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Composition and Development of the Intestinal Microbiome in Children and Its Changes with Certain Pathologies (Cystic Fibrosis, Multisystem Inflammatory Syndrome, Type 1 Diabetes, and Autism): Meta-Analysis

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ABSTRACT

Background: Establishment of the intestinal flora in childhood is a critical window for growth and development. **Objective:** The aim of the current meta-analysis is to investigate the composition, development of intestinal flora in children and its change with certain pathologies.

Material and methods: A comprehensive search was conducted in Scopus, PubMed, Google Scholar and Other engines. A total of 603 articles were identified of them only 11 fulfilled our inclusion criteria.

Results: Composition of the intestinal flora in children: *Firmicutes* (51.1%) and *Bacteroidetes (*36%) at the phylum level. *Bacteroidaceae*, *Lachnospiraceae* (17.5%) and *Ruminococcaceae* (13.9%) at family level. *Bacteroides*, *Prevotella*, *Faecalibacterium* and *Bifidobacterium* (16%, 8.69%, 7.51%, and 5.47%, respectively) at genus level. Children with cystic fibrosis had different intestinal microbiota structures compared to healthy children. Alterations of the intestinal microbiota could be a predisposing factor for the multi-systemic inflammatory syndrome. In SARS CoV-2: *Firmicutes*, *Bacteroidetes*, *Proteobacteria*, *Actinobacteria*, and *Verrucomicrobia* (51%, 25%, 12%, 9%, and 2%, respectively). In non-diabetic children: *Enterococcus* 28.4%, and in children with type 1 diabetes *Enterococcus* 22.8%. The diversity and stability of the microbial composition: *Bacteroidetes, Proteobacteria, Firmicutes, Actinobacteria, Fusobacteria, and Verrucomicrobia* are different in diabetic and non-diabetic children. The percentage of microbiota species in children with signs of constipation varies compared to children without constipation. In children and adults, there is variation in species composition at the family, phylum, and genus level. *Bacteroidetes* raised in the severe autistic group. Dysbiosis was elevated in autistic children compared to healthy children. *Sutterella* sequences were absent in healthy children. **Conclusion:** It is a very important to know the influence of the change in the microbiota predisposition to develop different pathologies or the opposite, which opens a wide range in this subject, hence the importance of carrying out more in-depth studies and research, especially in childhood.

Keywords: Intestinal microbiota, children, pathologies, meta-analysis, University Mohammed V.

INTRODUCTION

The intestinal microbiota is an important set of bacteria distributed along the intestinal tract and whose overall composition varies according to the location, the individuals, the age, the periods of the life of a same individual, the human intestinal microbiota is composed of about 10^{14} bacteria as well as other microorganisms such as viruses, fungi and archaea.

Intestinal microbiota research has revealed the fundamental role it plays in intestinal physiology but also in human health in a more general way, as a real "hidden organ", after bacterial colonization of the digestive tract, this transient microbiota is crucial for the growth of each person's unique intestinal microbiota and actually has a significant impact on how a newborn develops. We explain the structure and role of the intestinal microbiota as well as its implications in human pathology **(1)**.

Breast milk can encourage the proliferation of *Lactobacillus* and *Bifidobacterium* strains, whose function is to provide an acidic environment rich in short chain fatty acids with an intestine protective and nutritional function. Additionally, breastfeeding has been shown to provide a balanced gut microbiota to infants, which positively impacts their health **(2)**.

The intestinal microbiota is composed in a very large majority of anaerobic bacteria, 95% of the microbiota is represented by four bacterial phyla: *Firmicutes* (Firmus cutis: hard skin) are bacteria traditionally Gram-positive but of which certain classes are Gram-positive (we find in particular the genera: *Ruminococcus, Clostridium, Lactobacillus* (of which several strains are used as probiotics), and of *Eubacterium, Faecalibacterium and Roseburia* (producers of butyrate), *Bacteroidetes* is Gram negative with a phylum consisting of three major groups

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of bacteria widely distributed in the environment, including soil, sediment, seawater and animal intestines (in this group, *Bacteroides, Prevotella and Xylanibacter* degrade a wide variety of complex glycan molecules), *Actinobacteria* is a group of filamentous Gram-positive bacteria. Instead of living in the wild, most of these species have evolved as symbionts (this group includes the genera *Collinsella and Bifidobacterium* (including some known probiotic strains) and *Proteobacteria* are Gram negative (now officially renamed *Pseudomonadota* by ICS 2021), Most of the bacterial genera listed above *(Akkermansia, Oscillibacter, Faecalibacterium, Eubacterium, Ruminococcus, Roseburia, Bifidobacterium, Prevotella, Bacteroides)* are part of the dominant microbiota. Genera such as *Escherichia and Lactobacillus* are found in smaller quantities. Other rare bacterial groups were also detected, such as *Fusobacterium, Lentisphaerae* and *Spirochaetes*, in the archaea, only one genus, *Methanobrevibacter*, and more particularly the species Methanobrevibacter smithii, was first observed to be involved in intestinal methanogenesis [(3)].

Molecular biology (e.g., use of the cistron mcrA, as a molecular marker of methanogenesis, and of the gene encoding 16S rRNA) has shown that the diversity of the Archaea had been underestimated: before 2009, in the intestines of 63 humans alone (newborns, adults, and elderly), new phylotypes were discovered that were not included in any of the five previously described methanogenic orders. They could be methanogens and/or methanotrophs, perhaps affiliated with the Thermoplasmatales or cohabiting with as yet unknown members of these, these novel phylotypes were more present the older the host, which raises questions about their origin and role in the human intestinal microbiota, microbiological data and measurements of methane in exhaled air suggest that the human gut is not colonized by methanogens until 2-3 years of age, According to researchers in the year (1971 - 1996) or transiently only from the first year of life according to Palmer et al. in 2007, Before 2014, 75% of intestinal bacterial genomes were still unknown, this gives a better idea of the genetic richness of the bacterial ecosystem of the human gut: a metagenome of more than three million genes, 120 times more than the human genome. Statistical analyses of these gut communities will now be more accurate. In early 2019, a metagenomic analysis revealed 2,000 previously unknown species of intestinal bacteria [(4)].

Disturbances of the intestinal microbiota are involved in certain intestinal pathologies as well as in extra-intestinal pathologies. Also obesity, metabolic syndrome, chronic inflammatory bowel diseases like Crohn's disease or ulcerative colitis, some cardiovascular pathologies, certain allergy pathologies, and autism should be mentioned among these pathologies [(5)], Cystic fibrosis: Although the exact mechanism is yet unknown, intestinal bacteria may have an impact on the onset of both intestinal and widespread inflammation in cystic fibrosis illness. Numerous biomarkers have been used to identify intestinal inflammation in cystic fibrosis illness, eosinophil cationic protein, neutropenia elastase, Cancer necrosis factor-a, calprotectin, S100A12, IL-8, IgM, and IgG [(6)].

Pandemic COVID-19: Despite several strategies and improved immunization rates globally. According to circulating variations, pandemic prevention methods, community vaccination rates, hospitalizations, stays in a critical care unit, and deaths rates, the illness load, age distribution of SARS - CoV-2 in children, adolescents differed. Compared adult cases, number of COVID-19 cases among children and adolescents has been relatively low since the pandemic's beginning. However, children may experience multiple systemic inflammatory disease as long-term side effects from COVID-19 [(7)].

Multi-systemic inflammatory syndrome: is an uncommon systemic disease that is characterized by persistent fever and severe inflammation. This state can swiftly result in medical issues such insufficient blood flow in the body and the failure of one or more organs. After exposure to COVID-19, a persistent, unexplained fever with serious symptoms is a warning indication. Families should seek emergency medical attention, and the most severely afflicted children will need intensive care. Early signs frequently include severe stomach discomfort accompanied by vomiting or diarrhea in addition to a lingering fever. Low blood pressure as well as. Other symptoms may include skin rashes, a strawberry tongue, swollen hands and feet, enlarged lymph nodes, and red eyes. Numerous mental illnesses can manifest. Heart failure is frequent, and myocarditis has been recorded. A cellular storm may ensue, in which the child's innate immune system causes an overwhelming and uncontrolled inflammatory response. Clinical complications may include heart muscle damage, shortness of breath, higher blood clotting and acute renal injury. Coronary artery malformations (varying from aneurysm to dilatation) may occur, early detection and quick specialized care are crucial for treating this potentially fatal disease. Anti-inflammatory therapy have been utilized, with promising results from intravenous immunoglobulin (IVIG), with or without steroids, and oxygen is frequently needed. Clinical problems must be treated with supportive care, and most children who receive specialist medical attention survive. Research into this syndrome, which was recently discovered, is

advancing quickly. The signs and symptoms could mirror Kawasaki syndrome [8].

Autism: Diagnostic criteria for pervasive developmental disorders include the trio of stereotyped and repetitive actions, communication problems, and social abnormalities. Children with autism frequently report experiencing gastrointestinal issues, which may be related to how severe the autism is. Various functional impairments, altered inflammatory markers, and macroscopic and histological abnormalities are all connected with intestinal illnesses in autism [9].

Diabetes mellitus is a group of metabolic, endocrinological illnesses described severe hyperglycemia as a result of abnormalities in insulin secretion, insulin efficacy, or both, two basic etiopathogenic categories can be applied to categorize the vast majority of diabetes cases: in type 1 diabetes, loss of the insulin-secreting beta cells lead to disease; in type 2 diabetes, which is most typical, the causative factor is a combination of insulin resistance, inflammation, the gastrointestinal tract must distinguish between pathogenic, no pathogenic organisms and nutritional antigens, it is becoming clear that relationship between composition of intestinal microbiota, intestinal barrier, and mucosal immunity plays an important role in the development of hypersensitivity and autoimmune diseases. In type 1 diabetes, there is evidence of synergy between an aberrant gut microbiota, a "leaky" gastritis, the commensal flora, which maintains epithelial homeostasis by controlling inflammation and detecting potentially harmful pathogen Additionally, according to recent studies, type 1 diabetes is connected to subclinical enteropathy, which can be detected before the condition shows clinical symptoms. According to this, the small intestine may play a part. on how type 1 diabetes and gut immunology are related [10].

The effects of antibiotic therapy on the microflora among the many environmental factors likely to modify the macrobiota, antibiotic therapy appears to be one of the most powerful**,** these effects can be focused on one of the specific components of the microflora and induce the emergence of a bacterial population, but they can also persist for a long time after the cessation of an antibiotic treatment.

Goldenberg *et al.* have shown that after different broad-spectrum antibiotic treatments in a haematology patients, the quantity and quality of the bacterial species in the faecal flora changed, the fecal flora of children aged 1 to 3 months appeared considerably disturbed by antibiotics and oral medication, with an increase in *Enterobacteria* while *Bacteroides, Bifidobacterium and Lactobacillus* species were often undetectable [11]**.**

The aim of the current meta-analysis is to investigate the composition, development of intestinal flora in children and its change with certain pathologies, in particular phylogenetics and its change with certain pathologies such as cystic fibrosis, multi-systemic inflammatory syndrome, type 1 diabetes and autism over the past 12 years (2010-2022), Interested in phylogenetics, and some pathology.

MATERIAL AND METHODS

Systematic meta-analysis of studies found in the literature on composition, development of intestinal flora in children and its change with certain pathologies.

Type and period of the study:

This is a Meta-analysis on composition and development of intestinal microbiota in children on studies of the literature in the last 12 years found 7 countries (October 2020 – December 2022).

Search Strategy and Study Selection Criteria:

The databases used were: Scopus, PubMed Google Scholar and Other Engines. The search words: (intestinal * or gastro-intestinal*) and (microbiota * or microflora*or bacteria* or micro-organism* or fecal flora* or systemic inflammatory syndrome* or cystic fibrosis *or diabetic children* or type 1 diabetes in children* or autism in children*). Studies from every language were included in the searches. Options for searching the Scopus database included: “title, summary, and keywords”. We found a total of 603 articles in the databases (196, 167, 103.93 and 44 articles found in Scopus, Elsevier, PubMed Google Scholar and Other engines). For our purpose of analyzing the global data, 489 of the articles were excluded (see ***Figure 3*** which includes the reasons for elimination). And after processing the information, we finally selected 11 articles, 95 participants.

Exploitation criteria: The collection of articles for our meta-analysis using keywords: composition, gastro-intestinal, gut flora, cystic fibrosis, SARS-COV2, COVID-19, multisystem inflammatory syndrome, type 1 diabetes, and autism. We searched the literature for articles and studies related to the gut microbiota between 2010 and 2022, and we did not
distinguish on the language of publication.

Elimination criteria: The published data on intestinal microbiota, articles or studies that are on animals, outside the selected period, related to our research but in different directions, and not on the global data, were excluded. A meta-analysis was performed using GraphPad Prisma.

Ethical considerations: Faculty of Medicine and Pharmacy Ethics Committee of University Mohammed V, Rabat, Morocco, gave its approval to the study.

Analytical statistics:

We used two programs for the statistical analysis, each program with its own advantages and characteristics.

- GraphPad Prisma 9: for repeat and elimination criteria, and to graph years and regions of publication. A *p value* ≤0.05 was regarded as significant for statistical analyzes with a 95% confidence interval (95% CI).
- Microsoft Excel to create tables, collect and compare data.

RESULTS

II.1 Studies published in the period of (2010-2022) in the last 12 years in 7 countries on composition, development of intestinal flora in children and its change with certain pathologies:

We have graphically represented the number of studies published in the selected period (2010-2022), the majority of studies were in 2014, followed by 2016, 2022, 2010, 2012, 2013 and 2020 (**Figure 1)**.

The number of studies published in different countries in the same period where we found, three studies in the USA, two studies in Turkey and the Netherlands, and one in Italy, Finland, Australia and Spain (**Figure 2).**

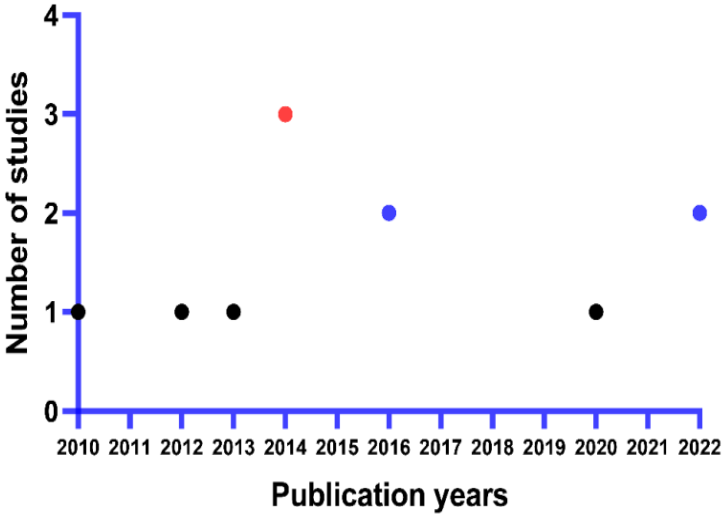

Figure (1): Number of studies published in 7 countries in the period of 2010-2022 on composition, development of intestinal flora in children and its change with certain pathologies.

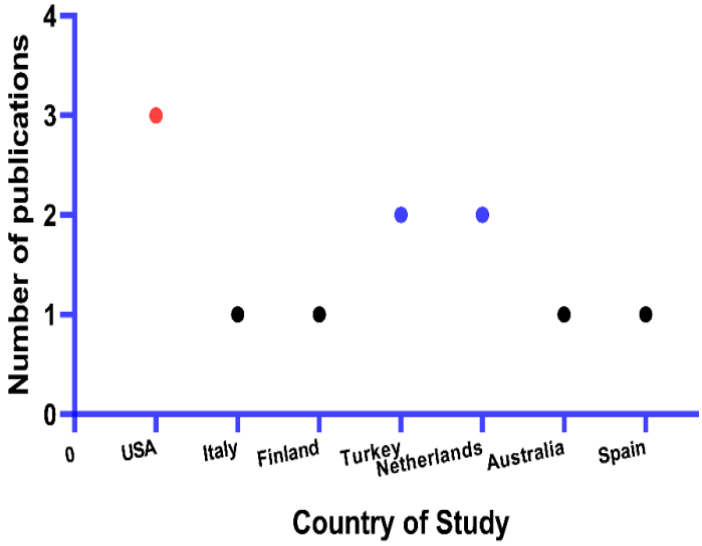

Figure (2): Number of studies published in 7 countries on composition, development of intestinal flora in children and its change with certain pathologies in the period of 2010 - 2022.

The studies' characteristics included in our meta-analysis: The eleven studies' primary traits and 95 participants in (7 countries) included in this systematic review. Most of these studies were based on laboratory controls, analytical studies and diagnostic surveys **(Figure 3).**

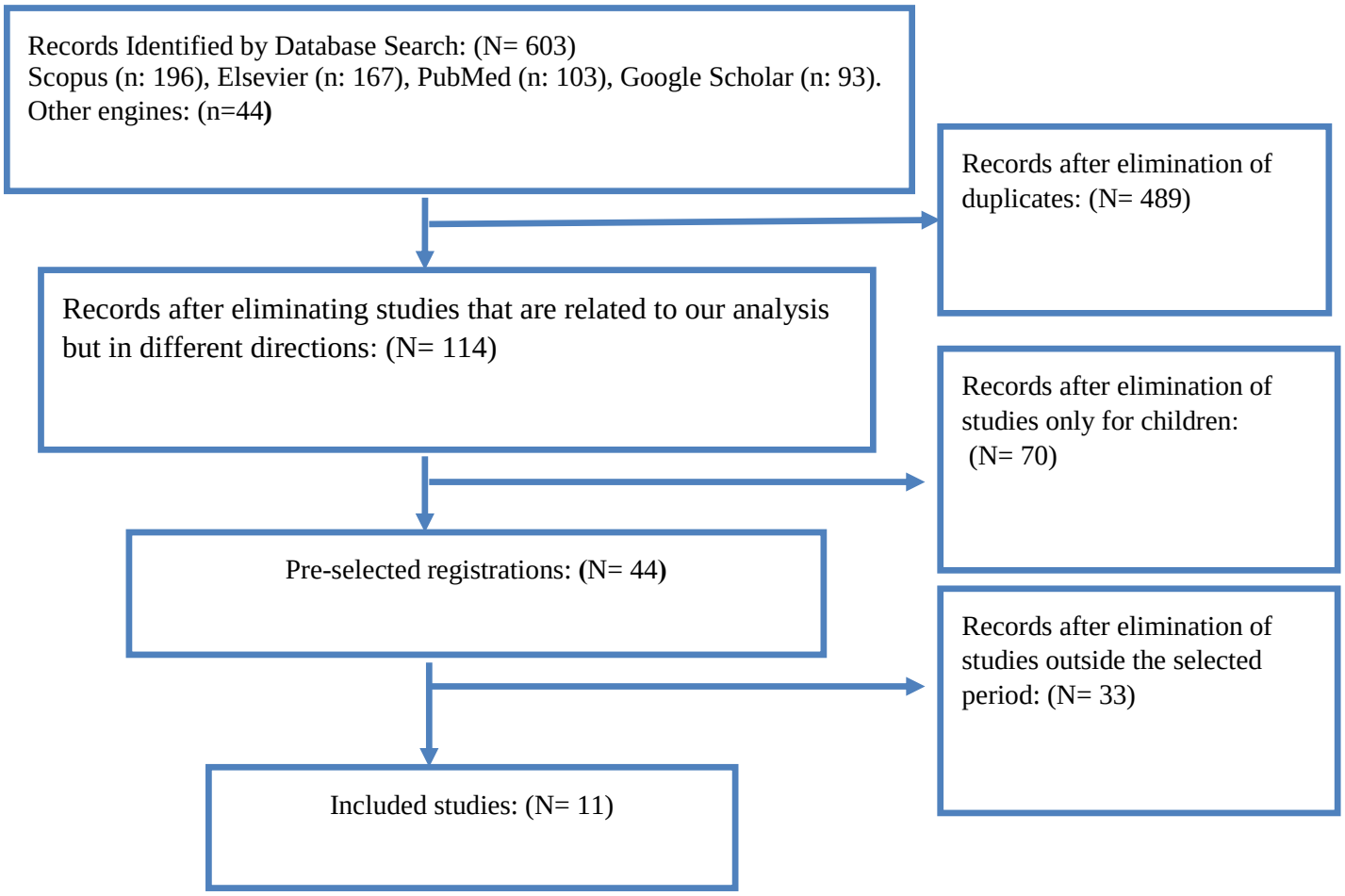

Figure 3: PRISMA Graphic for the selection of studies: shows the number of articles or studies included in our search found in the literature on composition, development of intestinal flora in children and its change with certain pathologies, harsh data processing, and criteria for elimination.

The study's characteristics included in our meta-analysis on composition, development of intestinal flora in children and its change with certain pathologies:

In each article, we indicated the year, location and study design, number of participants, age, of genetic study, the number of references on which each research was based and the number of samples in each study. And we added comments for each reference. The majority of studies were performed in 2014, with fewer studies performed in 2016, and in 2022, 2010, 2012, 2013, and 2020. Among the studies we analyzed, three studies were done and published in the United States of America, Two studies in Turkey and the Netherlands, and one in Italy, Finland, Australia and Spain (**Table 1)**

Table 1: Summarizes the studies that made up our meta-analysis

References	YEAR	Region	study design	Number of participants	Age category	Genetic study 16S rRNA and Region	comments	Rf.
Sydney M., Scot E, Viktoria G *et al.*[12].	2010	USA	Longitudinal	13	1 to 13 years	DNA high quality, no inhibiting substances (Extraction DNA in duplicate)	A particular diagnostic test may be affected if it turns out that a single micro flora is a causal or consequential component in this sort of autism.	43
Brent L, Mady H, Tanmay P *et al.*[13].	2012	USA	Longitudinal	4	Children	*Sutterella*-specific 16S rRNA gene **Region** V6–V8	*Sutterella* is an important major component of the intestinal microbiome of many children with autism and a weak digestive system, absent in children who suffer from these diseases.	44
Tamar R, Jing C, Yehuda R *et aL.* [14].	2013	USA	Transverse	8	1 to 2 years 21–60 years	Human intestinal tract chip (HITChip) 16S rRNA V1 and V6 regions and quantitative PCR	Identification of "windows of opportunity" for intervention techniques that can improve health and stop or slow the progression of disease processes can be made with the aid of knowledge of the microbiota and how it develops during the early years of life.	64
Eugenia B, Maria L, Valeria R *et al.* [15].	2014	Italy	Longitudinal	11	2 to 9 years	16S rRNA and Region V2-V3	There is a quantitative and qualitative change	34
Marcus C, Susana F, Bartholomeus V *et al.*. [16].	2014	Finland	Longitudinal	8	1 to5 years	HITCHip 16S rRNA	Results indicate that children without diabetes have a more balanced microbiota.	38
Erdogan S, Aynur G, Ayse C *et al.* [17].	2014	Turkey	Transverse	6	4 to 9 years	Unspecified	Compared to the control group, patients with type 1 diabetes had lower levels of *Bifidobacterium* colonization.	37
Tim G., Andries E., Evelien F *et al.* [18].	2016	Netherlands	Longitudinal	9	4 to 18 years	16S-23S rDNA and Region V1-V3	By phylum, children's microbial composition stability differed during the short and long periods.	54
Tim G, Evelien F, Anat E et a*L.*[19].	2016	Netherlands	Longitudinal	8	4 to18 years	16S-23S rDNA and IS Region	Optimizing microbiota-based interventions in constipated children warrants further characterization	36
Kane E, Amanda D, Therese A *et al* [20]	2020	Australia	Longitudinal	6	2,0 to 11,3 years	16S rRNA and Region V1-V8	Children's preadolescent gut microbiomes were mostly characterized by *Firmicutes, Bacteroidetes,* similar to the gut microbiome of an adult. Age, place of residence, and the 16S rRNA region	120
Pedro A, María R, Julio S *et al.* [21].	2022	Spain	Longitudinal	5	Children	Unspecified	The *Bifidobacterium* genus is involved. Nevertheless, differences between studies are a result of things like reporting bias, among other things.	58
Cansu S, Omer K, Dilek Y *et al.* [22].	2022	Turkey	Longitudinal	22	3 to 14 years	16S Region V3-V4 and SRAS –CoV rt PCR	A change in the proportion of bacteria was observed.	88

Abbreviation: Human Intestinal Tract Chip (HITChip)

Composition of intestinal microbiome in children and its change with certain pathologies

Characterization on composition of intestinal flora in children

A study published in 2020 in Australia, from 2010-2018, 42 studies included and over 2000 participants, the majority of the studies were from North America and Europe, Each study's total participant age ranged from 2 to 11 years.

Influence on a phylum level, of geographic location, age, 16S rRNA region: Entire taxonomic phylum, microbiota was dominated by *Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteries. Verrucomicrobia, Tenericutes, and Fusobacteria* (51.1%, 36%, 5.98%, 2.93%, 0.57%, 0.12%, and 0.05%, respectively) and a proportion not classified (3.07%) there was a lower proportion for *Firmicutes* in African children 31.6%, in Central American children 35.7%, compared to the Eastern region; Europe 67.7% versus North America 69%. *Firmicutes, Bacteroidetes* in European, Central American children was related meaning, in European, North Central American children *Bacteroidetes* ratio was greater than in African and Central American children. (3.21% and 3.88%, compared with 0.57% and 0.61%, respectively).and in Asian children *(Firmicutes, Bacteroidetes* 2.21%). Children from Asia had a substantially higher percentage of Actinobacteria than children from Central America.

Influence on a family level, geographic location, age, 16S rRNA region: In the family level: The microbiome was dominated by *Bacteroidaceae, Lachnospiraceae, Ruminococcaceae, Prevotellaceae, and Bifidobacteriaceae* (17.5%, 16.8%, 13.9%, 12.1%, and 5.09%, respectively).

These species, in comparison with other 7 species present about 95.0% of the classified bacteria, a limiting number of studies take the family rodent. Importantly, in an African study with a limited number of participants, the Asian children had high proportions of *Bifidobacteriaceae* and *Peptostreptococcaceae* (12.0% and 1.96%, respectively) compared to other averages (5.09% and 0.76%, respectively). In general, European children reported high proportions of *Ruminococcaceae* (27.8%, less compared to 13.9%), proportions with *Prevotellaceae* (1.96% compared to 12.1%). The majority of participants (90.9%) were from cohetes studies, with an average age of 8 to 10 years. and no research was done on children between the ages of 6 and 8. The largest percentages of *Bacteroidaceae* (31.05%) *and Prevotellaceae* (2.93%) were found in the age group (<4 years). In age group 8–10 years, the proportions of *Bifidobacteriaceae* were five times greater than in age group of 10+ years *Ruminococcaceae* with relative abundance in comparison with the other age groups hole. In the age group of 4-6 years, the proportion of participants (3.20%), *Prevotellaceae* was (33.4% compared 12.1%).greater group with the other groups. Non-classical bacteria were found in the 16S rRNA region V1–V3 (84.0%, 66.3%). The proportions of *Enterobacteriaceae* in V1-V3 region were 5 times higher (4.07% as opposed to 0.81% in the V6 region).

In contrast to outer group V4 region, the V4 region investigation revealed unidentified bacteria (3.82%), and it was characterized by a lack of *Prevotellaceae, Bacteroidaceae, Rikenellaceae* and *Alicaligenaceae*. contrast, the *Lachnospiraceae, Bifidobacteriaceae, Coriobacteriaceae, and Peptostreptococcaceae* fractions were higher in the V6 region study. Geographical location, age, 16S rRNA region have an impact at genus level. In taxonomic genus rodent, *Bacteroides, Prevotella, Faecalibacterium, Bifidobacterium, and Lachnospiraceae* (16.0%, 8.69%, 7.51%, 5.47%, 3.26%) unclassified these species in the 19 study, accounting for 89.0% bacteria classified in general. The family range (23.4%) has a higher percentage of unclassified bacteria than the phylum (3.07%) by a factor of nine. predominates in children of African descent (0.99% of participants), according to *Prevotella* intestinal microbiota 53. 0%, and it outnumbered the other population. Children in Central America were found to have higher ages of *Bacteroides* 23.1% than *Prevotella* 14.2%, *Lachnospiraceae* not classes 4.28%, *Ruminococcaceae* not classes 3.59), and *Bifidobacterium* 0.40%.

In contrast to various groups (5.69–97.71%). Comparing *Faecalibacterium* to other populations (4.0–10.0%, average = 7.5%) In the cohorts, the prevalence of *Bacteroides* in the 4 to 6 year age range was generally rising with age. *Prevotella and Dialister, Lachnospiraceae, Bifidobacterium,* unclassified *Ruminococcaceae, Clostridium XIVa, Clostridium,* and *unclassified Ruminococcaceae* all had similar percentages in children (4 years old). *Bacteroides, Prevotella,* Non-class *Ruminococcaceae,* and *Dialister* all had large percentages in the 86% of children older than 10 years old. In the area V1-V3 bacteria, Unclassified or unknown bacteria made up 67.9% of the population and Unclassified *Lachnospiraceae* made up 7.12%. According to the investigations, there are 11.5% more bacteria in the region V6 where *Bifidobacterium* is present, followed by *Faecalibacterium, Bacteroides,* and *Prevotella.*

Table 2: Influence at phylum, family and genus of geographic location, age and 16S rRNA region.

References	Year	Region	N. of samples	Age	16S rRNA and Region	Microbes					
						Family		**Phylum**		**Genre**	
Kane E, Amanda D, Therese A et al 2020	2010-2018	Australia and some countries in 5 continents	2000	2.0 to 11.3 years	16S rRNA and Region V1-V8	*Bacteroidaceae*	17.5%	*Firmicutes*	51.1%	*Bacteroides*	16.0%
						Lachnospiraceae	16.8%	*Bacteroidetes*	36.0%	*Prevotella*	8.69%
						Ruminococcaceae	13.9%	*Actinobacteria*	5.98%	*Faecalibacterium*	7.51%
						Prevotellaceae	12.1%	*Proteobacteria*	2.93%	*Bifidobacterium*	5.47%
						Bifidobacteriaceae	5.09%	*Verrucomicrobia*	0.57%	*unclassified Lachnospiraceae*	3.26%
								Tenericutes	0.12%		
								Fusobacteria	0.05%		
								Non classes portion	3.07%		

The intestinal flora and its distribution in children with cystic fibrosis (analysis criterion: 16S Region V3-V4 and SARS -CoV rt PCR)

The intestinal inflammation that symptom cystic fibrosis was reported in study, which was published in Turkey in 2022. Administration of probiotics may decrease pulmonary exacerbations' frequency and intestinal irritation. We studied the composition on intestinal microbiota in children with cystic fibrosis and analyzed its relationship with intestinal inflammation. Additionally, investigated at the microflora's composition during and after giving children with cystic fibrosis *Lactobacillus* (GG), antibiotics both with, without. A similar but more extreme trend noticed in children with cystic fibrosis, analysis sequence of bands indicated accession number (Table 3) had shown that the percentage was changed for the same microbiota before and after treatment, in the same analyses. Treatment presence in healthy controls' profiles: *(Roseburia faecis* 80%, *Ruminococcus bromii* 27%, *Ruminococcus gnavus* 18%, *Eubacterium rectale, Pseudobutyrrivibrio ruminis* 100%, *Roseburia faecis* 23%, *Ruminococcus bromii* 100%, *Ruminococcus gauvreauii Coprococcus comes Ruminococcus torques* 18.18%, *Robinsoniella peoriensis Hespellia porcina Lactonifactor longoviformis* 100%, *Faecalibacterium prausnitzii* 100%, *Bifidobacterium catenulatum B. pseudocatenulatum* 90%, *Bifidobacterium adolescentis* 36.36%, *Faecalibacterium prausnitzii* 100%).

Presence in the features of children with cystic fibrosis: (*Roseburia faecis* 7.69%, *Ruminococcus bromii* 0%, *Ruminococcus gnavus* 0%, *Eubacterium rectale, Pseudobutyrrivibrio ruminis* 53.85%, *Roseburia faecis* 42.86%, *Ruminococcus bromii* 36.36%, *Robinsoniella peoriensis Hespellia porcina Lactonifactor longoviformis* 53.84%, *Ruminococcus gauvreauii Coprococcus comes Ruminococcus torques* 0%, *Faecalibacterium prausnitzii* 15.38%, *Bifidobacterium catenulatum B. pseudocatenulatum* 53.85%, *Bifidobacterium adolescentis* 15.38%, *Faecalibacterium prausnitzii* 69.23%).

Composition of intestinal flora in children with covid 19 and children with Multisystemic Inflammatory Syndrome (endpoint: 16S rRNA and Region V2-V3)

This study published in 2022 in Italy was shown the evaluation of the intestinal microbiota, its composition in the Multisystemic Inflammatory Syndrome It explained us that the reduction of *F. prausnitzii* in children with the Multisystemic Inflammatory Syndrome and COVID-19, (Two) an increase in Eggerthella lenta which is related to autoimmunity; (Three) the predominance of *E.dolichum* is associated with metabolic dysfunctions and obesity in children with Multiple Systemic Inflammatory Syndrome. Modifications of the intestinal microbiota could be part the pathogenesis the predisposing factor the Multi Systemic Inflammatory Syndrome.

A total of 64 children, 25 cases with multi-systemic inflammatory syndrome, and 19 healthy children, in the multi-systemic inflammatory syndrome group (9.5) years in the COVID-19 group (8 years), The age distribution in the multi-systemic inflammatory syndrome, COVID-19, control groups were statistically similar p.v (< 0.05) in the multi-systemic inflammatory syndrome group, Nine children were overweight, and five were obese. One finding was that within COVID-19 group, Seven subjects were overweight, while five of the subjects were obese in the group of Multisystemic Inflammatory Syndrome the results showed that the levels phylum were as follows: *Verrucomicrobia* 3%, *Actinobacteria* 7%, *Proteobacteria* 11%, *Bacteroidetes* 32% *and Firmicutes* 46%, in the control group were: *Proteobacteria* 5%, *Actinobacteria* 6%, *Bacteroidetes* 23%, *and Firmicutes* 64%. In SARS Group CoV-2, the rates were: *Verrucomicrobia* 2%,

Actinobacteria 9%, *Proteobacteria* 12%, *Bacteroidetes* 25% and *Firmicutes* 51%. Regarding the presence of *Bacteroides*, Between SARS CoV-2 group, control group, no differences were seen; Nevertheless, *Bacteroides* were higher in systemic inflammatory syndrome group compared to other group

.

Table 3: Composition of intestinal microbiota in children with COVID-19, systemic inflammatory syndrome and its distribution with cystic fibrosis.

References	Year	Region	N.of samples	Age	16S rRNA and Region	Accession Number	Microbes			
Eugenia B, Maria L, Valeria R et al.2014	2014	Italy	22	2 - 9 years	16S rRNA and Region V2-V3	NR 042832	**Healthy controls**		**Cystic fibrosis**	
						L76600	*Roseburia faecis*	80%	*Roseburia faecis*	7.69%
						NR036800	*Ruminococcus bromii , Ruminococcus gnavus*	27% 18%	*Ruminococcus bromii , Ruminococcus gnavus*	0%
						AY804151 NR026315	*Eubacterium rectale, Pseudobutyrrivibrio ruminis*	100%	*Eubacterium rectale, Pseudobutyrrivibrio ruminis*	53.8%
						AY305310	*Roseburia faecis*	23%	*Roseburia faecis*	42.8%
						NR025930	*Ruminococcus bromii*	100%	*Ruminococcus bromii*	36.3% ,
						AF445285 AF445239 NR043551	*Robinsoniella peoriensis Hespellia porcina Lactonifactor longoviformis (R. p. H. p. L. l.)*	100%	*R. p. H. p. L. l.*	53.8%
						NR044265 EF031542 L76604	*Ruminococcus gauvreauii Coprococcus comes Ruminococcus torques (R. g. C. c. R. t.)*	18.18 %	*R. g. C. c. R. t.*	0%
						AJ413954	*Faecalibacterium prausnitzii*	100%	*Faecalibacterium prausnitzii*	15.3%
						NR041875 NR037117	*Bifidobacterium catenulatum B. pseudocatenulatum*	90%	*Bifidobacterium catenulatum B. pseudocatenulatum*	53.8%
						GQ227713	*Bifidobacterium adolescentis*	36.36 %	*Bifidobacterium adolescentis*	15.3%
Cansu S, Omer K, Dilek Y et al*2022*	2022	Turkey	45		16S Region V3-V4 and SRAS –CoV rt PCR		**Multi-systemic inflammatory syndrome**		**In the SARS Group CoV-2**	
							Firmicutes	46 %	*Firmicutes*	51 %
							Bacteroidetes	32 %	*Bacteroidetes*	25 %
							Protéobactéries	11 %	*Proteobacteria*	12 %
							Actinobactéries	7 %	*Actinobactéries*	9%
							Verrucomicrobies	3 %	There was no difference between SARS CoV-2 and control in terms of presence of *Bacteroides*; however, the Multisystemic Inflammatory Syndrome group had greater levels of *Bacteroides* than the other group.	

The intestinal flora and diabetes:

Composition of the intestinal flora in children with early type 1 diabetes

In this study, which was published in 2014 in Finland, the analyses highlighted the importance of age when comparing by age. At age less than 2.9 years, the abundance of the class *Bacilli* (especially *streptococci*) and the phylum *Bacteroidetes* was higher in children with diabetes, whereas the abundance of *C. IV, XIVa* was higher in healthy controls. Controls older than 2.9 years were characterized higher fraction of butyrate-producing in *C. IV, XIVa spp* compared to children of the same age or younger and diabetic children older than 2.9 had increased microbial diversity.

The intestinal flora of fecal 27 healthy controls, 28 diabetic children (age range 1.3 to 4.6 years; mean 2.7 ± 0.8; constituting 26 samples based on child age) was determined by analysis (HITCHip 16S rRNA gene sequences of more than 1100 intestinal bacterial phylotypes). This revealed that *C. XIVa* 56% and *IV* 11% groups were the most abundant, followed by *Actinobacteria, Bacilli* and *Bacteriodetes* (9.2%, 8.5%, and 7.5%).

Importantly, analysis of phylogenetic differences between diabetic, control children using PCA, redundancy analysis, and diversity analysis showed that the control-diabetics should be separated into two groups based on age, with a mean age of 3 years. Finally: Finnish diabetic children had a significantly higher abundance of non-butyrate-producing species of *C. IV, XIV* groups (0.4; 41% opposite 32%).

Differences in intestinal flora in healthy and diabetic children

In this study published in 2014 in Turkey, a total of 35 type 1 diabetic children, (16 Female, 19 Male an average age of 10.73 (SD 4.16) years, and control group of 35 healthy children (15 Females, 20 Males) with similar demographic characteristics, with an average age of 9.96 (SD 4.09) years, were chosen. were no significant differences between study, control groups with respect to age and sex. On no-selective media, selective and quantitative cultures were carried out under various thermal and atmospheric conditions.

A reduction in *Escherichia coli* colonies in three of the type 1 diabetic children 8.6% and an increase in colonies in 15 children 42.9% were identified. In control group, a reduction in colonies in two children 5.7% and an increase in colonies in 11 children 42.9% were identified, between the two groups, there were no statistically significant differences.

Only 13 children in type 1 diabetes group had *Enterobacteriaceae* colonies. About 37.1%, 3 children 8.6% in control group; this difference was statistically significant. 10 of the type 1 diabetic children, there was a reduction in *Enterococcus* colonies 28.4%, eight of the controls 22.9%. At the control, an increase in colonies was observed in two of type 1 diabetic children 5.7%, 4 of the controls 11.4%. No statistically significant differences were identified between two groups. 7 children with type 1 diabetes 20.0%, 1 of the controls 2.9%, there was a decline in *Bacteroides spp*. colonies. No statistically significant difference was found despite the stark differences between groups. 8 children with type 1 diabetes 22.8%, 1 of the controls 2.9% had less *Bifidobacterium spp*. colonies.

Decreased *Lactobacillu*s colonies was noticed in 18 of the children with diabetes 56.3% and in 14 of controls 43.8%. Only one diabetic child and none of the controls had increased *Lactobacillus* colonies, there was no discernible difference between groups.

Table 4: Composition of intestinal microbiota in children at onset of type 1 diabetes, differences intestinal flora in healthy and diabetic children.

References	Year	Region	N.of samples	Age	16S rRNA and Region	Microbes			
Marcus C, Susana F, Bartholomeus V *et al* 2014	2004–2010	Finland	55	2.3 to 4.6 years	HITCHip 16S rRNA	**Type 1 diabetes (control)**		**Type 1 diabetes**	
						Clostridium cluster XIVa	56%	Diabetic children (higher abundance of non-butyrate-producing species *Cluster of C. IV, XIVa).*	4. 41 %
						Actinobacteria	9.2%		
						Bacteriodetes	7.5%		
						Bacilli	8.5%		
						Clostridium clusters IV	11%	*contre*	32 %
Erdogan S, Aynur G, Ayse C *et al* 2014	-2011 2012	Turkey	70	4 to 9 years	Unspecified	*a decrease in E. coli and an increase*	5.7% 42.9%	A decrease in *E. coli* and an increase	(8.6% (42.9%
						Enterobacteriaceae	8.6%	*Enterobacteriaceae*	37.1%
						Enterococcus .	22.9%	*Enterococcus*	28.4%
						Bacteroides spp.	2.9%.	*A decrease in Bacteroides spp*	20.0%
						Bifidobacterium spp. .	2.9%	*Bifidobacterium spp*	22.8%
						Lactobacillus	43.8%	*Lactobacillus*	56.3%

The composition, stability of the gut microbiota in healthy and constipated children in Dutch population.

In this study published in 2016 in the Netherlands, was done to characterize composition and stability intestinal flora the short and long term in healthy children. Between 2011 and 2014, 61 children aged 2-18 years, from different regions of the Netherlands by new DNA-based detection methods. PCR and profiling (IS-pro16 , S-23S rDNA and Region V1-V3) was used to analyze available fecal, microbial diversity was calculated by Shannon Diversity Index and individual composition stability by comparing all collection times. This study found that the stability of intestinal flora in children varied by phylum, at both short, long-term. Healthy children appear to share a microbiome composed of a limited number of species, the phyla *Firmicutes, Fusobacteria, Actinobacteria, Verrucomicrobia, Proteobacteria and Bacteroidetes.*

Diversity and stability of intestinal flora over time varied by time point (P= 0.0005), phylum (P= 0.0005), with *Bacteroidetes* showing most composition, followed by *Proteobacteria, FAFV*. Stability declined quite rapidly for short intervals, but then stabilized at a level that decreased again very gradually for the longitudinal decrease were for: *Proteobacteria, Firmicutes,* and *Bacteroidetes* (3.41%, 5.32%, 1.33%). Overall compositional stability averaged 70% over an 18 month period. Also, it was found that the composition of *Bacteroidetes* was the most stable, while the stability of the composition of *FAFV, Proteobacteria* were, on average, lower. Although this effect was not statistically significant, it appeared that compositional stability increased slightly with age. With a median Shannon diversity index of 2.81, phylum *Bacteroidetes* had the highest level of diversity in the fecal samples, followed by phyla *Proteobacteri*a, *FAFV*. (2.62, 2.46). The stability the diversity indices through time was also evaluated, the phylum *Bacteroidetes* was have the highest stability.

A second study was published in 2016 in the Netherlands, it was a prospective study, conducted between 2012 and 2014, Children with signs of constipation who were referred by pediatricians and general practitioners from various hospitals in the Netherlands were between 4-18 years of age and diagnosed with functional constipation according to Rome III criteria. Roman III criteria were used to diagnose functional constipation in 76 children's feces. (range 4.2 ± 17.8, average age 8.0 years) were analyzed by IS-pro, and PCR-based assay. (16S-23S rDNA and Region IS), the results were compared with intestinal microbiota profiles of 61 healthy children (range 4.1 ± 17.9, average age 8.6 years). Microbiota identification was represented by principal coordinate analysis (PCoA), diversity was calculated by Shannon diversity index. To determine the most discriminating species on total microbiota profiles (all phylum combined) or phylum analysis, functional constipation and controls could be discriminated with 82% accuracy. The most discriminating species were *Bacteroides fragilis, Bacteroides ovatus, Bifidobacterium longum, Parabacteroides species* (functional constipation has increased) and *Alistipes finegoldii* (functional constipation has diminished): *Bacteroides fragilis, Bacteroides ovatus, Parabacteroides spp., FAFV*: *Bidobacterium longum), Proteobacteria*: *Proteus mirabilis*, Unknown species. Decreased abundance of functional constipation; *spp*. *Bacteroidetes: Alistipesnegoldii* and *FAFV*: *Ruminococcus*.

Table 5: Composition and stability of intestinal flora in healthy and constipated children in a population of Dutch.

References	Year	Region	N.of samples	Age	16S rRNA and Region	Microbes			
Tim G., Andries E., Evelien F et al *2016*	2011 - 2014	Netherlands	61	4 to 18 years	16S-23S rDNA and Region V1-V3	**Stability**		**Diversity**	
						Proteobacteria	3.41 %	*phylum Bacteroidetes*	2.81 %
						Firmicutes	5.32 %	*Phyla Protéobactéries*	2.62 %
						Bacteroidetes	1.33 %	*FAFV*	2.46 %
Tim G, Evelien F, Anat E et a*l.2016*	2012 - 2014	Netherlands	65	4 to 18 years	16S-23S rDNA and Region IS	*Phyla: combinés constipation fonctionnelle*	3,9%	*Contrôles*	3.8 %
						phylum: bactériodètes (constipation fonctionnelle	2,9%	*phylum: bactériodètes (constipation fonctionnelle*	2.9 %
						FAFV (fonctionnel constipation	2.6%	*FAFV (fonctionnel constipation*	2.6 %
						actéries (constipation fonctionnelle)		*actéries (constipation fonctionnelle*	

Abbreviation: FAFV*: Firmicutes, Actinobacteria, Fusobacteria, Verrucomicrobia,* **PCoA**: principal coordinate analysis.

Gut microbiota in children and adults

This study was published in 2013 in the United States to investigate the intestinal microbiota in children's and adults in the USA population, a total of 51 subjects (n/28) having a 2.7-year median age. (extremes 1-4). The population of (13/46%) male and (15/54%) female, (16/59%) white, (7/26%) black, (3/11%) Hispanic, (1/3.7%) Pacific Islander, and the ethnicity of one child was not registered.

The study's adult population (n/23) were between ages of 21 and 60, with a mean age of 28, (19/83%) female, (20/87%) white, (2/9%) black and (1/4%) Asian. Phylogenetic microarray analysis targeting 16S rRNA V1 and V6 regions by PCR detected (1038) 22 phylum groupings, (130) genus-like groups, species-like groups were found in the fecal samples of the study population (children, adults). *Actinobacteria, Bacilli, C. cluster IV, Bacteroidetes* were the predominant phylum groups showing differences between adults, young children.

Clostridium phylum cluster XIVa type group was also predominant in adults, young children and is therefore considered established at an early age. The gender level shows significant differences of 3.6 times (more or less) abundance of 26 genders between adults, young children. Also *Bifidobacterium* is significantly 3.5 times more prevalent in young American youngsters, compared to adults in the same location. Nevertheless, compared to adults, young children's microbiota is less diversified. Despite the fact that the gut flora resembles that of adults developing later than previously believed.

Table 6: Gut microbiota in children and adults in the USA population.

References	Year	Region	N.of samples	16S rRNA and Region	age	Microbes		
Tamar R, Jing C, Yehuda R et al 2013	2013	USA	51	Human intestinal tract chip (HITChi) 16S rRNA V1 and V6 regions (quantitative PCR)	1 to 2 years 21-60 years	**Relative contribution%**		
						Adults		**Children's**
						Actinobacteria		
						Bifidobacterium	2.893	10.958
						Bacilli		
						Lactobacillus plantarum et rel.	0.045	0.072
						Streptococcus bovis et rel.	0.672	2.617
						S. intermedius et rel.	0.127	0.289
						S. mitis et rel.	0.409	1.267
						Bacteroidetes		
						Alistipes et rel.	1.482	0.365
						B. intestinalis et rel.	0.525	0.159
						B, splanchnicus et rel.	0.808	0.268
						B, stercoris et rel.	0.956	0.151
						B, vulgatus et rel.	1.609	0.580
						Prevotella tannerae et rel.	0.808	0.287
						Tannerella et rel.	0.531	0.175
						Uncultured Bacteroidetes	0.011	0.005
						Clostridium cluster III		
						C. s, et rel.	1.963	0.511
						C.cluster IV		
						Eubacterium siraeum et rel.	0.517	0.517
						Oscillospira guillermondii et rel.	3.582	0.738
						Sporobacter termitidis et rel.	0.883	0.327
						C. cluster XIII		
						Peptostreptococcus micros et rel.	0.020	0.031
						Butyrivibrio crossotus et rel.	0.902	0.441
						Fusobacteria		
						Fusobacteria	0.016	0.023
						Proteobacteria		
						Campylobacter	0.018	0.026
						Helicobacter	0.012	0.017
						Klebsiella p, et rel.	0.013	0.020
						Proteus et rel.	0.011	0.016
						Vibrio	0.012	0.017
						Yersinia et rel.	0.010	0.016

The intestinal flora and autism

Fecal intestinal flora in autistic children

The first study we have analysis was published in the USA in 2010, has demonstrated that there is proof of a hereditary susceptibility to autism, but the percentage of autistic subjects is unknown. There are undoubtedly additional factors at play, such as environmental effects, may play a role in this illness. In the present study, they examined the fecal microbial 33 subjects with varying severity of autism, with gastro-intestinal symptoms.

Results on the flora in the stools of young children, autistics with gastro-intestinal symptomatology was statistically significant when comparing autistic and control subjects ranging from P-values <0.001 to 0.009 using parametric and nonparametric estimators. At the phylum level, *Firmicutes* and *Bacteroidetes* seen the highest difference between the groups of different autism severity. *Bacteroidetes* was found at high levels in the severe autism group, while *Firmicutes* was more predominant in the control group, there were also more subtle yet significant differences. In the *Actinobacterium* and *Proteobacterium* phyla, the species *Desulfovibrio* and *Bacteroides vulgatus* are present in significantly higher numbers in the stools of severely autism children than in controls.

A second study was published in Spain in 2022, had shown that dysbiosis in the intestinal microbiota of autistic children, which may be a determining factor on the development of the child through the microbiota-gut-brain axis. It is unclear, nevertheless, if autistic children have a particular strain of dysbiotic bacteria. According to a study, autistic children have a higher percentage of gut microbiota than children without the condition. In autistic children than healthy children, except for *Sutterella and Bifidobacterium* which are higher in healthy children.

The phylogenetic characterization of *Sutterella* species in intestinal biopsy from children with autism and gastro-intestinal disorders

In this Study published in 2012 in the USA, was shown that gastro-intestinal disorders in children with autism may be associated with changes in the composition of intestinal bacteria, in this study they studied the intestinal flora in ileal and caecal biopsy samples of children with autism, gastro-intestinal dysfunction (autism) and children with only gastro-intestinal dysfunction (healthy controls). By PCR assays and Western Immunoblot analysis the autistic children compared to healthy control children. Individual analysis of autism patients revealed that 46.7% (7/15) of the autistic patients had elevated levels of the *Sutterella* 16S rRNA gene. *Sutterella* sequences were absent from all samples in healthy children. In these seven autistic patients with *Sutterella* sequences, ileal *Sutterella* sequence abundance varied from 1.7 - 6.7%. For the same patients, abundance caecal *Sutterella* sequence ranged from 2.0 to 7.0% of the total number of bacteria reads As for PCR and Western Immunoblot analysis in autistic 65% and healthy controls 11%.

Showing that *Sutterella* is a significant component of microbiota in more than half of children with both gastrointestinal dysfunction and autism, but not in children with only gastrointestinal dysfunction.

Table 7: The intestinal flora, autism in children and *Sutterella* species' phylogenetic analysis in colon biopsy samples from kids with autism and digestive problems.

References	Year	Region	N. .of samples	16S rRNA and Region	age	Microbes			
Sydney M., Scot E, Viktoria G et al 2010	2010	USA	198	High quality DNA	Children	**Children autistic (Cases)%**		**Non-autistic children (Control)%.**	
						Bacteroides	35.544	*Bacteroides*	24.481
						Clostridium	10.343	*Clostridium*	17.748
						Faecalibacterium	10.173	*Faecalibacterium*	11.271
						Eubacterium	5.521	*Ruminococcus*	7.581
						Ruminococcus	3.329	*Eubacterium*	9.749
						Roseburia	2.033	*Alistipes*	2.621
						Dorea	0.297	*Roseburia*	0.742
						Hespellia	0.176	*Anaerofilum*	0.104
						Turicibacter	0.152	*Streptococcus*	0.600
						Akkermansia	7.344	*Turicibacter*	3.773
						Parabacteroide	5.222	*Parabacteroide*	1.980
						Alistipes	4.296	*Dorea*	3.504
						Sporobacter	1.173	*Veillonella*	0.740
						Bifidobacterium	0.258	*Akkermansia*	1.026
						Anaerostipes	0.223	*Sporobacter*	0.054
						Ethanoligenens	0.113	*Ethanoligenens*	0.477
						Anaerotruncus	0.092	*Papillibacter*	0.140
						Holdemania	0.084	*Holdemania*	0.107
						Phascolarctobacterium	1.382	*Weissella*	1.918
						Desulfovibrio	0.276	*Dialister*	0.032
Pedro A, María R, Julio S et al 2022	2020	Spain	93	Unspecified	Children	Bacteroidetes	14.33%	Bacteroidetes	10.97%
						Bacteroides	9.04%	*Bacteroides*	4.69%
						Firmicutes	13.42%	Firmicutes	10.77%
						Clostridium	0.74%	*Clostridium*	0.16%
						Roseburia	0.11%	*Roseburia*	0.09%
						Ruminococcus	2.90%	*Ruminococcus*	2.21%
						Proteobacteria	0.09%	Proteobacteria	0.02%
						Sutterella	0.11%	*Sutterella*	0.22%
						Actinobacteria	0.53%	Actinobacteria	0.43%
						Bifidobacterium	0.46%	*Bifidobacterium*	0.89%
Brent L, Mady H, T.P et al 2012	2012	USA	32	*Sutterella*- 16S rRNA gene R. V6–V8		**results of PCR tests and Western immunoblot analysis of *Sutterella* spp.**			
						Autistic		**Healthy controls**	
						S. stercoricanis	65 %	*S. stercoricanis*	11%
						S. wadsworthensis		*S. wadsworthensis*	
						S. parvirubra		*S. parvirubra*	
						S. sanguinus		*S. sanguinus*	

DISCUSSION

The importance of our study is to analyze the intestinal microbiota in the child in its composition and its physiological variations or its variations with certain pathologies, in our meta-analysis we have selected 11 articles and 95 participants carried out in the last 12 years in 7 countries to analyze and compare the data of these studies to conclude to an analytical and statistical knowledge on the intestinal microbiota of the child and its change with certain bills. The data can be complicated by the fact that it is first related to the immunity of the mother during pregnancy and after delivery, that it conditions the composition of the gut of the infant and its microbiota by selective consumption by commensal bacteria. Composition of the intestinal microbiota in children (2020 in Australia), Phylum-level impact revealed that the microbiota was dominated at the family level by *Prevotellaceae* 12.1%, *Ruminococcaceae* 13.9%, *Lachnospiraceae* 16.8%, *Bacteroidaceae* 17.5%, and *Verrucomicrobia* 0.57%, *Proteobacteria* 2.93%, *Actinobacteria* 5.98%, *Bacteroidetes* 36.0%, *Firmicutes* 51.1%, *Bifidobacteraceae* 5.09%. Asian children reported high concentrations of *Peptostreptococcaceae* (1.96%) and *Bifidobacteriaceae* (12.0%).

In the age (<4 years) there were larger proportions of *Bacteroidaceae* 31.05% and *Prevotellaceae* 2.93%. The proportions of *Bifidobacteriaceae* was five times greater than in the age over 10 years. In region V1-V3 was five times greater (4.07% compared to 0.81% in region V6) these findings agree with research conducted previously in Europe, Africa, and the USA[(23)], the impact at the level of taxonomic genus: bacteria were the children dominated by *Lachnospiraceae* 3.26%, *Bifidobacterium* 5.47%, *Faecalibacterium* 7.51%,*Prevotella 8.69%, and Bacteroides 16.0%.* Same results found in the USA [(24)], At the phylum level, children from Western geographic locations had a microbiome that was similar in North America, while children in Europe had higher proportions of *Firmicutes* than children from other geographic regions.

This similarity is also observed at the level of the family, in a less distinct way. The differences in sequence analysis are highly variable from one geographic location to another. For example, in the studies in North America there was a significant difference in all regions, but for the Asian, only significant difference in diversity was between studies from the V6 region, whole-genome (V4 region are not displayed). As discussed, some highly variable regions the V4 region, may provide a more accurate representation in China, USA and Canada [(25)].

Distribution the intestinal microbiota in children with cystic fibrosis in 2022 a study in Turkey, had shown that intestinal inflammation is a characteristic of cystic fibrosis. Had shown the Presence in the profiles of children with cystic fibrosis compared to healthy controls, children with cystic fibrosis had significantly different intestinal microbial. The levels of *Eubacterium rectale, Bacteroides vulgatus, Bacteroides uniformis, Bifidobacterium adolescentis, Faecalibacterium prausnitzii* and *Bifidobacterium catenulatum* were reduced in children with cystic fibrosis. There was a hypothesis the abnormal environment of small intestine of cystic fibrosis illness, which is characterized by abnormal acidic pH and electrolytes, could select specific bacteria (species and genera). In turn, compared to control subjects, children with Crohn's disease, ulcerative colitis, and indeterminate colitis may have an aberrant microbiota that causes intestinal inflammation as opposed to being the cause of it. in Italy [(26)].

Composition of intestinal microbiota in children with covid 19, children with Multisystemic Inflammatory Syndrome (2022 in Italy), alterations in the intestinal microbiota could be part of the pathogenesis of the predisposing factor to the Multisystemic Inflammatory Syndrome, in the group of Multisystemic Inflammatory Syndrome the results showed that the levels phylum were as follows: *Verrucomicrobia* 3%, *Actinobacteria* 7%, *Proteobacteria* 11%, *Bacteroidetes* 32% *and Firmicutes* 46% and in SARS Group CoV-2, the levels were *Verrucomicrobia* 2%, *Actinobacteria* 9%, *Proteobacteria* 12%, *Bacteroidetes* 25%, and *Firmicutes* 51%. A previous study showed an increase in the relative abundance of *Bacteroidetes*, a decrease in the relative abundance of *Firmicutes* in intestinal composition in China [(27)].

Composition of intestinal microbiota in children at the onset of type 1 diabetes, (2014 Finland), the abundance of the class *Bacilli* (especially *streptococci*), phylum *Bacteroidetes* was higher in diabetic children, whereas the abundance of *C. IV*, *XIVa* was higher in healthy controls. Controls older than 2.9 years were characterized by a higher fraction of butyrate-producing species in *C. XIVa* and *IV* compared to children of the same age or younger, and diabetic children older than 2.9 had increased microbial diversity. In a study involving 7-year-old Spanish diabetic children who had type 1 diabetes for 4

years prior, the *Blautia coccoides-Eubacterium rectale* group (*C. XIVa* group) was found to be less represented in diabetic children, there are several types of evidence on the importance of butyrate production with regard to the development of type 1 diabetes. Butyrate is colonic epithelium cells' primary source of energy, but also, type 1 diabetes in humans has been associated with intestinal permeability and inflammation in the UK and Finland [28].

Differences in intestinal microbiota in Healthy and diabetic children, (2014 Turkey), in children with type 1 diabetes, a colonization by *Enterobacteriaceae* 37.1%. A decrease in colonization by *Enterococcus* 28.4%. A baby born through a typical spontaneous vaginal delivery encounters *Enterococcus, Enterobacteriaceae, Streptococcus*, leading to the development of the infant's first bacterial flora. At birth, the digestive system of babies is free of bacteria. Environmental conditions cause the later development of anaerobic bacteria. exclusively at this age of two years that a child develops a bacterial flora similar to that of the USA [29], intestinal *Bifidobacterium, Bacteroides* are reduced. In addition, the development of intestinal flora in babies born by caesarean section is delayed until the age of 1 year. Numerous research shown that caesarean section causes a reduced in *Bifidobacterium, Bacteroides.* in Germany and Sweden [30].

The Netherlands (2016), Short, long-term composition, stability of the gut microbiota in healthy children, by new detection methods, healthy children seem to have shared microbiome with small number of species, the Phylum *Actinobacteria, Firmicutes, Fusobacteria, Verrucomicrobia, Proteobacteria* and *Bacteroidetes.* Studies have shown that the stability of intestinal microbiota differentiated by phylum in the Netherlands [31].

By time point (P= 0.0005), by branch (P= 0.0005), the diversity and stability of the microbial composition across time varied, with *Bacteroidetes* having the highest content, followed by *FAFV, Proteobacteria*. Also, it was found that the composition of *Bacteroidetes* was the most stable, while the stability of the composition of, *Proteobacteria, FAFV* were, on average, lower. (2016 Netherlands), in children with symptoms of constipation, the most discriminating species were *Bacteroides fragilis, Bacteroides ovatus, Bifidobacterium longum, Parabacteroides spp.* (functional constipation has increased) and *Alistipes finegoldii* (functional constipation has diminished): increase in the amount of functional constipation *Bacteroidetes: Bacteroides fragilis, Bacteroides ovatus, Parabacteroides spp, FAFV*: *Bidobacterium longum*) and *Proteobacteria*: *Proteus mirabilis,* Unknown species. Decrease in the abundance of functional constipation; *Bacteroidetes spp*: *Alistipesnegoldii* and *FAFV: Ruminococcus spp.* Similar to these results, a higher abundance of *Bifidobacteria* was observed in constipated subjects, classified at the species level as *Bifidobacterium Longum.* Constipation patients had fewer *Bacteroidetes* mostly (*Prevotella spp*), but more families, genera of the phylum *Firmicutes* were present. in the USA and Ireland [32].

Intestinal microbiota in this study was published in 2013 in the U. S.A to investigate the intestinal microbiota in children's and adults in the USA population, (2013 USA), *Actinobacteria, Bacilli, Bacteroidetes* and C. *cluster IV* are the predominant groups in the phylum that show differences between young children and adults. The results supported those reported in a previous comprehensive study that examined the 16S V4 rRNA variable area in the USA utilizing participants from three continents [23]. *Clostridium* phylum *cluster XIVa* also predominant in young children, adults and is therefore considered established at an early age. However, the microbiota of young children is less diverse than adults. Unlike all that has previously been observed, adult-like intestinal microbiota develops at a later age. In adults, composition of *Actinobacteria, Bacteroidetes* was more stable and that of *Proteobacteria* was less stable over time compared to the overall stability. *Firmicutes* showed a more variable pattern, Additionally, it was found that the stability varied by phylum: *Bacteroidetes* as the most stable component of the intestinal flora, followed by *Proteobacteria* and *FAFV,* Phylum-specific temporal changes in composition may be due to variation in individual diets, as most significant fluctuations have been described in bacterial species involved in food digestion, such as *Bifidobacterium adolescentis, Parabacteroides distasonis*, possessing carbohydrate-degrading enzymes, such as *C. clostridioforme, F. prausnitzii* in the USA, A temporal composition stability research comparing children from Bangladesh and the USA validated this theory of food influences on microbial dynamics, whereas *C. cluster XIVa* was found to be the most abundant bacteria group in adults, children in the USA and the genus *Bifidobacterium*, the most abundant genus in the genus, was the most important group that led to the separation of microbiota composition between children, adults. Higher levels of *Bifidobacteria* in children have already been reported in numerous Japanese, European, research and USA [33].

Fecal intestinal flora in children with autism, (USA 2010), at the phylum level, there is evidence of a genetic susceptibility to autism, *Bacteroidetes* was found at high levels in the severe autism group, while *Firmicutes* were more predominant in control group. The increased

intestinal flora of autistic children may contain harmful genera or species contributing to the severity of autistic symptoms. *Bacteroidetes, Firmicutes* are discovered to significant phylums, the UK [(34)].

Spain (2022), dysbiosis in autistic children's gut microbiota, which, via the microbiota-intestine-brain axis, may have an impact on the child's development. It is unclear, nevertheless, if autistic children have a particular strain of dysbiotic bacteria. Study was shown the percentage of intestinal microbiota in autistic children and healthy children that it is higher in autistic children than healthy children, except for *Sutterella* and *Bifidobacterium* which are higher in healthy children.

Demonstrated that gastrointestinal disorders and autism had a statistically significant association. These results blatantly depart from the initial findings made in Spain.[(35)]. Our findings revealed no proof of a pertinent connection between the *Bacteroidete*s, *Firmicutes, Proteobacteria,* and *Actinobacteria* phyla and gastrointestinal association (autistic). Only *Streptococcus* and *Bifidobacterium* revealed lower abundance in the autistic groups than in the controls when it came to bacterial species. Our findings differ from theirs because they discovered lower levels of *Bacteroidetes*, the *Firmicutes* phylum, and *Proteobacteria* in autistics. Additionally, observed that the autistic groups had lower levels of *Bifidobacterium* and greater levels of *Bacteroides*, *Clostridium*; only their results for *Bifidobacterium* were similar with ours. Nevertheless, the differences between our results and those [(35)]. (2012 USA), the intestinal microbiota in ileal, caecal biopsy from children with autism, gastrointestinal dysfunction (autism) revealed that 46.7% (7/15) of the autism patients had elevated levels of the *Sutterella* 16S rRNA gene. Were absent from all samples in healthy children. in Spain [(35)], the most abundant *Firmicutes* and *Bacteroidetes* genera were more numerous than sequences *Sutterella*, nevertheless not reported as a major component in Germany and USA [(24)].

The results of our meta-analysis on composition and development in children's intestinal microbiome, and its change with certain pathologies in the last 12 years, have shown the importance of studying the intestinal flora in children, and its variations due to several factors, further studies in this area that will help to characterize the relationship between the change of the intestinal flora the development of certain pathologies.

CONCLUSIONS

It is a very important to know the influence of the change in the microbiota predisposition to develop different pathologies or the opposite, which opens a wide range in this subject, hence the importance of carrying out more in-depth studies and research, especially in childhood.

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