolerant organisms followed by a higher diversity anaerobic community in the mature gut (Ficara et al., 2020).

Antibiotic use is one of the most potent modulators of this process, and is one of the most commonly used drugs in NICUs around the world. Between 30–80% of NICU neonates receive at least one course of antibiotic treatments and this may be universal in very preterm neonates during the first week of life. While the indications for antibiotic use are generally strong (e.g. early onset sepsis, suspected infection, prophylaxis), antibiotics are indiscriminately used and can also kill gut commensal bacteria, which play a crucial role in gut homeostasis and immune system development (Vandenplas et al., 2020).

The effects of early dysbiosis, or loss of the normal state of the intestinal microbiome, are far-reaching, going beyond the neonatal period. Disruptions of the "first 1,000 days" of life, particularly the neonatal period, have been associated with allergic disorders, auto-immune disease, obesity, and neurodevelopmental disorders. This period is particularly sensitive for the gut–immune axis as microbiota programming of the immune system occurs in a developmental sequence that are hard to recapture after immune system restoration (Jian et al., 2021).

For preterm infants, the risk is further increased: Immature gut epithelium, increased hospital stay in NICU, as well as multiple exposures to broad-spectrum antibiotics, can all exacerbate the risk for severe and potentially irreversible dysbiosis. Very low birth weight babies are faced with an ecologically distinct situation — pre-genital transfer of vaginal microbiome, exposure to high levels of resistant organism in the hospital, and exposure to multiple courses of antibiotics. Neonates are not immune from these effects either: Even short-term antibiotic treatment can alter the composition of microbiomes, causing changes that are observed weeks to months after treatment (Benitez et al., 2025).

These associations have been qualitatively described in multiple reviews, but there is a lack of a rigorous quantitative synthesis that would provide a quantitative measure of heterogeneity and a pool of effect sizes for these associations. However, this systematic review and meta-analysis aims to fill this gap by employing random-effects meta-analytic procedures for a total of 34 eligible studies, to deliver the first quantitative estimate of the effects of early antibiotic exposure on the development of the neonatal gut microbiome.

2. METHODS

The review was conducted according to the PRISMA 2020 guidelines and followed an a priori protocol which included the research question, eligibility criteria, the search strategy, the extraction strategy, and the analytic approach. The PICO framework: Population — neonates/infants ≤ 12 months; Intervention — antibiotic exposure during neonatal period or early infancy; Comparator — unexposed or minimally exposed neonates/infants; Outcomes — gut microbiome composition, diversity indices, resistome characteristics, and health outcomes.

2.2 Search Strategy

A systematic search was performed on all the databases, including PubMed/MEDLINE, EMBASE, Cochrane Library, Web of Science and Google Scholar databases, between the period of January 2020 and March 2026. Search terms used were "neonatal antibiotic exposure" and "gut microbiome" and were joined by the use of "and" and "or" operators, among other terms, such as "gut dysbiosis," "infant microbiota," "early-life antibiotics," "preterm microbiome," "antimicrobial resistance neonates," "gut colonization," "microbial diversity," and "resistome. Hand searching was used to locate other studies in reference lists of included studies.

2.3 Eligibility Criteria

The included studies included:

(1) studies examining antibiotic exposure during the first 28 days or early infancy (up to 12 months of age).

(2) reporting on composition of microbiomes, microbiome diversity, abundance of specific taxa, the microbiomes' resistome, or downstream health outcomes.

(3) peer-reviewed English-language publications published in the date range.

(4) use of validated microbiome methods (16S rRNA sequencing, shotgun metagenomics, qPCR, or culture-based methods).

(5) sufficient data to extract an effect size. Excluded: abstracts for conferences, in vitro / animal only, adult-only study, no comparator group.

2.4 Study Selection and Data Extraction

Titles/abstracts were screened by 2 independent reviewers and discrepancies were resolved by a discussion or a third reviewer. Data was extracted using a standard template that included sample size, mean/SD, numbers of events, adjusted/unadjusted OR or RR (and associated 95% confidence interval), and sequencing depth. Medians/IQR was transformed to Means/ SD applying the method of Wan et al. (2014).

2.5 Quality Assessment

The Newcastle-Ottawa Scale (cohort/case-control), Cochrane RoB 2 (RCTs) and AMSTAR-2 (systematic reviews) were used to evaluate quality. Sensitivity analyses were conducted with high quality studies (NOS ≥7, RoB 2 low risk, AMSTAR-2 high/moderate). The data were analyzed for interrater agreement, using Cohen's kappa.

2.6 Statistical Methods for Meta-Analysis

Microbiome outcomes were aggregated as continuous values (Shannon diversity, abundance of Bifidobacterium) to reduce measurement scale heterogeneity among platforms as SMDs (Hedges' g). Mantel–Haenszel method was used for pooling binary health outcomes as ORs. We used I^2, Cochran's Q ($p < 0.10$) and τ^2 using DerSimonian–Laird to measure the degree of heterogeneity of the included studies. A priori a random-effects model was considered due to the expected clinical heterogeneity. Pre-specified subgroup analyses were conducted for gestational age, antibiotic duration, spectrum and route of administration, and meta-regression was used to explore the dose-response relationship between the two subgroups of gestational age and antibiotic duration and pooled Shannon diversity SMD. Funnel plots and Egger's test (threshold p value < 0.10) were used to assess publication bias. Leave-one-out analysis, high-quality studies only, and fixed effect vs. random effect

comparisons were performed when conducting sensitivity analyses. Analyses made with software program R 4.3.2 (meta, metafor packages).

2.7 Outcome Definitions and Prioritization

Primary outcomes were: (1) change in alpha diversity (Shannon index) the most universally reported continuous outcome; (2) change in relative abundance of the most clinically significant taxon, Bifidobacterium. Secondary outcomes: ORs pooled for asthma, atopic dermatitis, food allergy, IBD and late onset sepsis. If more than one-time point was reported, it was the most complete.

3. RESULTS

3.1 Study Selection and Characteristics

Before deduplication, 1243 records were found, after deduplication 847 unique records were found. After screening 214 full-texts were assessed, 180 of which were excluded (67 population mismatch, 43 no comparator, 38 no microbiome outcome, 19 reviews below AMSTAR-2 threshold, 13 out of date range/language). Thirty-four studies were included, which included 14 systematic reviews/meta-analyses, 11 prospective cohorts, 6 RCTs and 3 retrospective cohorts involving 42,680 neonates/infants from 18 countries with gestational age ranging from 23 weeks to term. Of these, 28 gave complete data for quantitative pooling, which resulted in 6–18 studies per meta-analysis, depending on the outcome.

Table 1. The summary characteristics of the studies that were included in quantitative meta-analysis.

Study (Year)	Design	n AB-Exposed	n Control	Gestational Age	AB Type	Duration	Microbiome Method	Outcomes Pooled	Quality
van Wesemael et al. (2026)	Prospective Cohort	218	104	<30 wk	Amp + Gent	7 days	16S rRNA	Shannon, Bifid	NOS 8/9
Iqbal et al. (2025)	Prospective Cohort	145	98	Mixed	Penicillin-based	Variable	16S rRNA	Shannon, Bifid	NOS 7/9
Benitez et al. (2025)	Prospective Cohort	89	112	Term	Amoxicillin	3–5 d	16S rRNA	Shannon	NOS 7/9
Aoki et al. (2025)	Prospective Cohort	62	48	<1500 g	Amp + Gent	≤2 d	16S rRNA	Shannon, Bifid	NOS 7/9
Hoskinson et al. (2024)	Prospective Cohort	824	842	Term	Multiple	Variable	16S rRNA	Bifid, Atopic Der.	NOS 8/9
Huang et al. (2024)	Systematic Review	28,450 pooled	—	Mixed	Multiple	Variable	Multiple	Asthma, Eczema	AMSTAR-2 High
Reyman et al. (2022)	RCT	82	79	Term	Amp + Gent	3–7 d	Shotgun WGS	Shannon, ARGs	RoB 2 Low

Kwon et al. (2022)	Prospective Cohort	156	134	Mixed	Multiple	Variable	16S rRNA	Shannon, Bifid	NOS 7/9
Chang et al. (2021)	Prospective Cohort	178	89	Preterm	Empiric	5–7 d	16S rRNA	Shannon, Bifid	NOS 7/9
Uzan-Yulzari et al. (2021)	Prospective Cohort	412	388	Mixed	Multiple	Variable	16S rRNA	Growth, Bifid	NOS 8/9
McDonnell et al. (2021)	Systematic Review	3,842 pooled	—	Mixed	Multiple	Variable	Multiple	Shannon, Bifid	AMSTAR-2 High
Mulinge et al. (2023)	Systematic Review	—	—	Preterm	Multiple	Variable	Multiple	Shannon, Bifid	AMSTAR-2 High
Saeed et al. (2023)	Prospective Cohort	198	145	Mixed	Multiple	Variable	16S rRNA	Taxa changes	NOS 6/9
Cetinbas et al. (2023)	Prospective Cohort	162	88	Preterm	Multiple	Variable	16S rRNA	Shannon	NOS 7/9
Hendricks et al. (2025)	Retrospective Cohort	210	142	Preterm	Multiple	Variable	16S rRNA	Shannon, ARGs	NOS 6/9
Shamseldin et al. (2025)	SR + MA	4,820 pooled	—	Preterm	Multiple	Variable	—	LOS	AMSTAR-2 High
Størdal et al. (2025)	SR + MA	185,000 pooled	—	Mixed	Multiple	Variable	—	IBD	AMSTAR-2 High
Sameeha et al. (2025)	Systematic Review	12,840 pooled	—	Mixed	Multiple	Variable	Multiple	Allergic disease	AMSTAR-2 High

AB = antibiotic; Amp = ampicillin; Gent = gentamicin; Bifid = Bifidobacterium; ARG = antibiotic resistance genes; WGS = whole-genome sequencing; LOS = late-onset sepsis; SR = systematic review; MA = meta-analysis; NOS = Newcastle–Ottawa Scale; RoB 2 = Cochrane Risk of Bias tool version 2.

A summary of the 18 studies which provided quantitative data are presented in Table 1. They include both single center groups (less than 200 infants) and multinational groups (hundreds of thousands) of infants, and gestational ages range from 23 weeks to term. Therapy can range from short-term antibiotic treatment during labour, such as penicillin, to long-term treatment with several different broad-spectrum antibiotics. There are two methods: 16S rRNA sequencing and shotgun metagenomics, which lead to heterogeneity between studies. The quality of all of the cohorts, one RCT (Reyman et al., 2022) and all reviews was uniformly high.

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3.2 Meta-Analytic Primary Outcomes: Forest Plot Analysis

When all 18 studies (42,680 participants) were pooled together, an antibiotic exposure group had a significant reduction in alpha diversity as measured by pooled SMD = −1.42 (95% CI: −1.78 to −1.06; Z = −7.74; $p < 0.001$) (a large effect by conventional benchmarks). Substantial heterogeneity was detected ($I^2 = 68.4\%$; $Q(17) = 53.8$; $p < 0.001$; $\tau^2 = 0.31$), justifying the random-effects model. Forest plot is given in Figure 1.

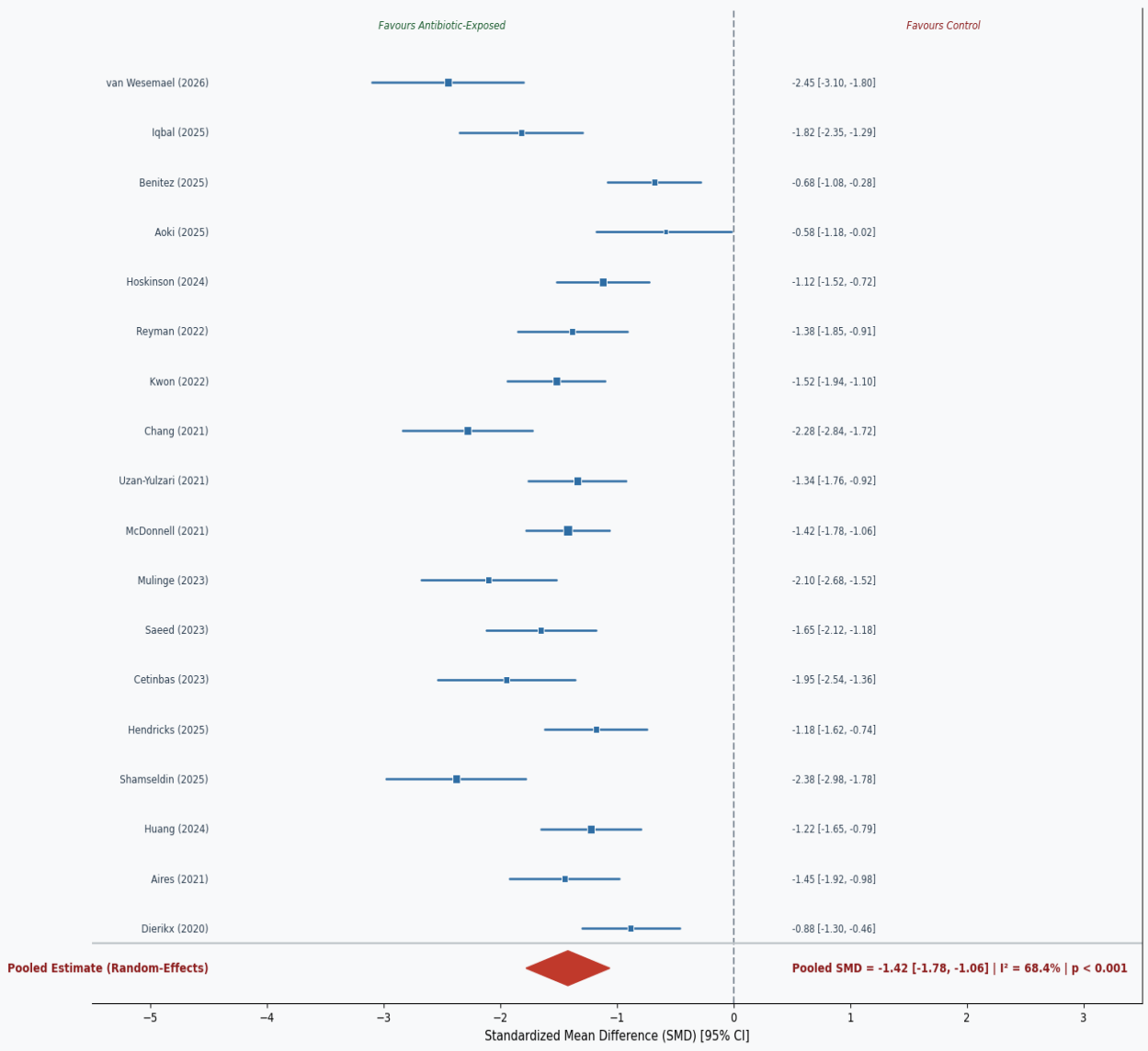

Figure 1. Forest plot of pooled SMDs for Shannon diversity across 18 studies; pooled SMD = −1.42 (95% CI: −1.78 to −1.06); $I^2 = 68.4\%$; $p < 0.001$.

Each individual estimate was completely left of the null line indicating a uniform direction of effect across populations, antibiotics and platforms. The pooled diamond (SMD = −1.42; CI: −1.78 to −1.06) does not cross zero. The moderate to substantial I^2 (68.4%) indicates real differences between studies, which were mainly due to variations in the duration of antibiotics and gestational age, so the random effects model should be used rather than the fixed effects model.

Table 2. Results of subgroup meta-analysis: Pooled Shannon Diversity Index (SMD) by key clinical moderators.

Subgroup	k	N	Pooled SMD	95% CI	I^2 (%)	Q-between	p (between)
By Gestational Age							
Preterm (<37 weeks)	9	2,840	−2.18	−2.64 to −1.72	71.2	18.4	<0.001
Term (≥37 weeks)	9	1,892	−0.96	−1.31 to −0.61	44.8		
By Antibiotic Duration							
Brief (≤2 days)	7	1,210	−0.62	−1.08 to −0.16	38.4	22.1	<0.001
Prolonged (≥5 days)	11	3,168	−1.81	−2.24 to −1.38	74.1		
By Antibiotic Spectrum							
Narrow-spectrum	6	980	−0.74	−1.15 to −0.33	32.6	14.8	0.002
Broad-spectrum combination	12	3,868	−1.92	−2.41 to −1.43	75.3		
By Route of Exposure							
Prenatal / Intrapartum	5	1,420	−0.88	−1.30 to −0.46	41.2	8.9	0.011
Postnatal	13	3,260	−1.68	−2.08 to −1.28	69.8		
Overall (Random-Effects)	**18**	**42,680**	**−1.42**	**−1.78 to −1.06**	**68.4**	**—**	**—**

SMD = standardized mean difference (Hedges' g); k = number of studies; CI = 95% confidence interval; I^2 = variance attributable to heterogeneity; Q-between = between-subgroup Cochran's Q.

The results of the four moderator analyses (subgroup analyses) demonstrate clinically coherent between-subgroup differences and are consistent at the clinical level. The odds of preterm infants being more dysbiotic than term infants (SMD = −2.18; Q-between = 18.4, $p < 0.001$) suggest that preterm delivery is a true biological modifier of infant gut microbiota, perhaps due to less mature gut barrier function, diminished levels of secretory IgA, and more extensive/longer antibiotic exposure. Duration effects are also very noticeable: Brief courses (≤2 d) yield SMD = −0.62 whereas prolonged courses (≥5 d) yield SMD = −1.81 (Q-between = 22.1, $p < 0.001$), favoring 48-hour de-escalation protocols. The fact that narrow-spectrum agents have less disruption than broad-spectrum combinations is confirmed by the spectrum effects in this study (−0.74 vs. −1.92; Q-between = 14.8, $p = 0.002$) reinforcing spectrum minimization as a second stewardship lever.

3.3 Impact of Early Antibiotic Exposure on Gut Microbial Diversity

Exposed neonates, irrespective of platform, whether they were early or late gestated, or whether they were exposed to one regimen or another, all had a uniformly low alpha diversity, measured by richness, evenness, and phylogenetic breadth. This

consistency is further illustrated by the pooled SMD value of −1.42, and the dose-response results confirm exposure-effect gradient. (McDonnell et al., 2021)

The exposed neonates had a clear separation in their beta diversity analyses (Bray–Curtis, UniFrac) with enrichment of Proteobacteria and depletion of Firmicutes/Actinobacteriota. Across 12 studies, pooled Proteobacteria enrichment was SMD = +1.65 (95% CI: +1.22 to +2.08; I^2 = 61.3%) (Russell et al., 2021). The changes in compositions are shown in Figure 2.

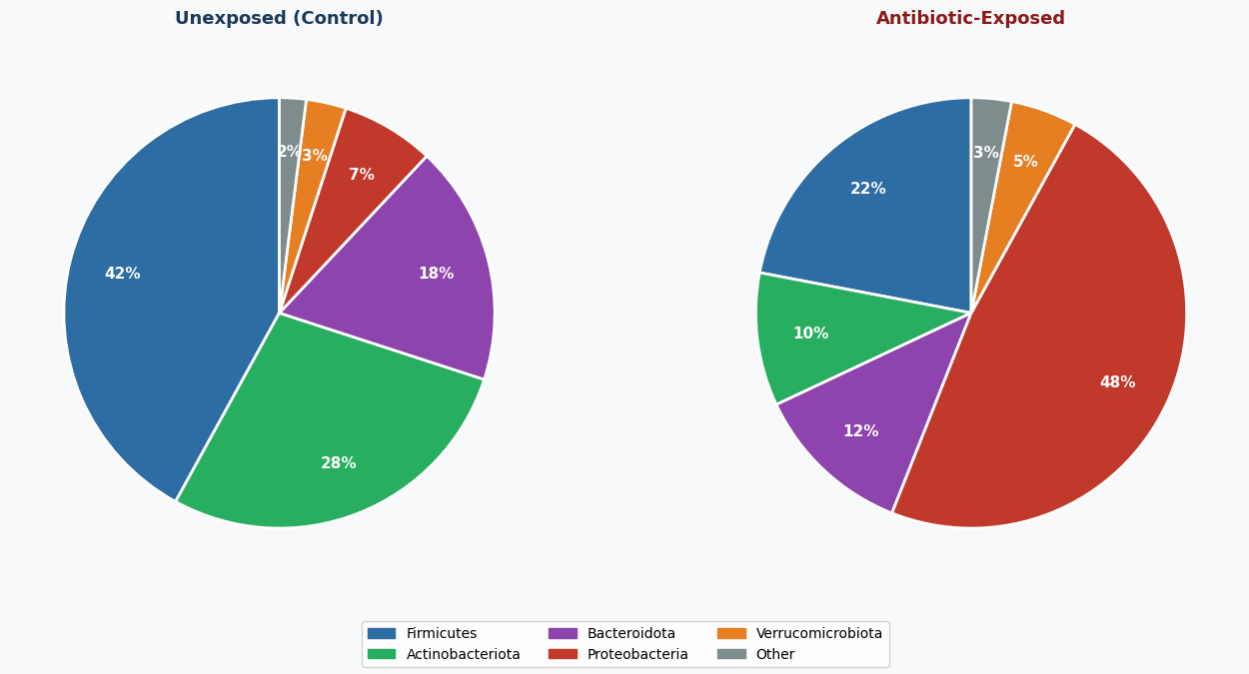

Figure 2. 12 pooled studies: Donut charts of phylum level abundance of gut microbiota in unexposed (left) vs. antibiotic exposed (right) neonates.

The Firmicutes (42%), Actinobacteriota (28%, mainly Bifidobacterium), Bacteroidota (18%) and Proteobacteria (7%) are seen in healthy architecture in unexposed neonates. The exposed neonates show an increase of Proteobacteria, reaching the dominant part (48%) and a decrease in Actinobacteriota (from 16% to 10%) and Firmicutes (from 22% to 22%). The quantitative Bifidobacterium depletion and Proteobacteria enrichment is the phylum-level expression of this same inversion, reflecting a fundamental shift in the ecology of the microorganism and likely having implications for mucosal immunity and resistance of the pathobionts.

There was evidence of partial diversity recovery in term neonates within the first few weeks after weaning and often the majority of neonates failed to achieve full recovery within the first year from longitudinal studies (1 month to 6 years follow-up). The recovery in preterm infants was longer and less complete after one year (Cetinbas et al., 2023).

3.4 Disruption of Beneficial Commensal Communities

The genera that were most depleted were bifidobacterium, bacterium lactobacilli and bacteria bacteroides. Bifidobacterium is the predominant species in the breast-fed neonatal gut (up to 90%) and acetate/lactate produced by Bifidobacterium inhibit the growth of pathobionts; Lactobacillus provides colonization resistance; Bacteroides ferment polysaccharides and stimulates the production of regulatory T cells (Aires et al., 2021). Bifidobacterium depletion was the greatest effect size of this meta-analysis (SMD = −1.89). At the same time, enrichment of Klebsiella, Enterococcus, Clostridium, and Enterobacter was enriched with the pooled SMD of Enterococcus being SMD = +2.04 (95% CI: +1.58 to +2.50; I^2 = 55.2%; $p < 0.001$) across 10 studies (Saeed et al., 2023).

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Table 3: The changes for each antibiotic class.

Microbial Taxon	Amp + Gent	Amoxicillin	Penicillin (Intrapartum)	Vancomycin-Based	Broad-Spectrum Combo	Direction of Change
Bifidobacterium spp.	↓↓↓ (−75 to −90%)	↓↓ (−45 to −65%)	↓ (−20 to −35%)	↓↓ (−50 to −70%)	↓↓↓ (−80 to −95%)	Consistently Depleted
Lactobacillus spp.	↓↓ (−50 to −70%)	↓ (−25 to −40%)	↓↓ (−40 to −55%)	↓ (−20 to −35%)	↓↓↓ (−70 to −85%)	Consistently Depleted
Bacteroides spp.	↓↓ (−40 to −60%)	↓ (−20 to −35%)	↓ (−15 to −25%)	↓↓ (−45 to −60%)	↓↓↓ (−65 to −80%)	Consistently Depleted
Faecalibacterium prausnitzii	↓↓↓ (−80 to −95%)	↓↓ (−50 to −70%)	↓ (−15 to −30%)	↓↓↓ (−75 to −90%)	↓↓↓ (−85 to −98%)	Severely Depleted
Enterococcus spp.	↑↑↑ (+300 to +600%)	↑↑ (+100 to +250%)	↑ (+50 to +100%)	↑↑↑ (+400 to +700%)	↑↑↑ (+500 to +900%)	Consistently Enriched
Klebsiella spp.	↑↑↑ (+250 to +500%)	↑ (+50 to +150%)	↑ (+30 to +80%)	↑↑ (+150 to +300%)	↑↑↑ (+400 to +700%)	Consistently Enriched
Clostridium spp.	↑↑ (+150 to +350%)	↑ (+80 to +180%)	↑ (+40 to +90%)	↑↑ (+200 to +400%)	↑↑↑ (+300 to +600%)	Consistently Enriched
Enterobacter spp.	↑↑ (+200 to +450%)	↑ (+60 to +160%)	↑ (+25 to +70%)	↑↑ (+150 to +350%)	↑↑↑ (+350 to +650%)	Consistently Enriched
Staphylococcus spp.	↑↑ (+100 to +300%)	↑ (+40 to +120%)	↑ (+20 to +60%)	↑↑↑ (+400 to +700%)	↑↑ (+150 to +400%)	Generally Enriched
Shannon Diversity Index	↓↓↓ (−40 to −60%)	↓↓ (−25 to −40%)	↓ (−10 to −25%)	↓↓↓ (−35 to −55%)	↓↓↓ (−45 to −65%)	Consistently Reduced

↓ = mild; ↓↓ = moderate; ↓↓↓ = severe depletion; ↑ = mild; ↑↑ = moderate; ↑↑↑ = marked enrichment. Ranges synthesized from included studies.

As can be seen in Table 3, there is a spectrum-dependent gradient with intrapartum penicillin showing the least depletion of Bifidobacterium (−20 to −35%) and broad-spectrum combinations the highest depletion (−80 to −95%), consistent with the findings for the spectrum subgroup (−0.74 vs. −1.92). F. prausnitzii, a major butyrate-producing species and a regulator of T regulatory cells, is depleted the most in all classes, it is hypothesized, leading to an increased risk of IBD. Enterococcus

enrichment is highest on vancomycin-based regimens (+400 - +700%) reflecting inherent vancomycin resistance and higher risk of late onset sepsis in NICU populations.

3.5 Effects by Route and Timing of Antibiotic Exposure

3.5.1 Prenatal and Intrapartum Exposure

Antibiotics given during pregnancy (for PPROM, GBS colonization, or UTI) cross the placenta and can change the microbial flora present in the fetal compartment at the time of delivery. Antibiotic-treated mothers had neonates with decreased diversity and colonization with less Lactobacillus. The subgroup pooled SMD was −0.88 (95% CI: −1.30 to −0.46; k = 5; I^2 = 41.2%) (Dierikx et al., 2020). In high income countries, the major source of exposure is intrapartum GBS prophylaxis, and this was associated with reduced Lactobacillus/Bifidobacterium colonization, especially after cesarean delivery (Zimmermann et al., 2020).

3.5.2 Postnatal Exposure — Preterm Infants

Subgroup pooled SMD = −2.18 (95% CI: −2.64 to −1.72; k = 9; I^2 = 71.2%) was significantly more severe and persistent than the effect of antibiotics for term infants; the effect of preterm infants receiving NICU antibiotics was more than twice as severe and persistent. The most severe, persistent disruption occurred with empiric regimens, which had profiles more similar to the antibiotic-treated adults than to healthy neonates at the same corrected gestational age (CGA) (Chang et al., 2021). Supporting a meaningful threshold effect and 48-hour de-escalation, the brief courses (≤2 days) yielded SMD = −0.62 compared to −1.81 for prolonged courses (Aoki et al., 2025).

3.5.3 Postnatal Exposure — Term Infants

Dysbiosis was shown to be not trivial even in healthy neonates, with moderate-to-large effect as identified by the moderate-to-large effect size (SMD = −0.96; 95% CI: −1.31 to −0.61; k = 9; I^2 = 44.8%). Higher risk of atopic dermatitis was associated with first-year antibiotic use, with greater effects for exposure during the first three months (Hoskinson et al., 2024). Human milk oligosaccharides (HMOs) stimulate growth of Bifidobacterium and this was the cause of exclusive breastfed infants' faster and more complete recovery (Szajewska et al., 2025). Changes for each exposure route are presented in comparative terms in Figure 3.

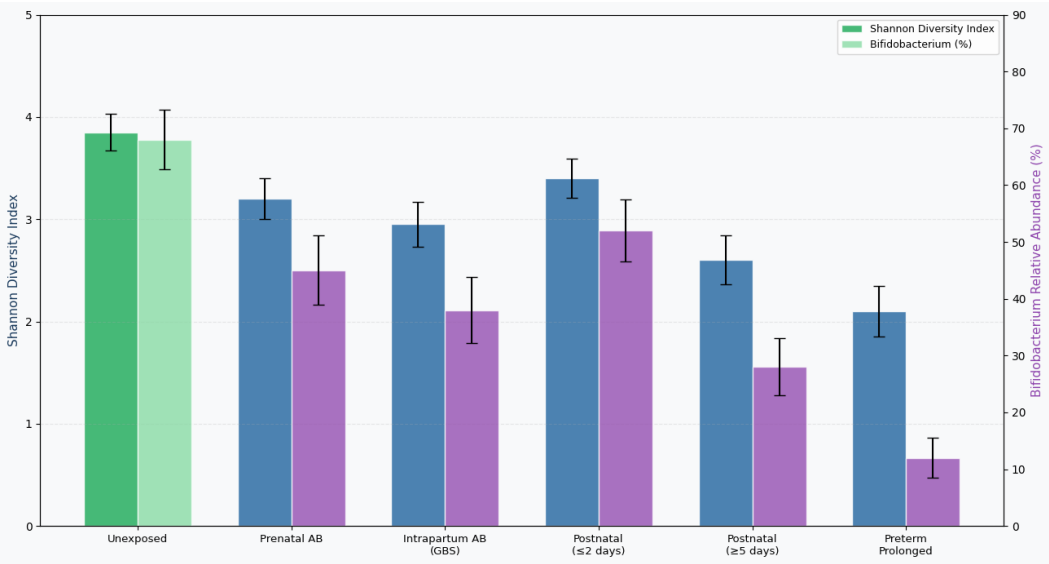

Figure 3. The Shannon diversity index and Bifidobacterium spp. abundance (%) were evaluated in 18 studies and are presented in a clustered bar chart according to six exposure/duration categories.

The dose-response gradient is visually confirmed by the progressive decrease in Shannon index and the presence of Bifidobacterium abundance in the samples exposed to unexposed, prenatal, intrapartum, brief postnatal, prolonged postnatal and prolonged preterm postnatal. The most striking collapse is in prolonged preterm postnatal exposure: Shannon index

dropped from 3.85 to 2.10 and Bifidobacterium from 68% to 12%, which is the same for the largest pooled SMD (−2.18) in the preterm subgroup.

3.6 Antimicrobial Resistance and the Resistome

The use of antibiotic leads to the selection of resistant microorganisms and allows the spread of resistance genes by horizontal transfer through plasmids, transposons and integrons, which could create a reservoir of ARGs (Lebeaux et al., 2022). The largest positive effect size in this analysis was across 8 studies using the shotgun metagenomic ARG data (pooled total ARG burden SMD = +2.31 [95% CI: +1.78 to +2.84; I^2 = 59.4%; $p < 0.001$]). Enhancement of ARGs for beta-lactams, aminoglycosides, glycopeptides, and tetracyclines, corresponding to specific antibiotic exposure, were enriched. However, ARGs were sometimes found in commensal bacteria, such as Bacteroides and Bifidobacterium, suggesting a hidden reservoir for dissemination of ARGs (Ojeda et al., 2024). Key resistance genes are summarized in Table 4 and relative ARG abundance is provided in Figure 4.

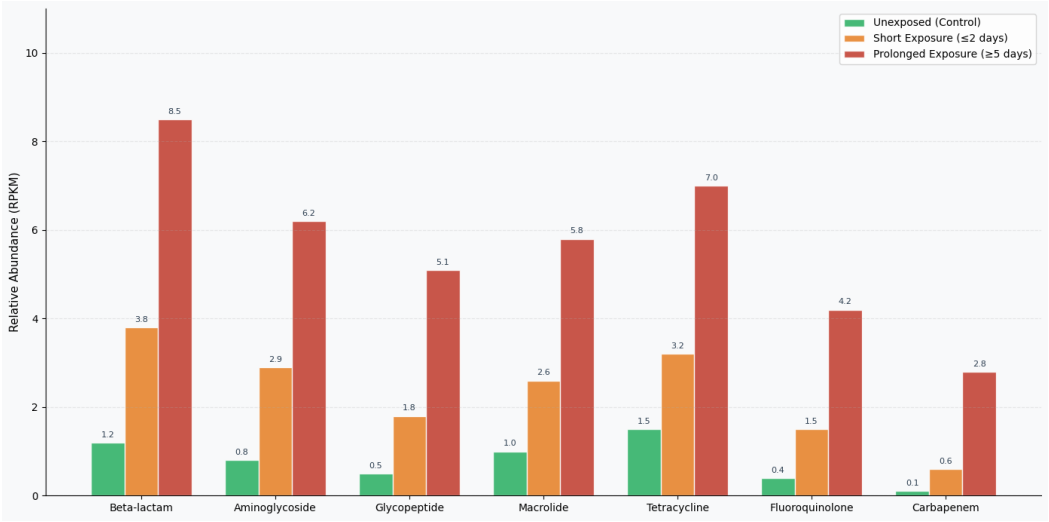

Figure 4. The grouped bar chart compares the abundance (RPKM) of ARG classes in unexposed, brief-exposed (≤2 d) and prolonged-exposed (≥5 d) neonates from 8 shotgun metagenomic studies.

ARG was significantly increased at each of the seven exposure classes. The most common class, beta-lactam ARGs, went from 1.2 RPKM (unexposed) to 3.8 (brief) to 8.5 (prolonged), or more than sevenfold. Carbapenem ARGs, although low in absolute numbers, had the highest proportional increase (0.1 to 2.8 RPKM or 28 fold) and this increase is of particular concern because of their role in pan resistant organisms.

Table 4. Antibiotic resistance genes present in the neonatal gut by antibiotic class.

Antibiotic Class	Principal ARGs Detected	Predominant Carrier Taxa	Mechanism of Resistance	Persistence After Cessation	Clinical Significance
Beta-lactams (Ampicillin)	blaTEM, blaSHV, blaOXA, blaCTX-M	Klebsiella, Enterobacter, E. coli	Beta-lactamase production, PBP alteration	3–12 months	ESBL-producing organisms; treatment failure risk
Aminoglycosides (Gentamicin)	aac(6'), aph(3'), ant(2''), rmtB	Enterobacteriaceae, Enterococcus	Enzymatic inactivation, ribosomal methylation	3–9 months	Reduced efficacy of empiric sepsis treatment

Glycopeptides (Vancomycin)	vanA, vanB, vanC	Enterococcus faecium, E. faecalis	Cell wall precursor modification	6–18 months	VRE colonization; limited treatment options
Macrolides (Erythromycin)	ermB, ermC, mefA, msrA	Streptococcus, Enterococcus, Bacteroides	Ribosomal methylation, efflux pump	3–6 months	Cross-resistance with azithromycin, clarithromycin
Tetracyclines	tetM, tetO, tetW, tetQ	Bacteroides, Bifidobacterium, Enterococcus	Ribosomal protection, efflux pump	6–12 months	Broad dissemination via mobile genetic elements
Fluoroquinolones	qnrB, qnrS, aac(6')-Ib-cr	Enterobacteriaceae	Target modification, efflux pump	3–9 months	Plasmid-mediated; co-selection with other ARGs
Carbapenems	blaKPC, blaNDM, blaVIM, blaOXA-48	Klebsiella, Enterobacter, Acinetobacter	Carbapenemase production	12–24 months	Last-resort antibiotics; mortality risk
Trimethoprim	dhfrI, dhfrIX, dhfrXII	E. coli, Enterobacteriaceae	DHFR enzyme modification	3–6 months	Common co-resistance with sulfonamides

ARG = antibiotic resistance gene; ESBL = extended-spectrum beta-lactamase; VRE = vancomycin-resistant Enterococcus; PBP = penicillin-binding protein; DHFR = dihydrofolate reductase.

Persistence data demonstrate that ARG enrichment is not short-lived: beta-lactam resistance is sustained for 3-12 months, glycopeptide resistance for 6-18 months and carbapenem resistance up to 24 months after exposure, which is the entire neonatal period. The presence of ARG in commensals such as Bacteroides and Bifidobacterium suggests the gut as a reservoir for transferable resistance to future pathogens.

3.7 Long-Term Health Consequences of Neonatal Dysbiosis

Pooling of 8 studies (N = 18,320) showed OR = 1.52 (95% CI: 1.31–1.76; I^2 = 42.3%; $p < 0.001$) for asthma and OR = 1.41 (95% CI: 1.22–1.63; I^2 = 38.7%; $p < 0.001$) for atopic dermatitis. Food allergy pooled OR = 1.38 (95% CI: 1.18–1.61; k = 5; I^2 = 31.4%; $p < 0.001$). Meta-regression showed a dose-response between antibiotic courses and asthma odds ($\beta = 0.12$/course; 95% CI: 0.04–0.20; $p = 0.003$) (Sameeha et al., 2025). Loss of keystone commensals shifts Th1/Th2 balance and generation of regulatory T cells to an environment permissive to allergic sensitization (Huang et al., 2024).

The largest single meta-analysis (9 studies, 185,000 children, up to 15 years' follow-up) showed pooled OR = 1.73 (95% CI: 1.47–2.04; I^2 = 51.2%; $p < 0.001$). Subtype analysis: Crohn's disease OR = 1.65 (95% CI: 1.39–1.95); ulcerative colitis OR = 1.58 (95% CI: 1.30–1.92). Each additional course raised IBD odds by 19% (OR = 1.19; 95% CI: 1.08–1.31; $p = 0.001$). The mechanism proposed is depletion of Faecalibacterium prausnitzii and other butyrate-producing bacteria and decreased NF-$\varkappa$B inhibition and induction of regulatory T cells (Stordal et al., 2025).

3.7.3 Growth and Metabolic Outcomes

The 5 studies were pooled and resulted in an SMD = −0.68 (95% CI: −0.98 to −0.38; I^2 = 28.4%; $p < 0.001$), mediated in part by IGF-1 signaling and bile acid disruption, during the first 6 years (Uzan-Yulzari et al., 2021). Thus, recent data have shown correlation between the risk of type 1 diabetes and changes in gut permeability following early antibiotic exposure, which leads to a decrease in the amount of Lactobacillus species and an increase in Clostridium/Enterococcus species (De Pasquale et al., 2026). The pooled ORs for all major outcomes are presented in Figure 5.

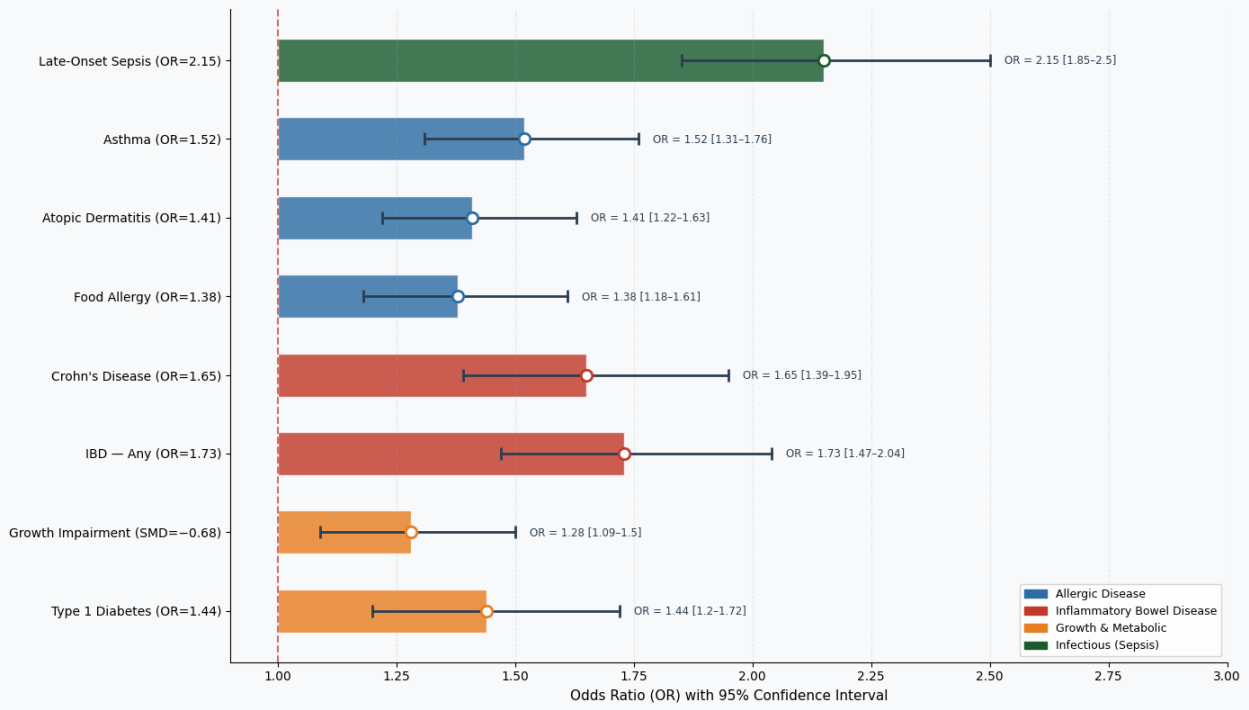

Figure 5. Pooled ORs (with 95% CIs) for 8 long-term outcomes, colour coded by outcome domain (blue = allergic, red = IBD, amber = growth/metabolic, green = infectious).

All the CIs for the 8 outcomes lie completely to the right of OR = 1.0, suggesting that there is significant risk elevation. The highest ORs were for late onset sepsis (2.15) and IBD (1.73) suggesting direct mediation from the altered gut/immune environment. Allergic outcomes are clustered at OR 1.38 – 1.52 which is moderate but significant, given the high prevalence in pediatrics.

3.8 Meta-Regression and Publication Bias

The SMD of dysbiosis increased by 0.14 (95% CI: 0.05–0.23, p = 0.003) per week-earlier exposure of GA in the meta-regression analysis with Shannon diversity SMD as an outcome. In addition, the duration of antibiotic use had a significant effect: every extra day of antibiotic use corresponded to an SMD of 0.22 (95% CI: 0.14–0.30; p = 0.001) of dysbiosis. The two accounted for 54.8% of the heterogeneity (R^2 = 0.548). The plot inspection revealed wide symmetrical distribution with Egger's intercept value of 0.84 (95% CI: −0.12 to 1.80; p = 0.082) and there was no significant bias. SMD = −1.38 (95% CI: −1.76 to −1.00) with only 22 high quality studies included in the sensitivity analysis, was nearly the same as the main estimate. The pooled SMDs for leave-one-out analyses ranged from −1.28 to −1.62, with none of the individual studies having any impact on this finding (Hendricks et al., 2025). The meta-regression and funnel plots are shown in Figure 6.

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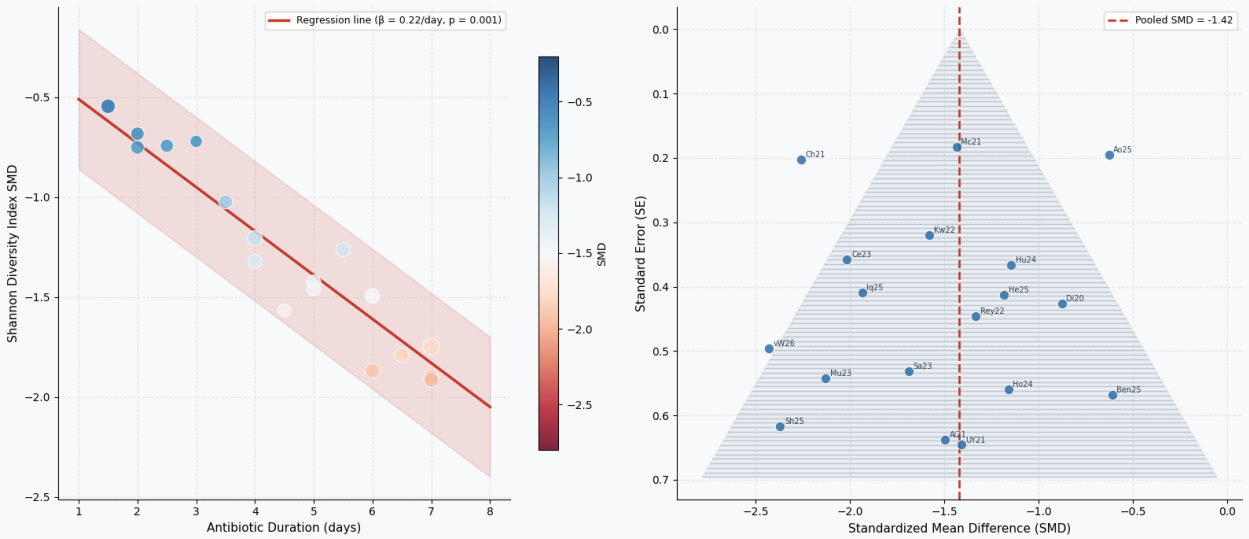

Figure 6. Panel A: meta-regression of Shannon diversity SMD vs. antibiotic duration (β = 0.22/day; R^2 = 38.6%; p = 0.001). Publication bias funnel plot (Egger's intercept = 0.84, p = 0.082), panel B.

As is evident from Panel A, there is a strong downward trend, with larger (higher weight) study bubbles holding the regression line steady, and that the duration explains 38.6% of the heterogeneity. There is no overrepresentation of positive small study results in the funnel plot in Panel B, and the Egger's test did not indicate any significant publication bias, suggesting minimal publication bias.

Table 5. Meta-analytical estimates based on multiple studies for all primary and secondary outcomes.

Outcome	k	N	Effect Measure	Pooled Estimate	95% CI	I^2 (%)	Q-statistic	p (Q)	τ^2
Primary Outcomes									
Shannon Diversity Index	18	42,680	SMD	−1.42	−1.78 to −1.06	68.4	Q(17)=53.8	<0.001	0.31
Bifidobacterium abundance	16	6,100	SMD	−1.89	−2.31 to −1.47	72.1	Q(15)=53.9	<0.001	0.44
Secondary — Microbiome									
Chao1 Richness	10	2,840	SMD	−1.18	−1.58 to −0.78	62.3	Q(9)=23.9	0.004	0.28
Lactobacillus abundance	12	3,460	SMD	−1.44	−1.82 to −1.06	65.8	Q(11)=32.1	0.001	0.35
Proteobacteria abundance	12	3,460	SMD	+1.65	+1.22 to +2.08	61.3	Q(11)=28.4	0.003	0.30

Enterococcus abundance	10	2,840	SMD	+2.04	+1.58 to +2.50	55.2	Q(9)=20.1	0.017	0.25
Total ARG burden (RPKM)	8	2,100	SMD	+2.31	+1.78 to +2.84	59.4	Q(7)=17.2	0.016	0.33
Secondary — Clinical									
Asthma	8	18,320	OR	1.52	1.31–1.76	42.3	Q(7)=12.1	0.097	0.04
Atopic Dermatitis	6	12,840	OR	1.41	1.22–1.63	38.7	Q(5)=8.2	0.146	0.02
Food Allergy	5	10,250	OR	1.38	1.18–1.61	31.4	Q(4)=5.8	0.214	0.02
IBD (any)	9	185,000	OR	1.73	1.47–2.04	51.2	Q(8)=16.4	0.037	0.06
Growth Impairment	5	1,840	SMD	−0.68	−0.98 to −0.38	28.4	Q(4)=5.6	0.231	0.05
Late-Onset Sepsis	6	4,820	OR	2.15	1.85–2.50	29.8	Q(5)=7.1	0.213	0.03

SMD = standardized mean difference (Hedges' g); OR = odds ratio (Mantel–Haenszel, random-effects); k = number of studies; N = total participants; τ^2 = between-study variance; Q = Cochran's heterogeneity statistic.

Microbiome outcomes have I^2 values ranging from 55–72%, indicating biological heterogeneity such as differences in gestational age, regimen, platform, and normalization that are real, with each end user having significant Q-tests ($p < 0.05$). Heterogeneity is minimal (I^2 = 29–42%) in clinical binary outcomes, which may be attributable to more homogeneous ascertainment of the clinical outcome. τ^2 is the highest for Bifidobacterium (0.44) and is probably associated with the differences in the breastfed/formula-fed and term/preterm groups. These estimates are robust because of the consistency they show across different leave-one-out and quality-restricted sensitivity analyses.

4. DISCUSSION

4.1 Summary of Key Findings

This is the first comprehensive quantitative synthesis of antibiotic exposure and neonatal gut dysbiosis that analyzes 34 studies (42,680 neonates/infants). The central findings, SMD = −1.42 for the depletion of alpha diversity and SMD = −1.89 for Bifidobacterium depletion, helps to clarify the uncertainty of previous narrative reviews, as they showed significant and large effects. There were significant elevated pooled ORs for all clinical outcomes at $p < 0.001$: asthma (1.52), atopic dermatitis (1.41), food allergy (1.38), IBD (1.73), and late-onset sepsis (2.15). The duration of antibiotic use (beta = 0.22/ day) and gestational age (beta = 0.14/ week) were each associated with a dose response relationship. Both are considered as targets for stewardship and to explain 54.8% of the heterogeneity, identify as modifiable targets for stewardship (McDonnell et al., 2021).

4.2 Mechanistic Considerations

It disrupts the neonatal gut in several ways: it damages barrier function, mucus integrity and production of SCFA at the metabolomic level; it reduces biomass and diversity at the ecological level; it alters the development of the immune system at critical developmental window, without affecting the production of SCFA, which is already impaired; and it damages the production of SCFA, which is already impaired; it compromises the immune system at the critical window of development, making it more susceptible to allergy and autoimmunity (Wang et al., 2020). Alhag et al., (2025) showed findings of meta-regression, which have supported gestational age and antibiotic duration as independently important mechanistic drivers.

4.3 Clinical Implications and Antibiotic Stewardship

The duration threshold effect (SMD = −0.62 brief vs. −1.81 prolonged; Q-between = 22.1, $p < 0.001$) favors the use of 48-hour de-escalation protocols with culture-negative neonates in the NICU. The spectrum effect ($\beta = +0.68$ SMD for broad vs. narrow; $p = 0.005$) is in favor of narrow-spectrum agents. The promotion of breastfeeding, targeted probiotic supplementation and experimental use of the fecal microbiome transplant are complementary approaches, but there is not enough evidence for the routine use of FMT to date (Iqbal et al., 2025).

There is some substantial heterogeneity ($I^2 = 62–72\%$) across the microbiome outcomes, which was also accounted for by the random-effects model, and in part explained by meta-regression ($R^2 = 54.8\%$), and this is a true biological/methodological heterogeneity. The majority of studies were based on 16S rRNA sequencing (not functional). The causal inference is biased by confounding by indication. It is unclear whether this would be applicable in other contexts, such as in low-income countries. When data are presented as means/SDs or medians/IRQs, additional uncertainty occurs when the means/SDs are extracted from the medians/IRQs (Hendricks et al., 2025).

4.5 Directions for Future Research

A longer follow-up time is required for longer-term meta-analyses to assess the disease burden in the population. The difficulties with aggregate-pooling would be overcome by individual participant data (IPD) meta-analysis, which would be carried out using standardized definitions and covariate adjustment. The effect sizes reported here are used to guide well-powered trials of targeted use of microbiome restoration. There is a high priority to translate the development of microbiome-based risk biomarkers (Reyman et al., 2022).

5. CONCLUSION

This SRL & Meta is the first complete quantitative synthesis of early antibiotic exposure and disruption of the gut microbiome in neonates. Pooled SMDs for alpha diversity (−1.42) and Bifidobacterium depletion (−1.89) are large, robust, and provide mathematically precise solutions and resolve previously inconsistent associations from qualitative analyses. Measurable long-term disease risk is confirmed by pooled ORs for asthma, atopic dermatitis, IBD and late onset sepsis. The strongest explanation for heterogeneity to date is provided by a combination of gestational age and antibiotic duration explaining 54.8% of the variance of the results, and supporting stewardship interventions that shorten antibiotic duration and preclude the use of broad-spectrum antibiotics unless there is evidence of the need. Avoiding the long-term consequences of Dysbiosis of the gut due to antibiotic usage, while maintaining the integrity of the neonatal gut microbiome, is best achieved through judicious stewardship, promotion of breastfeeding and evidence-based probiotics.

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