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Влияние способа родоразрешения и типа вскармливания на микробиом кишечника детей в постнатальном периоде

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АННОТАЦИЯ

Обоснование. Рост частоты кесарева сечения и искусственного вскармливания формирует предрасположенность к аллергическим заболеваниям, ожирению и сахарному диабету. Один из патогенетических механизмов этих процессов включает в себя изменения микробиома кишечника детей.

Цель — изучить влияние способа родоразрешения и типа вскармливания на состав микробиома кишечника детей.

Материалы и методы. В исследование включены 103 ребенка в возрасте 4–6 нед. жизни (1-я группа — 39 детей на грудном вскармливании, рожденных через естественные родовые пути; 2-я группа — 10 детей на искусственном вскармливании, рожденных через естественные родовые пути; 3-я группа — 31 ребенок на грудном вскармливании, рожденный путем кесарева сечения; 4-я группа — 23 младенца на искусственном вскармливании, рожденных путем кесарева сечения). Каждому ребенку производили забор кала для секвенирования генов 16S рибосомной РНК.

Результаты. Выявлены статистически значимые отличия по относительному содержанию бактерий рода *Akkermansia* [34,07 (29,29–38,85) % в 4-й группе и 0,01 (0,01–0,02) % в 1-й группе; $p = 0,011$], рода *Bifidobacterium* [30,68 (21,65–39,41) % в 1-й группе и 17,08 (9,86–21,68) % в 4-й группе ($p = 0,002$); 31,46 (24,30–52,97) % в 3-й группе и 17,08 (9,86–21,68) % в 4-й группе ($p = 0,001$)], а также рода *Enterococcus* [4,69 (1,01–8,59) % в 3-й группе и 0,58 (0,12–1,87) % в 1-й группе ($p = 0,003$); 4,29 (2,07–6,96) % в 4-й группе и 0,58 (0,12–1,87) % в 1-й группе ($p = 0,001$)]. Коэффициент корреляционной адаптометрии был максимальным для в группах, находящихся на грудном вскармливании. Анализ заболеваемости детей на первом году жизни выявил статистически значимые отличия по частоте встречаемости острой респираторной вирусной инфекции между детьми 1-й и 4-й групп (17,9 и 78,3 % соответственно; $p = 0,0064$) и 3-й и 4-й групп (32,2 и 78,3 % соответственно; $p = 0,018$).

Заключение. Относительное содержание бактерий рода *Bifidobacterium* зависит от типа вскармливания в большей степени, чем от способа родоразрешения. Способ родоразрешения при этом влияет на частоту выявления условно-патогенных бактерий рода *Enterococcus*. Корреляционный анализ продемонстрировал роль грудного вскармливания как одного из механизмов «обучения» и созревания иммунной системы ребенка.

Ключевые слова: микробиом кишечника; неонатальный период; естественные роды; кесарево сечение; грудное вскармливание; искусственное вскармливание.

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Impact of the method of delivery and feeding practice on the gut microbiome of infants in the postnatal period

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ABSTRACT

BACKGROUND: The increasing frequency of cesarean sections and artificial feeding creates a predisposition to allergic diseases, obesity, and diabetes mellitus. Pathogenesis of these involves changes in the gut microbiome of infants.

AIM: The aim of this study was to evaluate the impact of the method of delivery and feeding practice on the gut microbiome of infants.

MATERIALS AND METHODS: This study included 103 infants aged 4-6 weeks (group 1: 39 infants born vaginally and breastfed; group 2: 10 infants born vaginally and formula-fed; group 3: 31 infants born by caesarean section and breastfed; group 4: 23 infants born by caesarean section and formula-fed), each of whom had stool collected for 16S ribosomal RNA gene sequencing.

RESULTS: We found differences in the relative abundance of *Akkermansia* spp. [34.07 (29.29–38.85)% in group 4 and 0.01 (0.01–0.02)% in group 1; $p = 0.011$], *Bifidobacterium* spp. [30.68 (21.65–39.41)% in group 1 and 17.08 (9.86–21.68)% in group 4, ($p = 0.002$); 31.46 (24,30–52.97)% in group 3 and 17.08 (9.86–21.68)% in group 4 ($p = 0.001$)], and *Enterococcus* spp. [4.69 (1.01–8.59)% in group 3 and 0.58 (0.12–1.87)% in group 1 ($p = 0.003$); 4.29 (2.07–6.96)% in group 4 and 0.58 (0.12–1.87)% in group 1 ($p = 0.001$)]. The coefficient of correlation adaptometry was maximum for groups of infants who were breastfed. Analysis of the morbidity of infants in the first year of life revealed differences in the incidence of acute respiratory viral infections between infants in groups 1 and 4 (17.9 and 78.3%, respectively; $p = 0.0064$), as well as groups 3 and 4 (32.2 and 78.3%, respectively; $p = 0.018$).

CONCLUSIONS: The relative abundance of *Bifidobacterium* spp. depends on feeding practice to a greater extent than on the method of delivery. The method of delivery affects the relative abundance of opportunistic bacteria such as *Enterococcus* spp. Correlation analysis demonstrated the role of breastfeeding as a mechanism for "learning" and maturing the immune system of children.

Keywords: gut microbiome; neonatal period; natural childbirth; cesarean section; breastfeeding; artificial feeding.

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BACKGROUND

In this era of rapid development of medical technology, the birth process is becoming less and less physiological because of availability of numerous devices and medications. On the one hand, this decreases maternal and infant mortality, but alternatively, it inevitably increases the number of cesarean sections and, consequently, there need for artificial feeding of the infant [1–3]. Obstetricians are committed to ensuring that no cesarean section is performed without an indication, and neonatologists promote breastfeeding. However, there is a growing concern about the potential effects of operative delivery and artificial feeding on infants, especially on the composition of their gut microbiota [4, 5].

One of the most important differences between cesarean and vaginal delivery is the initial microbial exposure of the newborn [6]. During vaginal delivery, the neonate crosses the birth canal and encounters a diverse set of maternal microorganisms that provide the initial inoculation of the neonatal gut [7–9]. Maternal microbiota, including lactobacilli from the vagina and bifidobacteria from the gut, provide the basis for the establishment of a healthy microbial community in the newborn [10]. However, children born by cesarean section are exposed to environmental microorganisms prevalent under the conditions in medical institutions and on the mother's skin [11, 12].

The type of feeding following birth is regarded as more important than the mode of delivery. There are differences between the gut microbiota of infants exclusively breastfed and the formula-fed ones. The oligosaccharides present in breast milk are the primary components contributing to the composition of the gut microbiome of the infant. These oligosaccharides are complex glycans that are resistant to digestion and perform a range of functions in the distal part of the child's gastrointestinal tract [13]. There are more than 200 unique oligosaccharides, and maternal genetics influence the specific composition of oligosaccharides in breast milk [13]. Oligosaccharides are a prebiotic substrate for bacteria of the genus *Bifidobacterium* and also act as a trap receptor for pathogens [13]. The addition of oligosaccharides and other prebiotics to infant formulas over the past decade has probably led to some convergence of the microbiota of formula-fed infants and breastfed ones. Apart from oligosaccharides, infants receive a constant source of beneficial bacteria directly from breast milk itself. These bacteria include *Staphylococcus, Streptococcus, Bifidobacterium, Lactobacillus, Clostridium*, and *Veillonella*, which are all resident genera of bacteria occurring in the gut microbiome of the infant in the first few months of life. Additionally, the breast milk contains secretory immunoglobulins that support the immune system in the gut lumen of the newborn [14–16].

The functional activity of the gut microbiome of formula-fed infants is similar to that of adults [17]. The gut microbiome of these infants contains a high proportion of genes associated with bile acid and methane synthesis, and genes responsible for carbohydrate and lipid metabolism and fatty acid biosynthesis are less represented [18]. The microbiome of breastfed infants contains more genes involved in vitamin and cofactor metabolism, free radical detoxification, and glutathione metabolism than formula-fed infants [18, 19].

The composition of the intestinal microbiota of an infant in the first months of life has a lasting impact on the formation of the trajectory of his/her health. Sometimes, this impact predisposes the child to metabolic disorders (obesity, diabetes mellitus, and insulin resistance) and disorders of the immune system (allergic reactions, atopic dermatitis, and bronchial asthma) [20, 21].

The aim of this study was to examine the impact of delivery method and feeding type on the composition of the gut microbiome in infants aged 4–6 weeks.

MATERIALS AND METHODS

The study included 103 infants aged 4–6 weeks of age, examined at the Clinic of Professor Bushtyreva LLC according to the Order of the Ministry of Health of Russia dated August 10, 2017, No. 514n, "On the Order of Preventive Medical Examinations of Minors," from 2021 to 2022. The infants were fell into four distinct groups. Group 1 consisted of 39 infants who were delivered naturally and breastfed. Group 2 included 10 infants who were delivered naturally and formula-fed. Group 3 comprised 31 infants who were delivered by cesarean section and breastfed. Group 4 consisted of 23 infants who were delivered by cesarean section and formula-fed. Fecal samples were collected from each infant at 4–6 weeks postnatal for 16S ribosomal RNA gene sequencing. Inclusion criteria: healthy children aged 4–6 weeks, born as a result of full-term pregnancy, discharged from the maternity hospital on the 2–3rd day after birth.

Non-inclusion criteria:

- preterm births;
- children born to mothers with pregnancies complicated by pre-eclampsia, fetoplacental insufficiency, intrauterine growth restriction, severe extragenital and obstetric pathology;
- children who have been admitted to the neonatal intensive care unit following delivery, and
- children who are fed using a combination of different feeding methods.

The exclusion criteria included a refusal to participate in the study, the presence of acute respiratory viral or intestinal infection in the infant during the study period, and

the administration of any biological drugs known to affect the gut microbiota (pro-, pre-, syn-, sim-, and metabiotics) by the infant.

Each mother, acting as the infant's legal representative, provided informed consent for the infant to participate in the study. The study was approved by the local ethics committee of the Clinic of Professor Bushtyreva LLC.

Sample collection

Each fecal sample was collected with a dry sterile probe and placed in a tube containing a specialized sterile transport medium. The fecal matter was retrieved from the diaper on the day of the study after the infant's natural defecation, without the use of laxatives or enemas.

The fecal sample was placed in an Eppendorf tube containing a specialized transport medium with mucolytic properties (Central Research Institute of Epidemiology, Rospotrebnadzor, Russia). The material was stored at 4°C until DNA isolation was performed.

Total DNA was isolated from the fecal samples after homogenization in a lysing solution. Homogenization, enhanced with the use of beads, was followed by DNA extraction via the sorbent column method (Qiagen, USA), according to the manufacturer's instructions.

The libraries for 16S ribosomal RNA sequencing were prepared according to the Illumina protocol for preparing 16S metagenomic libraries for sequencing (Part #15044223 Rev. B). The initial amplification stage used the recommended primers for the V3–V4 region of the 16S ribosomal RNA gene, which include adapter sequences at the 5' end. In the initial round of amplification, 5 ng of genomic DNA was used, and 25 cycles of polymerase chain reaction were performed with the use of KAPA HiFi HotStart ReadyMix (2×) (Roche Diagnostics, Switzerland). Amplification products were purified on magnetic particles. For each sample, 10 ng of DNA was extracted and subjected to eight cycles of index polymerase chain reaction using KAPA HiFi HotStart ReadyMix and Nextera XT Index Kit (Illumina, USA). The prepared libraries were purified on magnetic particles, before they were pooled in an equimolar ratio, and sequenced on the MiSeq platform (Illumina, USA) using MiSeq Reagent Kits v2 (Illumina, USA) in paired-end mode with forward and reverse reads of 250 nucleotides each.

Data analysis

Bioinformatics processing of sequencing results was performed using an in-house bioinformatics pipeline implemented in R 3.6 and Python 3. In the initial processing phase, primer sequences were excised from paired-end reads, and reads lacking primer sequences were discarded. Subsequently, reads with inadequate quality (Phred score less than 10 points) and those of insufficient length (less than 200 bp) were excluded, and the remaining data underwent processing using the DADA2 pipeline to identify accurate sequence variants [22]. Thereafter, forward and reverse reads were concatenated, before the resulting sequences were subjected to taxonomic classification according to the Naive Bayes method [23] using the SILVA 138 reference database [24]. Bacteria were identified to species level using the exact match algorithm in DADA2 from the SILVA 138 sequences that had been appropriately pre-processed using custom scripts.

Statistical analysis

Where necessary, data were summarized using median and interquartile range values. The statistical significance of the results was calculated at a confidence level of 95%. To test for significant differences among the groups, a nonparametric Kruskal–Wallis test for independent samples was used. The nonparametric Spearman correlation coefficient was used to test for significant correlation between groups.

The decision trees algorithm (or classification trees) was used for statistical data processing and ROC analysis was used to provide supplementary tools for the analysis and verification of constructed models.

Preliminary indications were analyzed using the software applications Statistica 14.0.0.0.15, Microsoft Excel 2019, and IBM SPSS 27.0.0.0.1. The Ranfor (random forest) and Decision Tree (decision trees) algorithms with cross-validation were used to identify the critical rules using the SPSS package. To reduce the dimensionality of the initial parameters, the Predictor Screening module of the Statistica package was used.

The GVedit 2.39 package was used for the visualization of nonparametric correlations.

RESULTS

The intestinal microbiome of infants was subjected to taxonomic analysis at the generic level. A total of 81 microbial genera were identified. Out of these, 21 genera were identified using the decision trees method, to maximize the differences between the four groups (Table 1): *Escherichia*/*Shigella*, *Bifidobacterium*, *Streptococcus*, *Bacteroides*, *Enterococcus*, *Veillonella*, *Lactobacillus*, *Clostridium*_sensu_stricto_1, *Klebsiella*, *Gemella*, *Atopobium*, *Actinomyces*, *Parabacteroides*, *Akkermansia*, *Prevotella*, *Bilophila*, *Haemophilus*, *Blautia*, *Floricoccus*, *Faecalibacterium*, and *Collinsella*.

The relative abundance of these genera in the gut microbiome of infants from all four groups are shown in Table 2.

A comparative analysis of the bacterial genera occurring in the gut microbiome of Group 4 infants revealed the following. The mean relative abundance of the genus *Akkermansia* in the group of infants born via surgical delivery and formula-fed was significantly higher than in infants exclusively breastfed and those born via natural delivery (34.07%, 95% CI:

29.29–38.85 vs. 0.01%, 95% CI: 0.01–0.02, respectively; $p = 0.011$).

The mean relative abundance of the genus *Bifidobacterium* in the intestine exhibited a statistically significant difference between infants in groups 1 and 4, as well as between those in groups 3 and 4. In the cohort of breastfed infants born via natural delivery, these microorganisms constituted 30.68% (95% CI: 21.65–39.41) of the microbiome, which was statistically significantly higher than in group 4 [17.08% (95% CI: 9.86–21.68)], in which the relative abundance of *Bifidobacterium* was minimal ($p_{1-4} = 0.002$). The mean relative abundance of *Bifidobacterium* was significantly higher in Group 3 (infants born by cesarean section and breastfed) than in Group 4 ($p_{3-4} = 0.001$). The mean relative abundance was 31.46% (24.30–52.97) in Group 3 and 17.08% (9.86–21.68) in Group 4. Therefore, the mean relative abundance of *Bifidobacterium* was higher in the groups of breastfed infants, regardless of the mode of delivery, than in the groups of formula-fed infants.

Remarkably, the mean relative abundance of the genus *Enterococcus* in the gut of infants exhibited a statistically significant difference between groups 1 and 3 ($p = 0.003$) and between groups 1 and 4 ($p = 0.001$). The lowest relative abundance of bacteria belonging to this genus was observed in the group of breastfed infants who were born naturally [0.58 (0.12–1.87) %]. The highest mean relative abundance of this genus was record in the group of formula-fed children born via cesarean section, with a value of 4.29% (2.07–6.96%).

The data regarding the relative abundance of *Akkermansia, Bifidobacterium*, and *Enterococcus* as components of the gut microbiota in infants across the four groups are presented in Figure 1.

A correlation analysis was conducted to ascertain the extent of integration between the examined elements of the intestinal microbiome in infants. To facilitate intergroup comparison, the correlation adaptometry method was used to summarize the correlation weights within the groups under consideration.

The correlograms are presented in Figures 2, 3, 4, and 5 for groups 1, 2, 3, and 4, respectively. All correlations depicted in the figures were statistically significant ($p \leqslant 0.05$).

The correlation matrices in group 1 of breastfed children born by natural childbirth (Fig. 2) indicate that there was many positive and negative relationships between bacterial genera (ρ = 0.5). The genus *Bifidobacterium* only showed positive relationships with bacteria of the genera *Akkermansia* (strong relationship 0.96) and *Lactobacillus* (moderate relationship 0.5). *Enterococcus* showed a strong positive association with *Actinomyces* (0.9), a moderate positive association with *Veilonella* (0.5), and a negative strong association with *Gemella* (0.7). Additionally, the genus *Gemella* also showed a positive strong association with the genus *Haemophillus* (0.9). *Parabacteroides* showed a negative strong association with *Veilonella* (0.8) and *Escherichia* (0.8).

Table 1. Bacteria genera whose relative abundance had the greatest impact on differences between the four study groups

Таблица 1. Роды микроорганизмов, относительная представленность которых максимально влияла на различия между группами

Microbial genus	Criterion χ^2	*p*
Escherichia/Shigella	36.87988	0.000028
Bifidobacterium	29.41835	0.000051
Streptococcus	31.68864	0.000225
Bacteroides	21.95520	0.001234
Enterococcus	15.79585	0.001249
Veillonella	25.81723	0.002188
Lactobacillus	25.61182	0.002364
*Clostridium*_sensu_stricto_1	17.98182	0.006278
Klebsiella	35.31667	0.008621
Gemella	29.62479	0.013349
Atopobium	24.00000	0.020341
Actinomyces	9.55096	0.022795
Parabacteroides	27.70167	0.023513
Akkermansia	9.46939	0.023659
Prevotella	23.40000	0.024516
Bilophila	14.00000	0.029636
Haemophilus	22.59917	0.031328
Blautia	26.54167	0.032700
Floricoccus	8.31111	0.040001
Faecalibacterium	29.54340	0.042129
Collinsella	21.24364	0.046925

The value of the correlation coefficient of adaptometry for group 1 was 6.39, which was the maximum value among all four groups.

The analysis of correlation matrices in the group of infants born by natural birth and formula-fed (Fig. 3) showed a significantly fewer correlations than in group 1. A strong negative correlation was recorded between the genera *Streptococcus* and *Bacteroides* (0.9). Additionally, a strong positive relationship was observed between the genera *Streptococcus* and *Clostridium*_sensu_stricto_1 (0.8). The correlation coefficient for group 2 was 1.72.

Further analysis was conducted on the cohort of children who were delivered by cesarean section. The correlation matrices of the group of children who were delivered cesarean section and breastfed (Fig. 4) indicate a considerable number of positive relationships. The genera *Escherichia/Shigella* exhibited robust positive relationships with bacteria of the genera *Actinomyces* (0.9) and *Haemophilus* (0.7). The genus *Streptococcus* exhibited

Table 2. Relative abundance of bacteria genera for which the differences between study groups were the greatest

Таблица 2. Относительная представленность родов микроорганизмов с наибольшими различиями между группами

Microbial genus	Group 1 NC and BF (n = 39)	Group 2 NC and AF (n = 10)	Group 3 CS and BF (n = 31)	Group 4 CS and AF (n = 23)	p
Actinomyces	0.08 (0.04–0.13)	1.21 (0.33–2.09)	0.32 (0.09–4.72)	0.29 (0.10–0.78)	p = 0.126
Akkermansia	**0.01 (0.01–0.02)**	**1.66 (0.01–4.79)**	**0.12 (0.03–30.83)**	**34.07 (29.29–38.85)**	p_{1-4} = **0.011**
Atopobium	0.94 (0.86–1.02)	0.12 (0.11–0.13)	0.05 (0.04–0.07)	0.12 (0.03–0.22)	p = 0.198
Bacteroides	29.52 (9.95–37.09)	20.98 (0.03–27.81)	9.51 (0.11–28.77)	0.06 (0.03–0.07)	p = 0.125
Bifidobacterium	**30.68 (21.65–39.41)**	**21.00 (10.46–31.23)**	**31.46 (24.30–52.97)**	**17.08 (9.86–21.68)**	p_{1-4} = **0.002** p_{3-4} = **0.001**
Bilophila	0.34 (0.16–0.63)	1.54 (1.54–1.54)	1.47 (1.47–1.47)	0	p = 0.145
Blautia	0.80 (0.14–1.85)	2.52 (1.86–3.19)	0.92 (0.20–1.12)	3.73 (1.94–8.86)	p = 0.129
Clostridium_sensu_stricto_1	3.84 (0.09–23.52)	4.95 (0.95–11.09)	9.15 (1.71–17.43)	8.20 (5.63–10.56)	p = 0.854
Collinsella	6.32 (3.35–14.58)	2.54 (0.07–4.37)	3.38 (2.71–4.21)	7.53 (3.99–23.37)	p = 0.186
Enterococcus	**0.58 (0.12–1.87)**	**1.06 (0.11–2.35)**	**4.69 (1.01–8.59)**	**4.29 (2.07–6.96)**	p_{1-3} = **0.003** p_{1-4} = **0.001**
Escherichia/Shigella	6.89 (2.32–25.25)	19.19 (6.81–22.17)	17.68 (4.49–23.02)	14.40 (10.87–34.08)	p = 0.289
Faecalibacterium	0.04 (0.03–0.05)	0.06 (0.02–7.95)	0.08 (0.05–13.10)	0.04 (0.01–0.05)	p = 0.112
Floricoccus	0.09 (0.09–0.39)	0.30 (0.20–0.39)	0.06 (0.00–0.08)	0.03 (0.00–0.11)	p = 0.204
Gemella	0.04 (0.02–0.05)	0.04 (0.03–0.04)	0.08 (0.08–0.17)	0.36 (0.36–0.36)	p = 0.187
Haemophilus	0.26 (0.25–2.73)	1.71 (1.71–1.71)	1.05 (0.11–3.11)	5.50 (2.29–12.20)	p = 0.162
Klebsiella	11.81 (1.23–17.14)	18.50 (6.34–30.32)	4.96 (1.77–17.72)	7.16 (3.02–15.06)	p = 0.778
Lactobacillus	1.91 (0.08–4.18)	1.21 (0.95–2.27)	4.67 (2.29–13.41)	3.21 (1.39–9.17)	p = 0.088
Parabacteroides	1.78 (0.54–8.54)	0.53 (0.47–1.58)	4.50 (3.04–10.16)	1.14 (0.00–2.29)	p = 0.351
Prevotella	0.03 (0.02–22.25)	0.06 (0.01–1.96)	9.71 (0.16–19.27)	0.07 (0.07–0.07)	p = 0.513
Streptococcus	3.29 (1.90–13.7)	9.35 (1.79–25.1)	5.58 (1.92–8.90)	12.8 (5.94–24.9)	p = 0.082
Veillonella	2.43 (0.49–10.56)	24.24 (0.48–26.38)	1.22 (0.53–5.36)	12.45 (1.75–22.05)	p = 0.059

Note. Data are presented as median and interquartile range of percentages. NC, natural childbirth; CS, cesarean section; BF, breastfeeding; AF, artificial feeding.

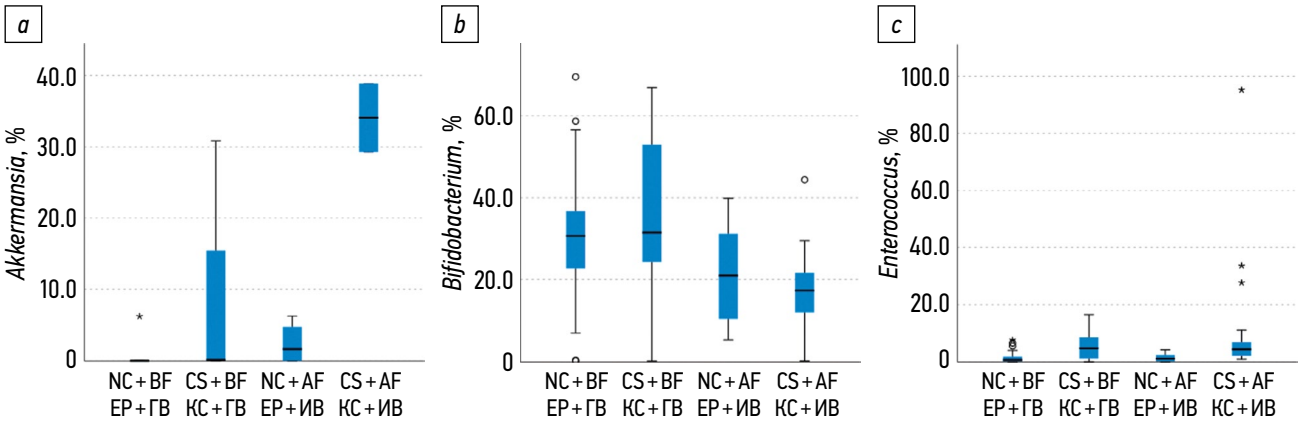

Fig. 1. Box plots of the relative abundance of *Akkermansia* (*a*), *Bifidobacterium* (*b*), and *Enterococcus* (*c*) bacteria in the gut microbiota of children in the four study groups. The bold line inside denotes the median value, the lower and upper parts of the box are the 25th and 75th percentiles, respectively, and "whiskers" denote the minimum and maximum values that are not extreme. * Denotes outliers; ° denotes extreme values; NC, natural childbirth; CS, caesarean section; BF, breastfeeding; AF, artificial feeding

Рис. 1. Диаграммы размаха относительной представленности бактерий родов *Akkermansia* (*a*), *Bifidobacterium* (*b*) и *Enterococcus* (*c*) в составе микробиоты кишечника детей четырех групп. Жирная линия отражает медиану показателя, нижняя и верхняя стороны прямоугольника — 25-й и 75-й процентили соответственно, «усы» — минимальное и максимальное значения, не являющиеся экстремальными. * Выбросы показателей; ° экстремумы показателей; ЕР — естественные роды; КС — кесарево сечение; ГВ — грудное вскармливание; ИВ — искусственное вскармливание

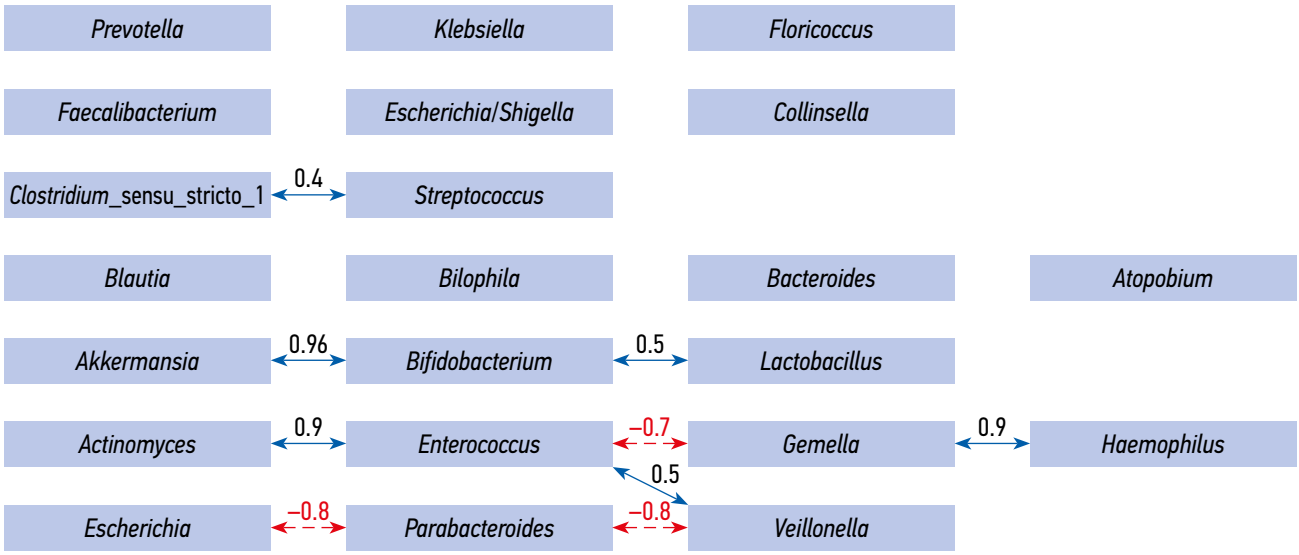

Fig. 2. Relationships between bacteria genera identified by 16S ribosomal RNA sequencing in the gut microbiome of the group 1 infants born vaginally and breastfed. Solid and dotted arrows indicate positive and negative relationships, respectively

Рис. 2. Коррелограмма связей между родами бактерий, выявленных в результате секвенирования 16S рибосомной РНК, в составе микробиома кишечника детей 1-й группы, рожденных через естественные родовые пути и находившихся на грудном вскармливании. Сплошными стрелками обозначены положительные связи, пунктирными — отрицательные

a medium-strength positive association with the genus *Haemophilus* (0.6) and a strong positive association with the genus *Collinsella* genus (0.9). *Clostridium* sensu stricto 1 had a negative correlation of moderate strength with *Lactobacillus* (0.6) and a strong positive correlation with *Klebsiella* (0.9). The correlation adaptometry coefficient for group 3 was 4.74.

The analysis of the correlation matrices in the group of born by cesarean section and artificially fed infants (Fig. 5) showed a few correlations. A strong positive relationship was recorded between bacteria of the genera *Clostridium*_sensu_strictu_1 and *Escherichia/Schigella* (0.8), and a strong positive relationship was recorded between the genera *Streptococcus* and *Klebsiella* (0.7). The coefficient

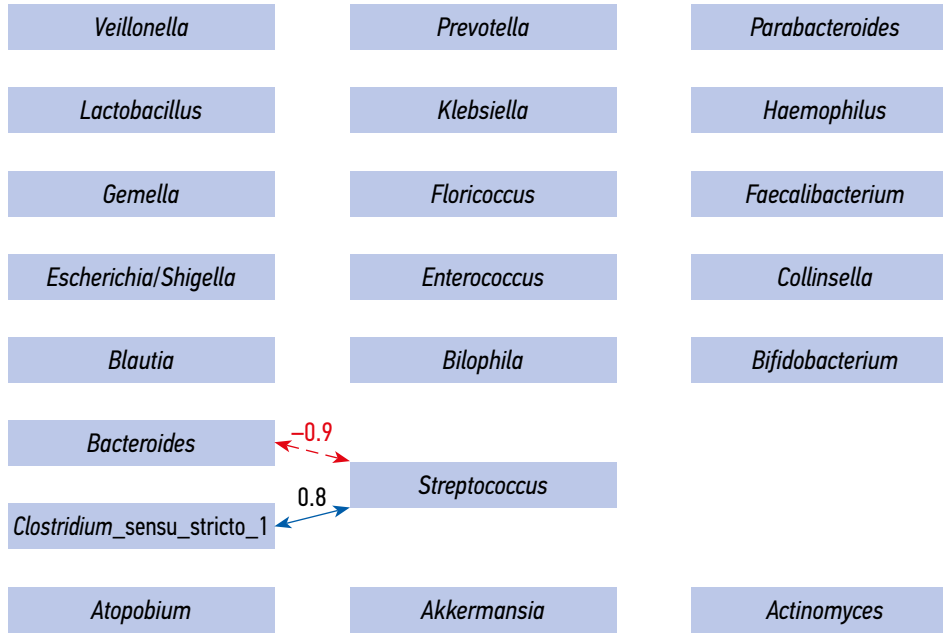

Fig. 3. Relationships between bacteria genera identified by 16S ribosomal RNA sequencing in the gut microbiome of the group 2 infants born vaginally and formula-fed. Solid and dotted arrows indicate positive and negative relationships, respectively

Рис. 3. Коррелограмма связей между родами бактерий, выявленных в результате секвенирования 16S рибосомной РНК, в составе микробиома кишечника детей 2-й группы, рожденных через естественные родовые пути и находившихся на искусственном вскармливании. Сплошной стрелкой обозначена положительная связь, пунктирной — отрицательная

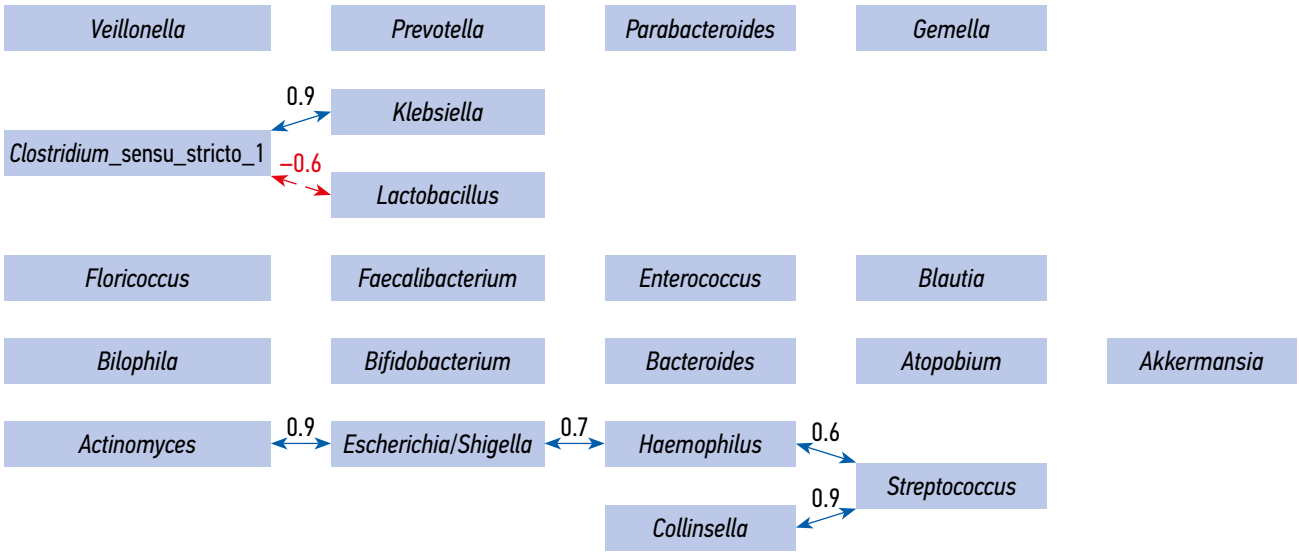

Fig. 4. Relationships between bacteria genera identified by 16S ribosomal RNA sequencing in the gut microbiome of the group 3 infants born by cesarean section and breastfed. Solid and dotted arrows indicate positive and negative relationships, respectively

Рис. 4. Коррелограмма связей между родами бактерий, выявленных в результате секвенирования 16S рибосомной РНК, в составе микробиома кишечника детей 3-й группы, рожденных путем операции кесарева сечения и находившихся на грудном вскармливании. Сплошными стрелками обозначены положительные связи, пунктирной — отрицательная

of correlation adaptometry for group 4 was minimal at 1.48.

All infants enrolled in the study continued to be monitored by the clinic's pediatricians. Before they reached one year of life,, the frequency of visits of the infans' parents to the pediatricians for specific illnesses was retrospectively assessed (Table 3).

The infant groups did not differ in the frequency of allergic diseases and episodes of acute intestinal infections in the first year of life. However, statistically significant differences were found in the incidence of acute respiratory viral infections (ARVI) between infants in groups 1 and 4. The incidence of ARVI was significantly lower in the group of children born naturally and breastfed than in the group of

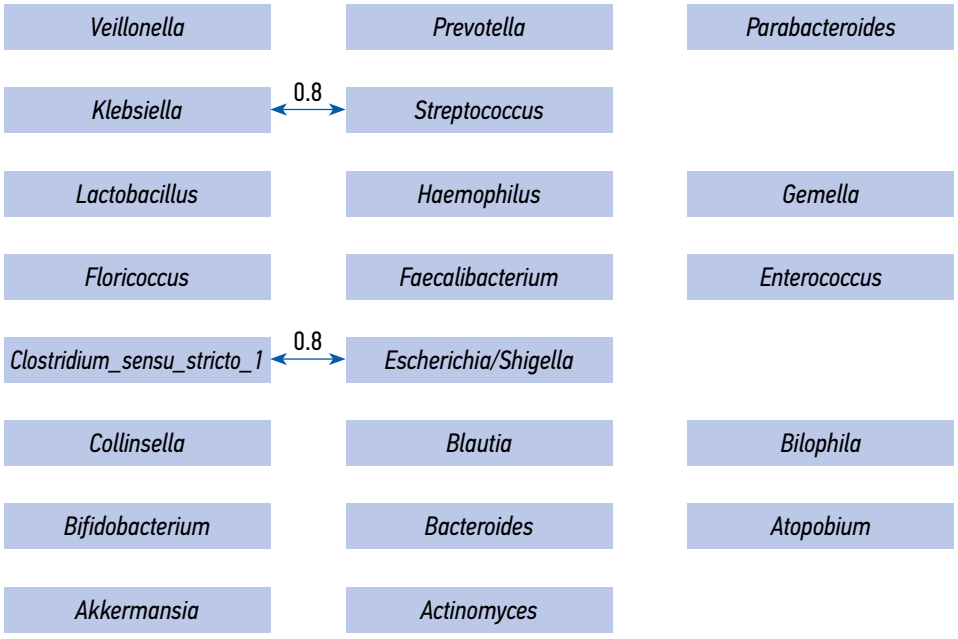

Fig. 5. Relationships between bacteria genera identified by 16S ribosomal RNA sequencing in the gut microbiome of the group 4 infants born by cesarean section and formula-fed. Solid arrows indicate positive relationships

Рис. 5. Коррелограмма связей между родами бактерий, выявленных в результате секвенирования 16S рибосомной РНК, в составе микробиома кишечника детей 4-й группы, рожденных путем операции кесарева сечения и находившихся на искусственном вскармливании. Сплошными стрелками обозначены положительные связи

Table 3. Frequency of morbidity in surveyed infants withn the first year of life

Таблица 3. Частота заболеваемости обследуемых детей на первом году жизни

Nosology	Group 1 NC and BF (n = 39), n (%)	Group 2 NC and AF (n = 10), n (%)	Group 3 CS and BF (n = 31), n (%)	Group 4 CS and AF (n = 23), n (%)	p
Allergic diseases	6 (15.4)	4 (40 %)	7 (22.6)	15 (65.2)	$p > 0.05$
Episodes of acute intestinal infections	2 (5.1)	1 (10 %)	3 (9.7)	6 (26.1)	$p > 0.05$
Acute respiratory viral infections	7 (17.9)	7 (70 %)	10 (32.2)	18 (78.3)	$p_{1–4} = 0.0064$ $p_{3–4} = 0.018$

Note. NC, natural childbirth; CS, cesarean section; BF, breastfeeding; AF, artificial feeding.

children born by cesarean section and artificially fed (17.9% and 78.3%, respectively; $p = 0.0064$). Additionally, the incidence of acute respiratory infections was significantly higher in the cesarean and formula-fed group than in the breastfed group (78.3% and 32.2%, respectively; $p = 0.018$).

DISCUSSION

Analysis of the composition of the gut microbiota of infants showed that the highest relative abundance of bacteria of the genus *Bifidobacterium* was found in groups 1 and 3, i.e., in children exclusively breastfed, regardless of the mode of delivery (30.68% and 31.46%, respectively). The lowest relative abundance of *Bifidobacterium* bacteria was recorded in the group of artificially fed children born by cesarean section. *Bifidobacterium* play a dominant role in the gut microbiota of healthy infants during the first year of life. Breast milk oligosaccharides are the major prebiotic component required for the growth of *Bifidobacterium* in the infant gut. These findings suggest that the mechanism of *Bifidobacterium* dominance in the composition of the gut microbiota is probably more influenced by the type of feeding than by the mode of delivery. At 4–6 weeks of age there was no difference between breastfed infants in the abundance of *Bifidobacterium* regardless of the mode of delivery. Thus, given the increasing frequency of cesarean deliveries, maintaining exclusive breastfeeding could ensure gut microbial health.

Analysis of the relative abundance the genus *Enterococcus* in the intestinal microbiota showed that their lowest relative abundance was in children of group 1, born by natural birth and breastfed, and its relative abundance was statistically significantly lower than in groups 3 and 4 (0.58, 4.69, and 4.29%, respectively). Exclusively breastfed infants have a lower microbial diversity and dominated by species of the genera *Bifidobacterium, Staphylococcus,* and *Streptococcus* in the gut microbiome. A more diverse microbiome is found in artificially fed infants, represented by the genera *Bacteroides, Clostridium, Enterobacteriaceae, Enterococcus*, and *Lachnospiraceae*, which may act as opportunistic microbiota under certain conditions and provoke the development of disease [25]. Additionally, gut bacteria that dominate the postoperative gut microbiome, such as enterococci, are involved in a wide range of chronic diseases and conditions, including obesity, metabolic syndrome, necrotizing enterocolitis, inflammatory diseases of the gastrointestinal tract, asthma, and various types of allergies [26–30]. Probably, the predominance of enterococci in the intestinal microbiota of infants after cesarean section (relative to their abundance in children born by natural delivery) increases the inflammatory potential of the intestine. Notably, the method of feeding does not influence the relative abundance of enterococci, but the method of delivery does.

A statistically significant higher relative prevalence of the genus *Akkermansia* was recorded in group 4 than in group 1 (34.07 and 0.01%, respectively). The genus *Akkermansia* was the most prevalent in the group of cesarean born and artificially fed infants. *Akkermansia muciniphila* is the main member of the bacterial genus *Akkermansia*, and is more common in people with a high content of dietary fiber in their diet and those who follow a Mediterranean diet. Adequate representation of *Akkermansia muciniphila* is associated with a low risk of diabetes mellitus and obesity. An analysis of the dietary data of the mothers of infants in group 4 indicated that mothers of children with high prevalence of *Akkermansia* had minimal weight gain during pregnancy (up to 8 kg), and their diets were dominated by fiber of plant origin and red meat. This probably contributes to the proliferation of this bacterium in the mother's gut and ensures its further transmission to the offspring. This might also explain the predominance of such an atypical bacterium for the infant gut microbiome in the group of born by cesarean section and formula-fed children.

Correlation analysis of the data showed some interesting patterns. The number of negative and positive connections in the groups of breastfed infants was greater than that in the groups of formula-fed infants. Additionally, t the type of delivery did not influence the number of connections between microbial births.

The correlation adaptometry coefficient reflects the tension of the system functioning when an external stimulus appears. Under an external stimulus, the number of internal connections between objects increases to maintain

the performance of the system, which eventually leads to adaptation and a decrease in number of correlations between the components. The increase in the correlation adaptometry coefficient reflects the transition of the system from the state of homeostasis to the state of homokinesis, and its decrease indicates a change from the state of homokinesis to the state of homeostasis.

The correlation coefficients of adaptometry were 6.39 for group 1, 1.72 for group 2, 4.74 for group 3, and 1.48 for group 4. These findings suggest that the intense interaction of bacteria among themselves in the composition of the infant's gut microbiome is maximum under breastfeeding and minimum under artificial feeding with adapted mixtures. Presumably, breastfeeding, which is evolutionarily the most favorable and effective way of feeding the newborn, should minimize the stress of adaptive processes in the formation of the infant's gut microbiota. However, it is likely that for a newborn with an immature immune system in the aggressive non-sterile conditions of the extrauterine environment, the stress of adaptation through breastfeeding is a survival strategy.

This phenomenon can be explained by a mechanism of "learning" by the infant's immune system at the expense of the intestinal microorganisms whose growth is supported by breastfeeding. This mechanism is still poorly understood, but the secretory immunoglobulin A (IgA) in breast milk seems to play a role in it.

Unlike other organic molecules, immunoglobulins are not secreted from mammary gland epithelial cells, but enter breast milk via serum or are transported by plasma cells from Peyer's patches in the intestinal wall directly into the mammary gland tissue [31, 32]. Once in the intestinal lumen of the infant, IgA binds to members of the four major bacterial families, namely, *Firmicutes, Actinobacteria, Bacteroidetes*, and *Proteobacteria* [33]. IgA binds to the membrane of pathogenic bacteria and prevents their colonization and further multiplication. For example, colonization by *Proteobacteria*, namely, a genus in the *Enterobacteriaceae* family, triggers the development of necrotizing enterocolitis and other inflammatory diseases of the gastrointestinal tract in newborns [34]. IgA in breast milk binds to *Enterobacteriaceae* and prevents the development of necrotizing enterocolitis in infants [35]. Another effect of IgAs is that they promote the adhesion of beneficial bacteria to enterocytes, such as *Bacteroides fragilis*, and their further proliferation [36]. The third effect of IgAs is that, being on the surface of intestinal bacterial cells, they trigger the inflammatory process in newborns, change the ratio of T cells in the colon (RORγt + Treg), and induce an immune response in the mucosa, thereby inhibiting development of the infectious process [37, 38]. These mechanisms, most probably, explain the high correlation coefficient of adaptometry in breastfed infants.

Another mechanism of immune system training is the presence in breast milk of microbiota that colonize the gastrointestinal tract of the newborn. *Staphylococcus, Streptococcus, Lactobacillus*, and *Propionibacterium* species are the most abundant species in the breast milk microbiome [39, 40]. When these bacterial genera enter the baby's intestinal lumen, they participate in the cascade of immune responses that "train" the newborn's immune system.

CONCLUSIONS

Improvements in laboratory technology are depening our understanding of the gut microbiome. The increasing frequency of cesarean sections and artificial feeding creates a specific type of gut microbiome in infants that predisposes them to the development of certain diseases.

The findings in this study suggest that the development and maturation of the intestinal microbiota of infants depends on the mode of delivery and type of feeding. For example, the relative abundance of b*ifidobacteria*, normally dominant in the intestinal microbiome of infants up to 1 year of age, is more influenced by the type of feeding than by the mode of delivery. Correlation analysis showed that after the first month of extrauterine life, the tension of adaptation processes, i.e., the state of homokinesis, is mainly characteristic of infants who received breast milk. This suggests that breastfeeding is the natural and most appropriate mechanism of adaptation of the infant's immune system to environmental conditions. Analysis of the incidence of various illnesses in the first year of life showed that children born by cesarean section and fed formula with adapted mixtures had more frequent ARVI than breastfed children.

Examining the dynamics of gut microbiome formation at various stages of children's lives can enhance the prospects for timely probiotic correction, which can probably reduce the incidence of childhood diseases in the future.

ADDITIONAL INFORMATION

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Author contribution. All the authors have made a significant contribution to the development of the concept, research, and preparation of the article as well as read and approved the final version before its publication.

Personal contribution of the authors: *V.V. Barinova* — concept and design of the study, collection and processing of material, text writing; *I.O. Bushtyreva* — concept and design of the study, collection and processing of material, editing; *D.E. Polev* — concept and design of the study; *V.V. Dudurich* — collection and processing of material; *E.E. Artouz* — collection and processing of material, text writing; *D.O. Ivanov* — editing.

Ethics approval. The Local Ethics Committee of LLC "Professor Bushtyreva's Clinic" approved this study (protocol No. 9 dated 25.01.2024).

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Источник финансирования. Исследование выполнено на собственные средства авторов без использования спонсорских средств и финансового обеспечения.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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