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Review

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Mother-to-infant vertical transmission in early life: a systematic review and proportional meta-analysis of *Bifidobacterium* strain transmissibility

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Early-life colonization is a critical developmental process influencing infant biological programming, with bifidobacteria playing a key role. This systematic review examines the transmissibility of *Bifidobacterium* strains from mothers to infants. Adhering to Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines, 31 articles from 2009 to 2024 were selected from 2825 screened titles and abstracts. Using a narrative synthesis and meta-analysis, the review focuses on studies employing strain-level metagenomic approaches (Protocol registry CRD: CRD42023490507). Ten studies using shotgun metagenomic sequencing identified specific strains of *B. adolescentis*, *B. angulatum*, *B. bifidum*, *B. breve*, *B. pseudocatenulatum, B. catenulatum*, and *B. longum* shared between mothers and infants. A meta-analysis of 810 mother–infant pairs revealed an overall species transmissibility estimate of 30% (95% CI: 0.17; 0.44), with *B. longum* strains persisting in infants' guts for up to 6 months. Strain transmissibility was higher in vaginally delivered infants compared to those delivered by caesarean section. This review highlights the high transmission rates of maternal *Bifidobacterium* strains in early-life gut seeding, particularly *B. bifidum* and *B. longum*. Despite ongoing research, uncertainties remain regarding the precise characteristics, transmission routes, and mechanisms of transmitted strains. Comprehensive approaches, including metagenomic sequencing and longitudinal studies, are needed to understand the role of vertical transmission in infant gut microbiome engraftment and its functional implications.

The human microbiota is a complex set of microorganisms that inhabit various human body sites, such as skin, oral cavity, nasopharynx, and genito-urinary and gastrointestinal tracts[1–5]. Its composition depends on multiple factors such as host genetics, dietary habits, and environment, and is subject to temporal changes[1,2,4,6,7]. The first 2 years of life are considered a "window of opportunity", where any physiological event may partake in biological (re)programming with consequential impact on both short- and long-term host health[1,8–10]. Thus, achieving adequate crosstalk or signaling between microbes, and between microbes and host cells through microbial metabolites[11], is essential, as well as establishing non-pathogenic microbial colonization by founder species[1,12]. The initial colonization process by members of the genera *Escherichia*, *Enterococcus* and *Lactobacillus* facilitates subsequent establishment of strict anaerobes, such as members of *Bifidobacterium* and *Bacteroides* genera, which

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become dominant in the healthy full-term infant gut within 1–4 weeks from birth[2,9,13–17].

Strain-level metagenomic profiling studies have revealed that the maternal microbiome serves as a source of bacteria for the infant during and after birth[13,18–20], a phenomenon known as vertical transmission of microbial elements from mother-to-infant[15,21]. Strain transmission frequency seems to substantially vary between species[13,15], and there are numerous factors influencing mother-to-infant transmission and associated persistence of such early bacterial colonizers in the developing gut microbiota, such as maternal and baby diet, use of antibiotics, mode of delivery, gestational age, environment and genetic factors, among others[21–24]. Importantly, it has been shown that strains acquired from the mother elicit a high persistence level in the infant gut microbiome[15,17,21,25].

Approximately 11% of these early colonizers belong to the *Bacteroides* and *Bifidobacterium* genera, persisting throughout the first year of life[26]. Members of the genus *Bifidobacterium* usually increase their relative abundance (RA) during the first months following birth[13] and dominate the gut microbiota of breastfed infants[27], due to eco-physiological characteristics that facilitate the initial colonization of the infant gut[28]. This initial acquisition and persistence of bifidobacterial strains in the infant is facilitated in part by the specific bifidogenic effect of dietary carbohydrates, in particular human milk oligosaccharides (HMOs) found in human milk (HM)[29,30]. The absence, depletion or reduction of bifidobacteria in the infant gut during the first months following birth has been associated with an increased risk of acquiring antibiotic resistance, asthma, allergy and infectious diseases[31–36].

Due to the importance of transfer of specific microbiota components from mother to infant, this phenomenon has been previously explored in a variety of literature reviews[22,28,37,38]. However, these studies did not comprehensively or specifically address vertical transmission of bifidobacteria, which refers to the transfer of specific microbial strains[39], from mothers to infants during the first months of life. Therefore, our objective was to systematically investigate the occurrence of vertical transmission of *Bifidobacterium* members and their persistence by reviewing existing literature.

Methods

Protocol and registration

This systematic review followed the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) guidelines[40] for quality, transparency, and replicability, and has been registered on PROSPERO registry [#CRD42023490507]. Please see the end of the Supplementary Material for the PRISMA 2020 Checklist.

Review question(s)

We aimed to explore and quantify the phenomenon of vertical transmission of *Bifidobacterium* species transmissibility from mother to infant through the formulation of the following research questions (Box 1) inferred via a Population, Exposure, Comparator, Outcome, Time frame, Study design (PECOTS) approach (Table 1):

Eligibility criteria

The eligibility criteria have been described in Box 2. Additionally, we only included healthy control groups from case-control studies.

Search strategy

The literature search was conducted until December 2023, as guided by the inclusion and exclusion criteria, and using the public databases PubMed, Cochrane Library, Web of Science, and Scopus. This search adhered to the Peer Review of Electronic Search Strategies (PRESS) guidelines[41], incorporating search strings with Boolean and proximity operators (Supplementary Table 1), reviewing references, and deliberately avoiding filters by date of publication to ease literature saturation.

Study selection, and data extraction and synthesis

Using the Rayyan software[42], two reviewers blindly screened the title and abstract, and then the full text in two separate stages. In addition, between screening stages, disagreements were resolved between reviewers. A pilot-test table was developed to agree upon the necessary data to be extracted. To facilitate a narrative synthesis of the data, a tabulation was created to include details such as study design, and other details of interest stratified by the origin of the maternal sample, and year of study due to the evolution of technologies and bioinformatic pipelines used to investigate vertical transmission. The extracted data was cross-checked by a second author to confirm that data had been accurately extracted (Supplementary Tables 2 to 6). As per the quantitative synthesis, this process included reviewing the pooled number of mother-infant pairs sharing *Bifidobacterium* species and strains, extracted from the main manuscript, main figures, supplementary documents, and, when needed, by contacting authors for clarification of studies that had conducted shotgun metagenomic techniques.

To obtain a graphical representation of the studies that had explored transmission of bifidobacteria from mother to infant, the packages ggplot2[43], maps[44], mapdata[45], and dpylr[46] were used in R software with RStudio environment[47]. In addition, to conduct a meta-analysis, we selected the species- and strain-level metagenomic analysis outputs. Subgroup analysis by taxonomy was then performed using the extracted counts of shared *Bifidobacterium* strain events. Additionally, we considered studies that had conducted metagenomic shotgun sequencing and utilized specific pipelines to perform strain-level analysis (StrainPhlAn[48], Constrain[49], Instrain[50], etc.), aiming to reduce potential sources of heterogeneity in the random-effects meta-analysis. The input for meta-analysis can be found in https://github.com/EFV1995/VT_proportional_MA. To calculate the proportion of strains shared within shared *Bifidobacterium* species between mothers and their infants, we used the equation provided below:

$$\text{Strain Transmissibility} = \frac{\textit{Number of mother} - \textit{infant pairs with shared strains}}{\textit{Number of mother} - \textit{infant pairs with shared species}}$$

The meta-analytical technique and forest plots were generated using the tidyverse[51], metafor[52] and the meta[53] packages in R software with RStudio environment[47]. The scripts and pooled data for the meta-analysis, along with the map, are available at: https://github.com/EFV1995/VT_proportional_MA. The technique included an inverse variance method, Der Simonian-Laird estimator for tau^2, Jackson method for confidence interval of tau^2 and tau, Freeman-Tukey double arcsine transformation, and Clopper–Pearson 95% confidence interval (CI) for individual studies to perform a random effect model and a forest plot.

Box 1 | Research questions

- What is the existing scientific evidence regarding vertical mother-to-infant transmission and persistence of *Bifidobacterium* during the first 24 months of life?
- What are the main routes for mother-to-child *Bifidobacterium* transmission?
- What are the main factors affecting vertical transmission of *Bifidobacterium*?
- How frequently does vertical transmission occur and what proportion of infant gut bifidobacteria is maternally derived?
- What are the current technical limitations of identifying mother-to-infant transmission events with better confidence and increased resolution?

Table 1 | Population, Exposure, Comparator, Outcome, Time frame, Study design (PECOTS) approach

Participants (P)	Mother-infant pairs within the first 24 months following birth including both breastfed and non-breastfed infants
Exposure (E)	*Bifidobacterium* in HM, skin, vaginal, oral, and gut microbiota of mothers and their infants as based on fecal sample analysis.
Comparator (C)	Transmission events of *Bifidobacterium* members from the maternal microbiota to the corresponding fecal-based infant gut microbiota, as well as the contributions and dominance of the different samples collected from mothers.
Outcomes (C)	Species transmissibility for each detected Bifidobacterium species defined as the number of mother-infant pairs with shared strains divided by the number of mother-infant pairs with shared species.
Time Frame (T)	First 24 months of life.
Study design (S)	Observational cross-sectional, longitudinal studies, and intervention studies.

Box 2 | Eligibility criteria

Inclusion criteria

- Studies exploring vertical transmission of microbiota, including *Bifidobacterium*, from different anatomical body sites and HM samples to the infant gut regardless of their breastfeeding status.
- Observational cross-sectional, longitudinal, and intervention studies.
- Human participants.
- Studies sampling one or more time points during the first 24 months of life.
- Studies utilizing Next-generation sequencing (NGS) technologies and that had explicitly acknowledged the concept of "vertical transmission", understanding that while the term may be mentioned, not all methodologies employed in these studies may infer transmission.

Exclusion Criteria

- Not available in English.
- Had not included microbiota analysis.
- That included mothers with mastitis, vaginosis, diseases, or treatments that could have severely compromised the body's immune system (e.g., HIV), or microbiota.
- Mother-infant pairs under antibiotic, probiotic, dietary intervention, or food supplementation treatment effect.
- Premature infants, infants born with very low birth weight, or with other diseases, or infants admitted to hospital during the study.
- Animal studies.

Critical appraisal

To evaluate the methodological rigor and risk of bias we used the checklist from Joanna Briggs Institute[54] to assess the cross-sectional, and longitudinal studies, and randomized controlled trials (Supplementary Tables 7 and 8).

Results from literature search

Descriptive overview

The search across four different search engines yielded a total of 2825 articles. After removing duplicates using automated tools and evaluating titles and abstracts, 2447 articles did not meet the inclusion criteria and were excluded (Fig. 1). During the full-text screening of the remaining 122 articles, 91 articles were excluded. These articles did not address strain sharing, acquisition or persistence specifically analyzing bifidobacteria. Among these, some studies[55–62] explored maternal and infant microbial compositions as clusters thus not allowing the isolated study of bifidobacteria. Additionally, ten articles[63–72] did not provide a clear definition for vertical transmission or strain sharing, therefore these were excluded to preclude misinterpretations, and seven articles used molecular techniques (Random Amplified Polymorphic DNA (RAPD), Amplified Fragment Length Polymorphism (AFLPs), Multilocus sequence typing (MLST) and targeted Polymerase chain reaction (PCR))[73–79]. Finally, 31 studies assessed *Bifidobacterium* transmission events from different body sites or HM of the mother to the corresponding infant gut microbiota using DNA sequencing technologies (Supplementary Table 6), highlighting the highly heterogeneous definitions for "*vertical transmission*" from the included studies (Supplementary Table 7). Vertical transmission has primarily been investigated in European cohorts ($n = 21$), with a comparatively small number of studies conducted in Asian countries ($n = 6$), the United States ($n = 4$), Africa ($n = 3$), and South America ($n = 2$) (Fig. 2), with varying sample sizes. These studies encompassed a range of sample sizes, including less than 20 mother-infant pairs[18,25,80–92], between 20 and 50 pairs[15,19,93–98], 50 to 100 pairs[39,99–103] and with more than 100 pairs[13,14,104,105], including 24 studies that had followed a longitudinal prospective study design[13–15,18,19,25,80,81,83,85,86,88,91,93–96,98–105], and 7 cross-sectional designs[82–84,88,90,97,106] (Supplementary Tables 2–5).

Inference of vertical transmission of *Bifidobacterium* members

Studies utilizing shotgun metagenomic sequencing report *Bifidobacterium* genus abundances in infant gut ranging from 52%[13] to 67%[90]. The majority of studies investigated either the transfer of bifidobacteria to the infant gut only from HM through vertical transmission ($n = 9$)[81,84,90,93,94,96,102,104,106], from maternal fecal contents ($n = 13$)[14,19,39,73,82,85,86,92,97,99–101,103] or from both mother gut and milk ($n = 12$)[13,18,25,80,83,87,88,90,91,95,98,105]. Other regions have been explored less frequently, including oral cavity ($n = 3$)[13,15,90], breast skin upper area ($n = 2$)[15,90], rectum ($n = 2$)[78,90], and vagina ($n = 6$)[13,15,39,90,92,103]. From these, Ferretti et al.[15] and Feehily et al.[13] studied simultaneously four potential maternal anatomic regions in 25 Italian and 132 Irish mother-infant pairs, respectively. Furthermore, the time intervals for sample collection varied, spanning from days[39,92,105], to several weeks[78–80,83,86–88,93], months[13–15,19,25,81,82,85,90,94,96,98,102,103,106], and some extended to years[18,84,95,97,99–101,104]. In certain cases, follow-up periods extended up to 2 years[99,100] and 5 years[84] (see Supplementary Tables 2–5 for detailed information regarding the time points for sample collection)[19,73,82,85,86,97,99–101].

Bifidobacterium species transmission from the maternal gut to the infant gut

Most studies employed maternal fecal samples as a source of *Bifidobacterium* strains for the infant´s gut[13–15,18,25,82,92,97,98]. A longitudinal study conducted in 2018[15] shotgun metagenomic sequencing was used to analyze strain sharing among 25 healthy mother–infant pairs in Italy over a period of 4 months. The participants included 56% who were breastfed, 16% exclusively formula fed, and 12% who received mixed feeding. Strain distances were compared using PanPhlAn and StrainPhlAn. A threshold of 0.1 indicated strains as the same or different based on their genetic similarity, as determined from a bimodal distribution of all-versus-all normalized species-specific strains distances. Applying this definition, the authors observed clear maternal routes of transmission, confirmed by Single Nucleotide Variant (SNV) identity patterns. Specifically, they observed one strain sharing event of *B. breve* and *B. longum* from maternal stool samples to infant stool samples, yet no sharing events were detected for *B. bifidum*[15]. In a multi-cohort cross-sectional study spanning Colombia, Argentina,

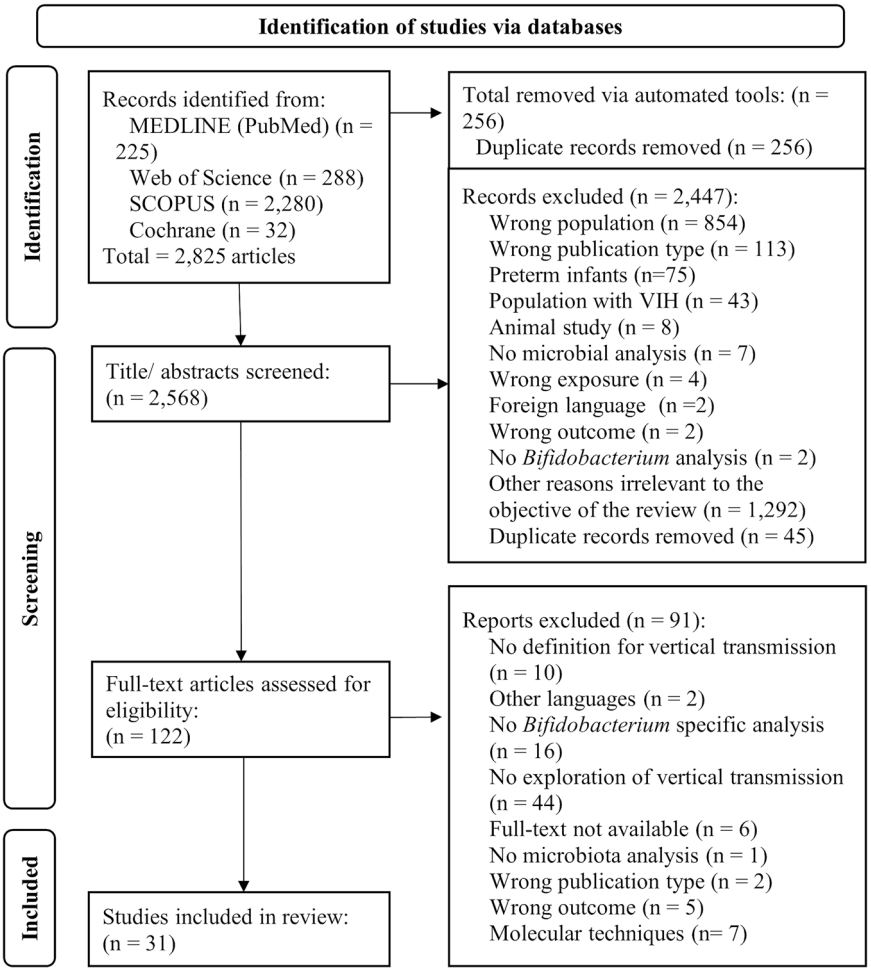

Fig. 1 | A Flow chart depicting the process of study selection and application of exclusion criteria. Literature search was conducted in MEDLINE (via PubMed), Cochrane Library, Web of Science, and SCOPUS search engines until December 2023.

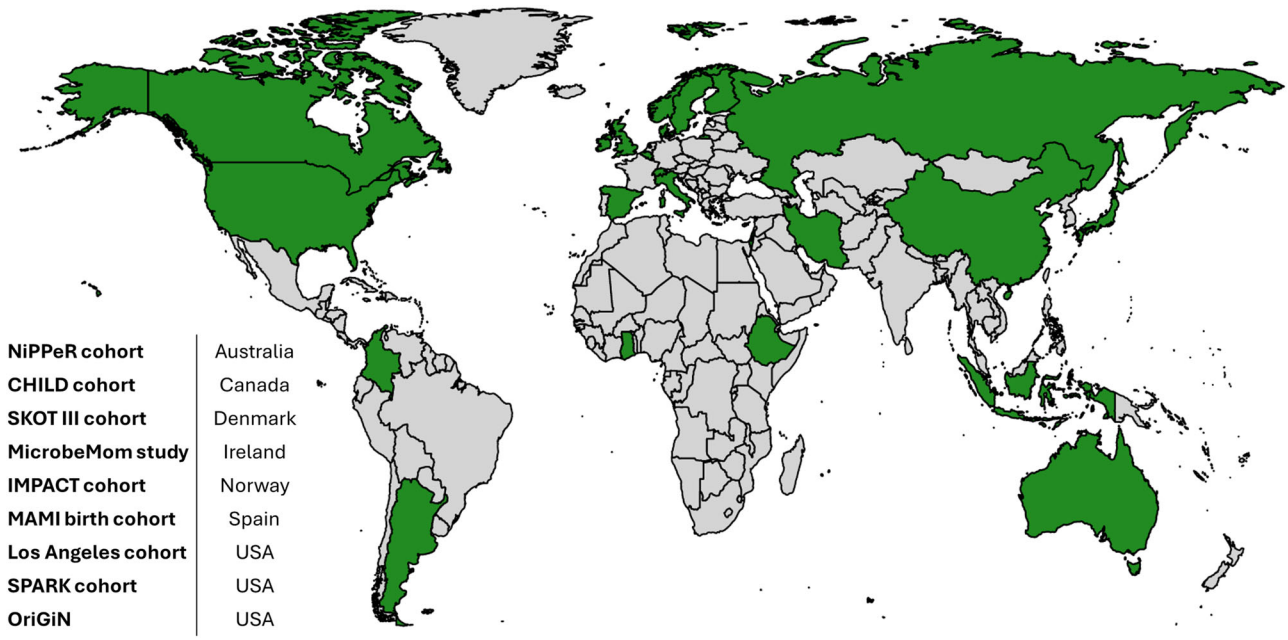

Fig. 2 | Geographical distribution of studies investigating transmission of bifidobacteria from mothers to infants (in green). The names of some cohorts retrieved per country (when available) are indicated in the square.

China, Guinea-Bissau, Italy, and the USA (38), 87% of paired fecal samples from mothers and infants shared identical *B. bifidum* strains, indicating high species transmissibility. Through StrainPhlAn strain level analysis, a total of 13,278 instances of mother-to-infant shared *B. bifidum* strains were identified, with a transmissibility rate of 0.93. Notably, *B. longum* strains were consistently shared in pairs from high income countries datasets but strain-sharing events were absent in low- and middle-income counties datasets, highlighting distinct transmissibility patterns.

In a separate study[13], evidence of vertical transmission was found in a 3-month longitudinal study utilizing a genomic-cultivation-based approach in stool samples from 132 Irish mother–infant pairs. Of these pairs, almost 50% were exclusively breastfed, 31% received mixed feeding, and 20% were exclusively formula-fed. The authors identified *Bifidobacterium* strains exhibiting an Average Nucleotide Identity (ANI) exceeding 99.9%. Although transmitted at apparently low RAs, among the 36 shared species, the most prominent ones were *B. longum* subsp. *longum* with an RA of 2.09% and a detection rate of 311 out of 368, and *B. adolescentis*, with an RA of 2.42% and a detection rate of 253 out of 368 maternal stool sample[13]. Additionally, another metagenomic sequencing study, a 3-month longitudinal study of 44 Finnish mother–infant pairs, identified 7 and 5 strain-sharing events between samples of *B. longum* and *B. adolescentis*, respectively[19], referring to the observation of highly similar nucleotide variation patterns in two individuals. Moreover, Manara et al.[97] conducted a cross-sectional study in 25 Ethiopian mother-infant pairs from a rural area, categorizing them into an under 1 year and a 12-year-old group, where a similar definition of strain sharing was applied through the construction of phylogenetic trees to establish a phylogenetic distance threshold. The study found that *Bifidobacterium* species were all present, yet no specific strains were shared in pairs from low- and middle-income country populations. Notably, Shao et al.[14], conducted a longitudinal prospective study with a follow-up of 12 months, 175 British mother–infant pairs, using the StrainPhlAn profiling tool, and stablishing as a criteria to infer transmission, a strain distance threshold of 0.1. The study reported that delivery mode influences significantly species transmissibility, being higher in vaginal deliveries when compared to c-section deliveries (Supplementary Table 3).

Bifidobacterium species transmission from the maternal vagina to the infant gut

Vaginal swab samples were analyzed in six studies[13,15,39,90,92,103]. Wampach et al.[92] found that within the first five days postpartum, infants delivered vaginally exhibited multiple strains of *Bifidobacterium* derived from vaginal swabs collected at birth, on the 3rd day, and on the 5th day, with a species transmissibility of 71%. Notably, no such strains were observed in infants delivered via cesarean section. However, strain profiling of over 9500 metagenomes in a multi-cohort study substantiated these findings, indicating that vaginal delivery significantly increased strain transmission rates[39]. Moreover, a cross-sectional study[90] conducted in 2020 among 20 mother-infant pairs from the United States, performed shotgun metagenomic sequencing on vaginal microbial samples that had been collected on the 3rd and 111th day after birth, but did not show evidence of vertical transmission nor of abundance of *Bifidobacterium* nor of *B. breve*. Conversely, in a more recent study in samples with very low RAs, Feehily et al. [13] showed via a cultivation and shotgun metagenomic sequencing, that vaginal delivery had significantly higher sharing occurrence of *Bifidobacterium* transfer from mother to infant, including 9 sharing occurrences of *B. adolescentis*, 12 of *B. bifidum*, 13 of *B. breve*, 1 of *B. catenulatum*, 15 of *B. longum*, and 1 of *B. pseudocatenulatum*, when compared to pairs that had been delivered by cesarean section. Additionally, almost 50% of the participants were exclusively breastfed (Supplementary Tables 4 and 5).

Bifidobacterium strain transmission from other maternal anatomical regions to the infant gut

A small number of studies explored *Bifidobacterium* strains derived from maternal oral cavity[13] or tongue dorsum[15], upper breast skin[15], areola[90], and rectal swabs[90,103]. Kordy et al.[90] collected areolar skin samples and rectal swabs from 20 mother–infant pairs in the United States between the 3rd and 111th day after birth, with 30% of the infants being breastfed. They conducted strain-level analysis using ConStrains[90], along with 16S rRNA gene sequencing. The study identified in 1 out of 20 mother–infant breastfeeding pairs a shared strain of *B. breve* between maternal rectal swab samples, areolar skin cultivation-detect and infant stool samples in a C-section delivery. Contrarily, Mitchell et al.[103] conducted a study evaluating the effects of delivery on species transmissibility in 75 American mothers–infant pairs. Shotgun metagenomic sequencing identified only one instance of species sharing, specifically *B. breve*, but did not identify strain sharing events, independently of delivery mode. Nonetheless, Feehily et al.[13], used a cultivation and shotgun metagenomic sequencing approach, and identified shared stains at low RA of *B. longum, B. pseudocatenulatum, B. catenulatum, B. breve, B. bifidum*, and *B. adolescentis* derived from maternal stools, HM, and vaginal swabs. Conversely, a longitudinal study[15] did not detect transmission events from tongue dorsum and upper breast skin *Bifidobacterium* strains to infant gut. This study from Ferreti et al.[15] was based in Italy among 25 mother–infant pairs that had collected tongue dorsum samples at day 1 and day 3 after delivery, and infant stool samples at day 7, 1st month, and 4th month after delivery. Of these participants, 56% were exclusively breastfed (Supplementary Table 5).

Bifidobacterium strain transmission from HM to the infant gut

To investigate strain transmissibility from HM to the infant gut, research has utilized shotgun metagenomic and genomic sequencing methods to identify bifidobacterial strains in HM samples[13,18,25,90]. Due to problems related to low microbial biomass and higher human DNA, metagenomic approaches are limited[18,25]. To overcome this, a longitudinal study spanning 3 months after birth combined cultivation techniques and whole genome of HM bacterial isolate, involving 132 Irish mother-infant pairs. Within a subset of 34 pairs, 13 shared strains between HM and infant stools were identified[13] (Supplementary Tables 2, 4, and S5).

Findings from the proportional meta-analysis of transmission events

Although 12 studies had performed shotgun metagenomics sequencing[13–15,18,19,25,39,82,90,97,98,103], only 10 studies (10/12, 83.3%) had performed strain-level microbial profiling through StrainPhlAn[13–15,18,39,82,92,97,98]. The meta-analysis explores the species depicted in the forest plot (Fig. 3), estimating the overall proportion of species transmissibility across all *Bifidobacterium* strains to be 0.298 [95% CI: 0.17; 0.44], observed based on 810 mother-infant pairs with shared *Bifidobacterium* species. This indicates that ~30% of mother-infant pairs that share a *Bifidobacterium* species, harbor the same strain. The high I^2 value of 91% suggests substantial heterogeneity across the studies, indicating that the observed transmissibility proportions vary significantly. Subgroup analysis by species shows varying proportions among different *Bifidobacterium* strains, with significant heterogeneity within each subgroup. The test for subgroup differences indicated that the observed differences in species transmissibility among *Bifidobacterium* species were non-significant ($P = 0.54$). In addition, *B. pseudocatenulatum* and *B. bifidum* species showed relatively high overall species transmissibility (0.451 [95% CI: 0.006; 0.958] and 0.389 [95% CI: 0.091; 0.732], respectively), with substantial heterogeneity suggesting variability in study results. Moreover, *B. breve* represented a species transmissibility under the overall estimate (0.077 [95% CI: 0.000; 0.264]), with low heterogeneity ($I^2 > 36\%$), indicating consistent findings across studies. *B. longum* exhibited moderate species transmissibility (0.251 [95% CI: 0.053; 0.513], with substantial heterogeneity, reflecting varied results in studies ($I^2 > 90\%$). Furthermore, *B. angulatum* and *B. catenulatum* species denoted a high although heterogenous transmissibility (0.45 [95% CI: 0.000; 1.0] and 0.746 [95% CI: 0.000; 1.0], respectively) with moderate heterogeneity, indicating potential differences in transmissibility among studies ($I^2 = 83\%$ and $I^2 = 80\%$, respectively). Some studies did not identify transmission events for *B. adolescentis*[97], *B. breve*[39,97], *B. longum*[97], *B. bifidum*[15,92,97], *B. angulatum*, and

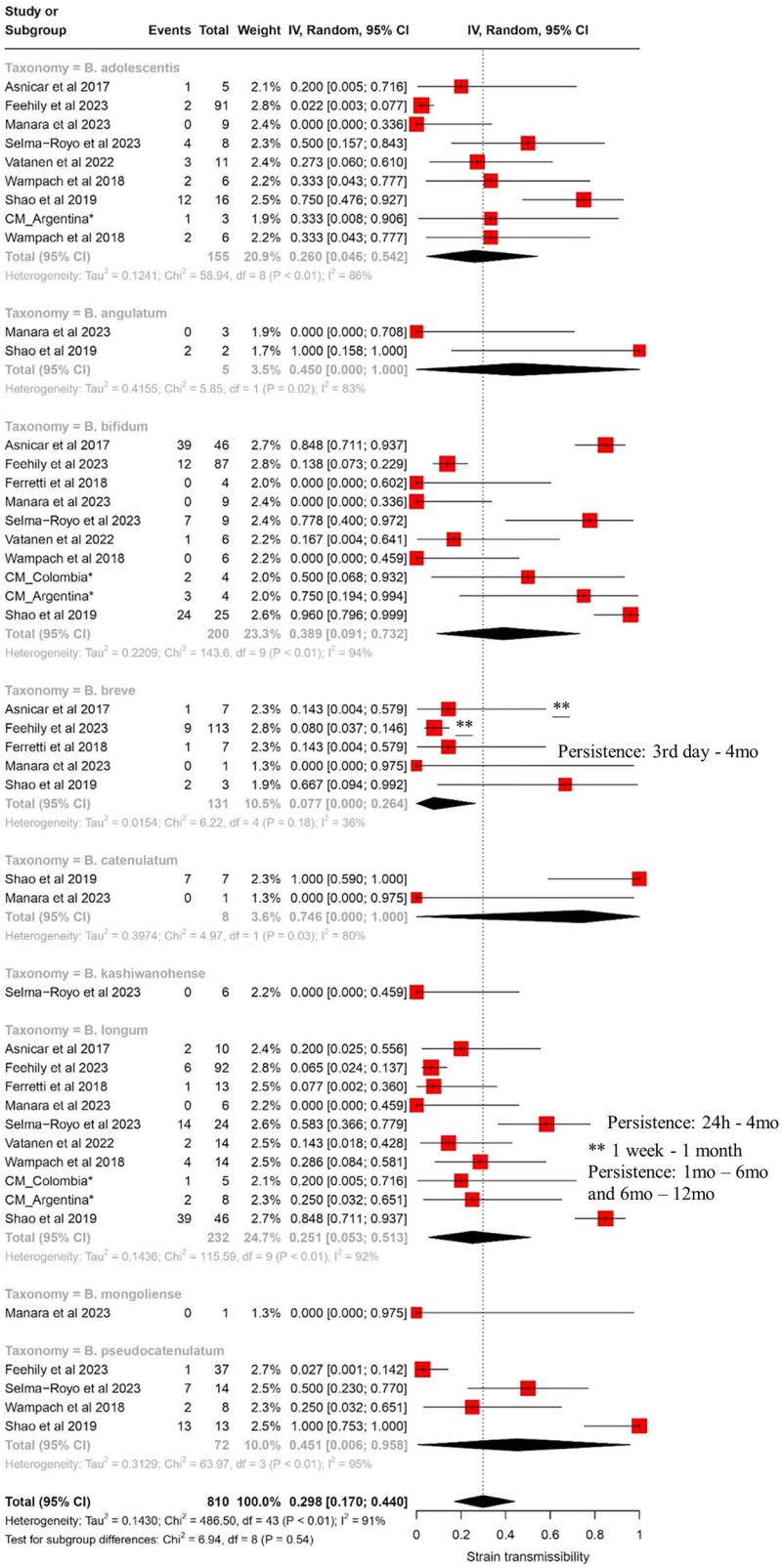

Fig. 3 | Transmissibility of *Bifidobacterium* species. Calculation based on the pooled number of mother-infant pairs with shared strains and the number of mother-infant pairs with shared species. The analysis includes studies that had conducted metagenomic sequencing using the computational tool StrainPhlAn. Red squares represent the point estimates of strain transmissibility for each study, reflecting the proportion of shared strains. Horizontal lines through the squares indicate the 95% Clopper-Pearson confidence intervals, illustrating the range within which the true proportion is expected to lie with 95% certainty. The diamond at the bottom represents the pooled effect size, summarizing the overall estimate across all studies, with its width depicting the combined confidence interval. *Data extracted from Valles-Colomer et al 2023. ** No strain retention observed over time.

B. catenulatum[97]. In contrast, Valles-Colomer et al.[39], collated data from several datasets observing high species transmissibility rates for *B. pseudocatenulatum* reaching more than 60%, *B. adolescentis* 82%, *B. longum* almost 60%, *B. bifidum* 93%, *B. angulatum*, 80%, and *B. catenulatum* 76%, approximately (Species transmissibility and observed persistence is shown in Fig. 3).

Discussion

In this systematic review we reported the occurrence of vertical transmission of *Bifidobacterium*, identifying studies that had explored which and how *Bifidobacterium* genus, species and strains are transmitted, mainly from HM or fecal samples, and from other maternal body sites with lower microbial abundances including oral cavity, skin, rectum, and vagina. Furthermore,

we run a random-effect meta-analysis (Fig. 3) demonstrating, that on average, *Bifidobacterium* strains identity explained about 30% (95% CI: 0.17; 0.44) of all shared *Bifidobacterium* species instances between mother to infant samples. Significant heterogeneity between species was observed ($I^2 = 91\%$; p-value < 0.01), with *B. longum* having the highest weight in the meta-analysis (24.7%). In addition, among the included species in the meta-analysis, and considering the high amount of observed shared species, *B. bifidum* showed the highest transmission rate at 96% in one study[14].

What are the main routes for mother-to-child *Bifidobacterium* transmission?

The main source for mother-to-child *Bifidobacterium* transmission is the maternal gut, as detailed in the metagenomic studies[13,15,19,87,98]. Nevertheless, this might have been inferred by oversampling of maternal stool samples, and the exact route(s) for transmission remain unknown[107]. Furthermore, although we hypothesized that delivery mode could play a critical impact, other early fecal-oral transmission routes could occur, and there are insufficient studies looking at other body sites. A number of studies[25,80,81,84,90,93,95,96,102,104] did not conduct cultivation or shotgun metagenomic sequencing, and transmission cannot be inferred by targeting single or variable regions, such as V3-V4[108] (Supplementary Table 6). Nevertheless, studies have identified bifidobacteria in maternal feces, HM and neonatal feces[81]. Metagenomic sequencing has shown transmission of strains from mother to infant feces, as shared strains have been identified in HM, and mother-infant fecal samples[13], however there is currently no convincing evidence supporting proposed theories such as the enteromammary pathway.

What are the main factors affecting the vertical transmission of *Bifidobacterium*?

Most of the included studies have not assessed this aspect; thus, this represents a gap in knowledge that further research will need to address. Some studies have suggested that factors such as membrane rupture during birth, country of birth, delivery mode, antibiotic treatments of the individual, and bifidobacterial status of infants influence strain transmissibility[13,14,97,98]. It is important to note that studies examining the impact of delivery methods often fail to specify the methodology for obtaining vaginal swabs[90], which may lead to the collection of superficial samples prone to fecal contamination. A number of studies identify higher *Bifidobacterium* species transmissibility in vaginally delivered infants[13,14,97,98,109], finding that the delivery mode significantly influenced the transmissibility of *Bifidobacterium* strains. Specifically, these studies observed a higher transmissibility rate in vaginal deliveries compared to cesarean sections. In addition, strains of *Bifidobacterium* subspecies that harbor genes coding for glycoside hydrolases or HMO degradation exhibit higher transmissibility and persistence. Shotgun metagenomic sequencing, as shown in studies[13,98], indicates that *B. longum* subsp. *longum* not only has enhanced capabilities for adapting to diverse dietary environments but also demonstrates higher transmissibility rates. These findings suggest that the genetic and enzymatic profiles, which vary across subspecies and strains, significantly influence their ability to establish and maintain populations within the host gut. Such genetic and enzymatic variability may explain the differences observed in the meta-analysis of *B. longum* subgroups, highlighting the impact of genetic diversity on ecological success.

There is indeed need for more research, where populations from low- and middle-income countries have scarcely studied vertical transmission of bifidobacteria, and we identified only two studies comparing populations by geolocation that have shown differences between Asian and European[105], and western and non-western populations[39,97]. These studies indicate different rates of transmission and response to the exposome, influenced by factors such as the mode of delivery, breastfeeding practices, and the use of antibiotics[104], and it also remains unclear how maternal diet and health status influence the bacterial transmission to the infant's microbiome. Furthermore, the environment also influences these processes, with notable variations in initial infant gut seeding and vertical transmission events between mother–infants pairs in industrialized and non-industrialized areas[110]. Nevertheless, this knowledge has been blurred by the bias of studies that only involve industrialized countries and urban areas. In addition, there is a gap to study the strain functionality via the combination of 'omics' sciences including transcriptomics of the vertically transmitted bifidobacteria as it appears to be more important than individual bacterial strains in influencing health outcomes, where a list of bifidobacteria genes are involved in its capabilities[111], and the expression of these genes matters in *Bifidobacterium* strains to be vertically transmitted and to colonize a host. To unveil this matter a comparative of bifidobacteria strains that have and that have not been vertically transmitted is required to explore the differences, such as the transcription of bifidobacterial exopolysaccharide biosynthesis[112], where certain *B. bifidum* strains lack exopolysaccharide gene clusters[113], which set them apart from other *Bifidobacterium* members.

What are the current technical limitations of identifying mother-to-infant transmission events with better confidence and increased resolution?

To analyze the transmission events, different methods have been used, ranging from PCR-based techniques[73–76] to cultivation, sequencing and sequencing-cultivation based approaches (Supplementary Table 6). The compelling evidence on mother–infant vertical transmission of *Bifidobacterium* during the first months of life have led to a conceptual dilemma, where the definitions for "vertical transmission" and "strain" have been highly heterogenous (Supplementary Table 7), leading to misconceptions. Consensus on the definition of "microbial strain" in the microbiome context has not yet been reached[39,114,115], and there are a number of studies that have conducted 16S rRNA gene sequencing to explore the phenomenon of "vertical transmission", also using OTU or ASV assignments which do not possess sufficient resolution to reach the necessary depth to establish strain transmission, however, both ASVs and OTUs have been found to generate biologically meaningful and comparable results[116]. Moreover, Feehily et al.[13] identified difficulties in strain definition, where a clade of *B. breve* strains was found with very high ANI values in a wide range of mother-infant pairs. Although shotgun metagenomic sequencing can provide the throughput needed to infer the transmission of many members of the microbiome at once[117], when planning studies, researchers need to consider sequencing depth, and length, and type of sample, among other factors. On the other hand, cultivation-based techniques allow the identification of some viable bacteria, thus, to study the phenomenon of initial seeding and persistence of the infant gut bacteria[15]. Another source of variability in the meta-analysis is the sequencing length, depth and the sequencing platforms used in different studies, as shown in Supplementary Table S6. These differences range from 100 bps[103] to 300 bps[13], sequencing depths from 0.5 million reads[103] per samples to 517 billion reads per sample[39], and various technologies such as the Illumina NextSeq500[90], Illumina HiSeq 2000[25], Illumina HiSeq 2500[18], and Single-molecule real-time sequencing by PacBio[13]. Such variability may indeed contribute to the observed heterogeneity in the individual strain transmissibility events. For instance, studies with higher sequencing depths[18,39,97,98] have shown higher strain transmissibility rates *B. adolescentis*, compared to those with lower reads[103]. However, for other species such as *B. longum*, this was not observed.

We need more longitudinal studies that combine metagenomics, the study of genetic material recovered directly from samples, with cultivation-based techniques methods that involve growing microorganisms in laboratory culture and whole genome sequencing. These studies are necessary to analyze not only vertical transmission of strains with low RA but also the persistence of viable bacteria[13], and of genomic signatures that may facilitate vertical transfer and colonization. Additionally, to investigate in an integrative manner the routes and mechanisms of bifidobacteria transmission, particularly from HM or fecal samples to the infant gut, studies will require a combination of in vitro experiments, animal models, and molecular biology techniques. This may involve co-culture systems using human-derived cell lines to simulate interactions between bifidobacteria strains and host epithelial cells, as well as Transwell assays[118] to

assess bacterial translocation across epithelial barriers. To mimic human microbial colonization patterns and investigate transmission dynamics in vivo, animal models such as gnotobiotic mice or germ-free animals could be employed. Furthermore, to delineate colonization patterns, fluorescence labeling combined with microscopy techniques of bifidobacteria in host tissues may aid, along with other molecular biological techniques such as whole-genome sequencing which will allow for the quantification and identification of shared strains.

Moreover, bioinformatic methods for detecting strain transmission have primarily relied on tools such as StrainPhlAn, with other utilized tools including inStrain[13] and ConStrains[90]. However, when analyzing metagenomic samples, these tools often exhibit discrepancies. These inconsistencies manifest in varying ANI calculations among genomes with known in silico mutations, deviations from the ideal 100% ANI in genomic comparisons within defined microbial communities, and differences in stringency for identifying identical microbial strains[50]. Such nuances highlight the need for further refinement and standardization in bioinformatic workflows to accurately assess strain transmission.

Strength and limitations

This review has followed the PRISMA and PRESS guidelines to ensure quality and to explore the complex concept of transmission within a systematic approach, with a particular focus on *Bifidobacterium* members, while acknowledging the challenges posed by evolving technologies and inconsistent terminology. It conducts an evaluation of the risk of bias in included studies (Supplementary Tables 7 and 8), revealing methodological shortcomings in many cases, such as unreliable measurement of bacterial strains thus of the phenomenon of vertical transmission, small sample sizes, and limitations inherent in cross-sectional study designs. Additionally, the review highlights the potential impact of low RAs of *Bifidobacterium* in HM samples on study outcomes, emphasizing the necessity of metagenomics-based sequencing techniques, and culture-based approaches.

Conclusion

This systematic review has identified the literature on vertical transmission of *Bifidobacterium* and their relevance on seeding the infant gut microbiome during the first months after birth. While there is considerable evidence for potential transmission of *Bifidobacterium* species from mothers to infants, there are only limited data to support the transmission of specific *Bifidobacterium* strains. The main routes studied for mother-to-child *Bifidobacterium* transmission identify *B. longum* species with the highest weight in the meta-analysis, while *B. bifidum* strains had the highest transmissibility rates from feces to the infant gut. However, the characterization of the *B. bifidum* strains, as well as their differentiation from the strains that were not transferred, including the transmission paths, remains unknown. The current metagenomic sequencing technologies which have shifted the concept of vertical transmission, allow high-throughput results hence a higher strain resolution and technological capacity to keep track of strains. Future studies applying: (1) metagenomic sequencing techniques combined or not with cultivation of bacteria; (2) more time points; and (3) different body sites will allow a greater understanding of *Bifidobacterium* strains transmission, persistence and pathways and their impact in infant gut microbiome development.

Data availability

All metadata extracted from the studies that had performed metagenomic sequencing and that was used as an input for the proportional meta-analysis is stored in the GitHub repository at https://github.com/EFV1995/VT_proportional_MA. All R code necessary to replicate the proportional metanalysis and to create the world map is stored in the GitHub repository at https://github.com/EFV1995/VT_proportional_MA.

Code availability

All metadata extracted from the studies that had performed metagenomic sequencing and that was used as an input for the proportional meta-analysis is stored in the GitHub repository at https://github.com/EFV1995/VT_proportional_MA. All R code necessary to replicate the proportional metanalysis and to create the world map is stored in the GitHub repository at https://github.com/EFV1995/VT_proportional_MA.

List of abbreviations

RA	Relative Abundances
HMO	Human milk oligosaccharides
HM	Human milk
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
NGS	Next-generation sequencing
PRESS	Peer Review of Electronic Search Strategies
CI	Confidence Interval
JBI	Joanna Briggs Institute
RAPD	Random Amplified Polymorphic DNA
AFLPs	Amplified Fragment Length Polymorphism
MLST	Multilocus Sequence Typing
PCR	Polymerase Chain Reaction
SNV	Single Nucleotide Variant
ANI	Average Nucleotide Identity

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Author contributions

E.F.V., M.C.C., and M.E.T.: conceptualization, supervision, and project administration. E.F.V., M.C.C., and M.E.T.: methodology, validation, investigation, writing—original draft preparation, and resources. E.F.V.: software, formal analysis, data curation, and visualization. E.F.V., M.E.T., M.C.C., M.V.C., N.S., L.J.H., O.K., D.S., and M.G. contributed to writing—review and editing, and read and agreed to the final version of the manuscript.

Competing interests

E.F.V., M.E.T., M.G., D.V.S., L.J.H., and M.V.C. declare no financial or non-financial competing interests. O.K. serves as Editors-in-Chief of this journal and had no role in the peer-review or decision to publish this manuscript. O.K. declares no financial competing interests. N.S. serves as Associate Editor of this journal and had no role in the peer-review or decision to publish this manuscript. N.S. declares no financial competing interests. M.C.C. serves as co-editor special issue "Women and their microbes" of this journal and had no role in the peer-review or decision to publish this manuscript. M.C.C. declares no financial competing interests.

Additional information

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