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The Impact of Delivery Mode on the Human Microbiome: A Global Perspective

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A Global Perspective: The Impact of Delivery Mode on the Human Microbiome

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Abstract

The mode of childbirth in humans (vaginal or cesarean section) is considered to be one of the most influential factors in the development of gut microbiota of an infant. A microbiome is defined as a collection of microorganisms that are concentrated together in a single location or body site. The genetic material of all microbes, including bacteria, viruses, and fungi, comprises this complex ecosystem. The gut microbiota regulate digestion and strengthen the immune system in humans, helping to maintain homeostasis and are at the early stages of life, dictated by the method of delivery. Vaginal versus cesarean deliveries have increased amounts of microbial diversity, which is considered part of a ‘healthy’ microbiome. Literature has documented associations between cesarean delivery and the risk of developing illnesses such as ADHD, autism spectrum disorders, obesity, type 1 diabetes, and asthma. However, most research in this field has been dominated by studies originating from metropolitan areas within the United States, thus not giving a complete picture of the extent to which birthing methods impact human microbiomes on a global scale. This literature review discusses how these different delivery methods have affected the gut microbiome of infants in regions around the world (including countries in North America, Europe, Australia, Asia, and Central America).

Introduction

The term 'microbiome' refers to a community of microorganisms that are clustered in a specific location. These microbes can vary across their host organisms as each microbiome is unique to a species and considered to be essential for development, immunity, and nutrition. The microbiome is the genetic material of all microbes including bacteria, viruses, and fungi. These microbes may interact in commensalistic, mutualistic or pathogenic manners. Symbiosis or a steady interaction between the human body and its microbiome develops from birth. The largest concentration of the human microbiome is found in the gut, as these organisms are seen to form a complex ecosystem. Interactions between the human host and the gut microbiota are important in maintaining a balanced microbiome. A balanced microbiome plays an important role in the maintenance of the health and well-being of an individual. When it is altered, it results in dysbiosis which is a reduction in both the microbial richness or diversity in the microbiome, where one genus or species of microbe may become the most abundant. This can increase an individual's likelihood for developing life-threatening health conditions such as cancer, inflammatory bowel disease, cardiovascular disease, and many others (Ogunrinola et al., 2020).

The gut microbiome is vital for the development of an infant and can be affected by several factors. The gut microbiome population can be attributed to exposure to antibiotics, environmental upbringing, and most importantly, vaginal versus cesarean births. Vaginally delivered newborns have a gut microbiome that is very similar to the mother's vaginal and fecal flora. This is due to the vertical transfer (parent to offspring) of microbes as the infant is delivered through the birth canal. The gut microbiome of an infant born by cesarean section contains bacteria that are horizontally transferred from the environment and the mother. This

could occur through the transmission of bacteria from the mother or a shared caregiver's hands and can usually be prevented by proper hand hygiene (Morinis et al., 2011).

When a newborn is first delivered, they immediately come in contact with a multitude of microorganisms even in a sterile hospital setting, including those from the air, nearby individuals, and perhaps even tools used to aid in delivery. Most of these microbes however are received from the mother through vertical transmission. An important bacteria found in the gut of vaginally delivered newborns is *Lactobacillus*. The presence of lactobacilli through gestation aids in maintaining a relatively lower pH which prevents bacteria from infecting the uterus, placenta, and amniotic sac (Mueller et al., 2015). However, this presence can change after a few months when the infant develops its unique cluster of microbes. An important bacteria found in the gut of cesarean-delivered newborns is *Staphylococcus spp.* which resembles the human skin microbiota. These infants contain less overall diversity in the number of microbes present in their gut after birth than their vaginally-born counterparts. It was seen that around 64% to 82% of reported cases of methicillin-resistant *Staphylococcus Aureus* (MRSA) skin infections in newborns occurred in cesarean-delivered infants (Dominguez-Bello et al., 2010). An increase of bacteria belonging to the *Staphylococcus* genus may be why infants born via cesarean section are much more susceptible to pathogens infections compared to vaginally delivered infants (Neu et al., 2011). It was hypothesized that the direct transmission of bacteria from the vaginal canal may serve as a protective role by reducing colonization of MRSA or other harmful pathogens. (Dominguez-Bello et al., 2010).

Overall, the general consensus regarding the infant's microbiome is that delivery mode plays a pertinent role in the development of important bacteria and can also affect the development of future illnesses.

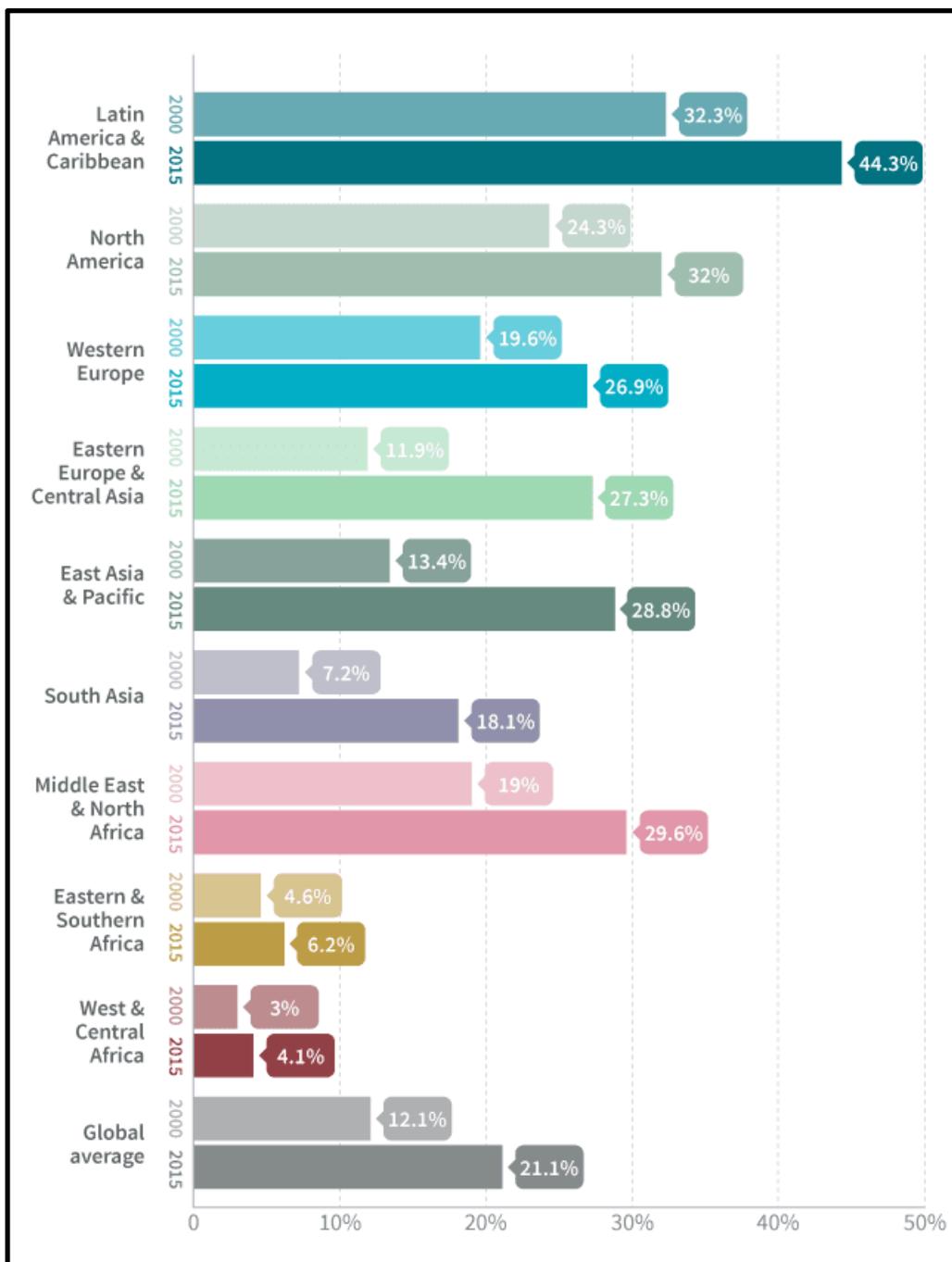


Figure 1: This figure from 2019 shows how there has been a global increase in cesarean deliveries by almost twice the amount in the span of 15 years. This suggests that other parts of the world have increased the amount of cesarean-sections performed due to advances in medical technology. In the present literature review, we will assess a multitude of studies from different regions of the globe and determine the extent to which vaginal births are considered ‘more healthy’ for an infant’s microbiome. *C-sections: What to expect: AXA - Global Healthcare*. AXA. (2019). Retrieved November 22, 2021, from <https://www.axaglobalhealthcare.com/en/wellbeing/pregnancy/caesarean-section/>.

The Effect of the Mode of Delivery on an Infant's Microbiome: Around the World

North America

A multitude of research in the field of delivery method impact on microbiome has already taken place within the United States and can be seen in a number of publications within the US that have examined the human microbiome (Rutayisire et al., 2016). As such, we will focus the majority of this review on publications outside of the United States, as they are commonly under cited in the current literature.

A study performed in Canada in 2013 sought to describe the influence of cesarean deliveries on the gut microbiota of Canadian newborns. A study of Canadian newborns showed that *Escherichia-Shigella* bacterium was underrepresented in cesarean deliveries, compared to their vaginally-born counterparts. This microbe has been linked to producing a toxin that can result in life-threatening disease (Azad et al., 2013). This is surprising because cesarean-sections are more commonly seen to have more adverse infant outcomes than vaginal births. This study links this finding to a previous European culture-based study that reported delayed colonization by *E.Coli* in cesarean-born infants. It was also found that the bacteria phylum *Bacteroidetes* was undetectable in infants born by cesarean delivery which is linked to performing carbohydrate digestion through a series of metabolic pathways. Unsurprisingly, bacterial diversity was lowest among cesarean born infants, yet highest among emergency cesarean deliveries.

Further research out of Canada suggested an association between birth mode and intergenerational obesity (Tun et al., 2018). The study utilized 16S ribosomal RNA (16S rRNA) sequencing taxonomic classification to analyze the participants. There were 935 mother-infant pairs, including many in the overweight/obese category, discovered that infants born vaginally to overweight or obese mothers were 3 times more likely to become overweight at age 1 year. On

the other hand, cesarean-delivered infants of overweight mothers had a 5-fold risk of being overweight at the age of 1 year and similar risks were observed at the three year mark. It was seen that birth mode and infant gut microbiota, most specifically, the *Lachnospiraceae* family regulated the link between maternal pre-pregnancy obesity and childhood obesity. Bacterial samples belonging to the *Lachnospiraceae* family were more abundant in infants of overweight mothers; however, the samples observed of *Lachnospiraceae* differed between infants delivered vaginally and those delivered via cesarean birth. This bacterium is important because it degrades complex polysaccharides to short-chain fatty acids, which can be important for the breakdown of fat in the body. Overall, this study concluded that *Lachnospiraceae* plays a novel role in mediating a pathway involving birth mode and intergenerational transmission of obesity (Tun et al., 2018).

A study in Mexico aimed to explore the relationship between delivery mode and gut microbiome profiles in healthy infants. Fecal samples of 57 term infants were used to characterize the microbiota composition using high-throughput 16S rRNA gene sequencing (Murata et al., 2020). A high amount of Proteobacteria was found in the gut microbiota of all Mexican infants studied, regardless of delivery method. Feces from infants born by C-section had low levels of *Bacteroidetes* and high levels of *Firmicutes*. This high ratio of *Firmicutes* /*Bacteroidetes* (F:B) has been linked to cesarean-deliveries and the development of diabetes and obesity. Alternatively, samples enriched in *Bacteroidetes* and low F:B ratios, were strongly associated with vaginal delivery (Murata et al., 2020). This study not only showed a significant difference in microbial diversity between the two delivery methods but also suggested that C-section births may contribute to obesity and other unknown pathologies in Mexican children. The richness of *Proteobacteria* found in the Mexican infant population is much higher than that

found directly in the soil and this amount has remained high until 3 years of age. The high abundance of *Proteobacteria* that was found in Mexican infants could represent a future risk factor that may lead to inflammatory bowel disease or other metabolic disorders (Rizzatti et al., 2017). Furthermore, this study proposes that health policies in Mexico should be developed and promoted by physicians to encourage vaginal delivery in order to decrease the risk of developing obesity worldwide

Europe

A number of studies from Europe in the field of delivery methods are associated with Scandinavia, as the government has invested in long term health studies that begin at a young age. A study from Denmark involved 700 children from the Copenhagen Prospective Studies on Asthma in Childhood 2010 (COPSAC2010) birth cohort in which fecal samples and hypopharyngeal aspirates were taken at one week, one month, and one year of age. A total of 78% (549) were born by means of natural delivery, 12% (85) by means of emergency cesarean section, and 9% (66) by means of elective cesarean section. Colonization of the intestinal tract by *Citrobacter freundii*, *Clostridium species*, *Enterobacter cloacae*, *Enterococcus faecalis*, *Klebsiella oxytoca*, *Klebsiella pneumoniae*, and *Staphylococcus aureus* was significantly associated with cesarean birth at 1 week, whereas colonization by *Escherichia coli* was associated with natural birth. Children who are born by natural birth get *E.coli* mostly by transmission from their mothers, whereas those born by cesarean section primarily harbor hospital strains of *E. coli*. Most surprisingly, variation between delivery modes was less noticeable at 1 month and nonexistent at 1 year. This suggests that we could just witness the colony attaining a state of equilibrium over time, regardless of disease impacts. (Stokholm et al., 2016).

Further studies in Denmark using COPSAC2010 children investigated whether gut microbial disturbances caused by delivery mode were linked to an increased risk of asthma in the first six years of life. Seventy-eight percent of the babies were born naturally, 12% via emergency cesarean section, and 9% via elective cesarean section. Colonization of the intestinal tract by *Citrobacter freundii*, *Clostridium species*, *Enterobacter cloacae*, *Enterococcus faecalis*, *Klebsiella oxytoca*, *Klebsiella pneumoniae*, and *Staphylococcus aureus* was significantly associated with cesarean birth at 1 week, whereas colonization by *Escherichia coli* was associated with natural birth. These changes were less noticeable at 1 month, and they were completely absent by 1 year, similar to the previous study. This study suggested that children born by cesarean section had an increased asthma risk only if their gut microbiota composition at 1 year of age still closely resembled their initial microbial signature. (Stokholm et al., 2016).

Another study from Scandinavia in Sweden investigated the association between obstetric mode of delivery and autism spectrum disorder (ASD). Similar to COPACS2010, the cohort was extensive, including all live births in Sweden from January 1, 1982, to December 31, 2010. Mode of delivery was divided into 4 categories: unassisted vaginal delivery (VD), assisted VD, elective CS, and emergency CS. A total of 2,697,315 participants were included in this study. A total of 2,161,148 children (80.1%) were born via non assisted VD, 164,305 (6.1%) via elective CS, 175,803 (6.5%) via emergency CS, and 196,058 (7.3%) via assisted VD. A total of 28,290 children (1.0%) were diagnosed as having ASD. The study revealed that elective CS and emergency CS were significantly associated with ASD while vaginal delivery was not. A sibling study showed that 13,411 discordant sibling pairs on ASD, and 2,555 pairings were also discordant on birth mode (with one sibling born by unassisted VD). The results showed there was no association between assisted VD or elective CS and ASD. (Eileen et al., 2015).

A follow up study from Sweden investigated the association between mode of delivery and ADHD in a large, population-based cohort with survival analysis both in the general population and among siblings. There were 1,722,548 participants in the cohort. Majority of them were delivered through non-assisted VD (1,353,845; 78.6%), followed by assisted VD (130,007; 7.6%), and emergency CS (124,621; 7.2%) and elective CS (114,066; 6.6%). In total, there were 47,778 cases of ADHD (2.8%), with the majority of them receiving medication at some time. When compared to vaginal delivery, CS birth was associated with a 14% – 16% greater risk of ADHD, according to the survival analysis. However, in sibling-matched studies, the correlation was significantly reduced, implying that the link may not be causal but rather owing to familial or environmental confounding. Among siblings the association only remained for emergency CS. (Eileen et al., 2016).

Research from Italy in 2017 sought to assess the impact of delivery mode on the microbiota of colostrum on a quantitative and qualitative level (bacterial abundance and microbiota network). Human colostrum is a nutrient-dense fluid that is critical for a newborn's early development. Colostrum is produced by the mammary glands from the moment the baby is born until the fifth or sixth day of life. Colostrum helps infants adjust to their new environment outside of the womb, and it also lowers the chance of gastrointestinal disorders. *Staphylococcus*, *Streptococcus*, and *Bacteroides* species are among the bacteria found in colostrum. The study included 29 Italian mothers (15 vaginal deliveries compared to 14 cesarean sections). The results showed that there were numerous differences between cesarean section and vaginal delivery colostrum. When compared to cesarean section colostrum samples, vaginal delivery colostrum had much less *Pseudomonas spp.*, *Staphylococcus spp.*, and *Prevotella spp.* Furthermore, the mode of delivery had a significant impact on the microbiota network, with colostrum from a

cesarean section having a higher number of bacterial diversity than colostrum from a vaginal delivery, which only shared 5 detected bacterial types. Women who had a cesarean section had more environmental bacteria in their colostrum than mothers who had a vaginal birth. Finally, both colostrum from a cesarean section and colostrum from a vaginal delivery had more anaerobic bacteria species. The study shows how mode of delivery has an impact on the microbiota of colostrum. However, more research is needed to better understand the changes in colostrum microbiota between cesarean section and vaginal birth. (Toscano et al., 2017).

Australia

Although not abundant compared to North America, several studies from Oceania investigated links between birth method and bacterial abundance. A study from Australia in 2019 explored the risk of type 1 diabetes in children born via caesarean section to children born via vaginal delivery. Similar to Europe, data was derived from a longitudinal health study, the South Australian Early Childhood Data Project, containing all births between 1999 and 2013. Inpatient hospitalizations were used to identify type 1 diabetes cases between 2001 and 2014. Between 1999 and 2013, a total of 286,058 children were born, resulting in 200,252 person-years, of which 557 developed type 1 diabetes. A total of 90,546 (31.7%), of all deliveries were caesarean, with 53.1% occurring before labor and 46.9% occurring during labor. The adjusted hazard ratio for type 1 diabetes was 1.05 for caesarean, 1.02 for pre-labor caesarean, and 1.08 for intrapartum caesarean as compared to vaginal delivery. Hazard ratio (HR) is the level of risk associated with conditions defined by two levels of descriptive variables. The study states that although there was a slight increase in the risk of type 1 diabetes after a caesarean section, it was not significant. Because of the smaller estimate for prelabor compared to intrapartum caesarean it concludes that the newborn vaginal microbiome is likely not involved in type 1 diabetes. (Begum et al., 2019).

Research from New Zealand in 2021 was done to assess a randomized controlled experiment to examine if vaginal seeding by oral administration at birth could help infants with CS develop their gut microbiome. Vaginal seeding refers to the practice of inoculating a cotton gauze or a cotton swab with vaginal fluids to transfer the vaginal flora to the mouth, nose, or skin of a newborn infant. The intended purpose of vaginal seeding is to transfer maternal vaginal bacteria to the newborn. The Early Colonization with Bacteria After Birth (ECOBABe) trial was used for this study. Pregnant women who were scheduled for a CS were subjected to a thorough prenatal pathogen screening. The 80 pregnant women included 45 planning a CS and 35 a vaginal birth. Healthy newborns were given a 3 ml solution of maternal vaginal bacteria or sterile water at delivery. Shotgun metagenomic sequencing was performed on infant stool samples and maternal vaginal extracts from CS mothers. Over the course of the study, babies were evaluated at three different times: at birth (24 hours), one month, and three months. The results showed at one month or three months of age that there was no difference in the microbial makeup of stools collected from CS infants who received vaginal seeding compared to those who got the placebo. It was shown that CS-born infants have lower relative abundances of *Bacteroides spp.* Although maternal pathogen screening reduces the chance of infection, the hazards associated with transplanting microbiota, particularly in newborns with weak immune systems, necessitate continued caution. The argument for this procedure's utility in reducing illness risk in CS-infants may now be irrelevant, given that it was unable to reverse gut microbiota development. Future study is also needed to evaluate whether microbiota restoration might meaningfully reduce the chance of acquiring other CS-related illnesses, such as obesity, according to the article. (Wilson, et al., 2021).

Asia

A study performed in China in 2015 explored the bacterial community structure present in different delivery modes in Chinese newborn. The purpose of this study is to identify differences in bacterial taxa during cesarean births that may influence the health of the infant. A cross-sectional study was performed using fecal specimens from 25 vaginally delivered infants and 16 cesarean section infants. As with other studies, these samples were analyzed using 16S rRNA gene sequencing. It was determined that vaginally delivered and cesarean delivered infants did not differ in the richness of their bacterial community, but did differ in their bacterial taxa. In vaginally delivered infants the predominant taxa was *Escherichia Coli and Bacteroides sp.* Both of these bacteria are found in the gut and perform digestive and metabolic functions that are necessary in digesting the food an infant consumes. While in cesarean delivered infants the predominant taxa was *Staphylococcus sp. and Streptococcus sp.* These bacteria can facilitate the occurrence of several human diseases and may be involved in inflammation and pneumonia. Overall, researchers concluded that the delivery mode has a significant influence on the structure of intestinal microbiota in Chinese newborns. (Liu et al., 2015)

An unrelated analysis also performed in China in 2015 looked at the relationship between the mode of delivery and childhood hospitalization for asthma and other wheezing disorders. The authors of this study acknowledge that this association has not been extensively tested in Eastern nations and should be investigated especially in highly polluted regions. The purpose of this study was to determine if the mode of delivery and hospitalizations for asthma were significant in non-Western areas that have high rates of C-sections. A population sample of 8,327 Chinese children ages 9 days to 12 years were used in Hong Kong. The association between mode of delivery with public hospital admissions for asthma, bronchitis, and

bronchiolitis was assessed for each participant. It was determined that cesarean section accounted for 27% of the cohort's births but was not clearly associated with hospitalizations for asthma and other wheezing disorders. This study suggests that delivery by cesarean section and childhood wheezing disorders may differ based on one's environment, but it is important to have further research to address the question of whether the microbiome plays a significant role in the manifestation of childhood lung disorders (Leung et al., 2015).

A Japanese study in 2019 looked at the effect of delivery mode on the nutrition and gut microbiome of infants. The aim of this study was to determine the effect of prebiotic-rich breast milk on gut microbiota dysbiosis. The study used stool samples from 36 Japanese infants which were obtained at 4 days and 1 month of age. It was determined that at 4 days old, infants who were delivered vaginally had higher diversity of bacteria than those who were born via cesarean section. Most specifically, Bacteroidales and Enterobacteriales were seen to be overrepresented in vaginally delivered infants. Bacteroidales is an order of bacteria helpful for breaking down food and obtaining valuable nutrients, while Enterobacteriales is an order of bacteria that contains both harmless and pathogenic bacteria. Infants born via cesarean section had Bacillales and Lactobacillales overrepresented. Bacillales and Lactobacillales are both present in the gut microbiome; their role on the human body together still requires more research to be performed. From these results it was concluded that cesarean section reduced the diversity of infant gut microbiome resulting in dysbiosis (Akagawa et al., 2019).

Further recent research in Japan around 2020 looked at whether vaginal microbiota is associated with premature labor and preterm delivery. It examined a total of 64 women, 47 of whom had threatened premature labor and the remaining 17 did not have threatened premature labor. It was determined that there were no significant differences between vaginal microbiota

between threatened and non-threatened premature labor groups. However, a significant difference between preterm and full-term delivery groups was seen regarding the amount of *Lactobacillus* present, the amount of bacteria present, and the positivity of *Ureaplasma* species present. It was concluded that since cesarean sections are often used in times of high-risk pregnancies where the infant is born preterm this can result in a significant difference in the bacterial composition of newborns (Shi, Y., et.al., 2020). The absence of the *Lactobacillus* species in pregnant women increases the risk of preterm delivery and low infant birth weight compared to women with rich *Lactobacillus* vaginal flora during pregnancy. As poor obstetrical outcomes have been linked to imbalanced vaginal flora, the role of *Lactobacillus* is significant in preventing high-risk pregnancies from occurring (Farr et al., 2015).

A study performed in India in 2012 analyzed the fecal microflora of healthy full-term infants born via different delivery modes. This study was carried out in Maharashtra, India using 24 infants (12 cesarean-born, 12 vaginally-born). All infants used in this study were delivered healthy full-term and the results obtained from this study revealed that fecal microbiota of vaginally born infants differed evidently from those born via cesarean section. The most prevalent bacterial species noted in vaginally-born infants was *Acinetobacter sp* and *Bifidobacterium sp*. *Acinetobacter sp* is associated with infections and *Bifidobacterium sp* are linked to aiding in digestion. For cesarean-born infants it was noted that fecal microbiota was primarily composed of *Citrobacter sp*. and *Clostridium difficile*, both of which are linked to the development of gastrointestinal infections (Angela et al., 2017). It was seen that the intestinal microbiota in cesarean-born infants was more diverse in terms of bacterial species than those born via vaginal delivery, in which the *Bifidobacteria* species was present. (Pandey et al., 2012).

Central America & South America

A Venezuelan study in 2010 examined the entire community's idea of the effect of delivery mode as well as physical location in the child's first microbiota. The study included nine women between the ages of 21 and 33 years old, as well as their ten babies. Three males and one female were born vaginally to four women (two Mestizo and two Amerindians). Five women (four Mestizo and one Amerindian) gave birth to three females and three males via C-section, including male dizygotic twins. To characterize bacterial communities from mothers and their newborn offspring, this study used multiplexed 16S rRNA gene pyrosequencing. The mothers' skin, oral mucosa, and vagina were sampled one hour prior to delivery, and their babies' skin, oral mucosa, and nasopharyngeal aspirate were taken 5 minutes after delivery, and meconium was sampled 24 hours later. The findings revealed that vaginally delivered infant's acquired bacterial communities similar to their mother's vaginal microbiota, dominated by *Lactobacillus*, *Prevotella*, or *Sneathia spp.*, whereas C-section infants acquired bacterial communities similar to those found on the surface of the skin of many adults, dominated by *Staphylococcus*, *Corynebacterium*, and *Propionibacterium spp.* This implies that accidental skin bacteria exposure in the hospital environment may contribute to the microbiome of C-section neonates. The importance of designing prospective studies to track the successional development of the baby's microbiome in different body habitats and after different modes of delivery, as well as the effects that any associated microbial community shifts may have on infant health, is highlighted in this study. (Dominguez-Bello et al., 2010).

In a study conducted in Brazil, researchers looked for bacterial DNA in carefully collected meconium and subsequent transitional stools from 59 newborns (13 born through planned C-section and 46 born via vaginal birth). They used polymerase chain reaction (PCR) to amplify

the Variable region 4 of the 16S rRNA. The PCR is a technique for amplifying small segments of DNA and is quick and inexpensive. Using this method, they discovered bacterial DNA in the majority of meconium samples and noticed that bacterial diversity in the neonatal digestive tract diminishes in the first days of life, from meconium to transitional stool. The results showed that there were no significant differences in clinical features between moms or neonates who had meconium with detectable bacterial DNA and those who did not. However, in transitional-stool samples, delivery modality was substantially linked with bacterial structure, composition, and anticipated microbiota metabolic function. *Bacteroides*, *Parabacteroides*, and *Clostridium* were found in lower amounts in the transitional stool of C-section delivered newborns. As a result of these discrepancies, C-section neonates had a reduced expected abundance of microbial genes linked to amino and nucleotide sugar metabolism, but a greater predicted abundance of genes associated to fatty-acid metabolism, amino-acid degradation, and xenobiotics biodegradation. (Mueller et al., 2017).

Africa

Early research performed in Malawi aimed to compare the gut microbiota in 6 month old infants living in Rural Malawi with children of the same age living in urban Finland. Both groups of infants were breast-fed and ate an age-appropriate diet that was typical of their respective regions. There were 44 Malawian 6-month old infants compared with 31 Finnish 6-month old infants. Both cohorts used infant stool samples and utilized flow cytometry fluorescent in situ hybridization and quantitative polymerase chain reaction research methods. Results indicated that *Bifidobacteria*, a harmless probiotic, was present in both infant groups in different proportions 70% Malawian and 46% Finnish. There was no information provided on the modes of delivery of Malwaian participants since cesarean-sections are rare in rural Malawi.

The majority of infants were presumed to be born vaginally and this factor was not compared exclusively to Finnish infants of which 24 out of the 31 infants were born vaginally. It was concluded that the gut microbiota of 6-month old infants in a low income country differed significantly from infants in a high-income country. (Grześkowiak et al., 2012). Since the majority of Finnish infants were born vaginally, *Bifidobacteria* is seen as a common between both cohorts of infants as a common gut colonizer.

Conclusion

This literature review examines how delivery procedures (vaginal or cesarean section) have influenced the gut flora of infants all across the world (North America, Europe, Australia, Asia, and Central America). The data discussed in this review is summarized in Table 1, which documents which microbes increased or decreased with the method of delivery. In North America two studies were performed in Canada, one study aimed to report the impact of cesarean births on the gut microbiota of neonates in Canada, and the other study examined how birth mode and an infant's gut microbiome affect intergenerational obesity. The studies showed that obesity and decreased microbial richness in cesarean births were found to have a significant relationship. Another study in the southernmost region of North America investigated the association between delivery technique and gut microbiota patterns in healthy Mexican newborns which showed that infants born by cesarean section are more likely to have lower amounts of *Bacteroidetes* present in their gut. In Europe two studies were performed in Denmark, the first study described the effects of delivery mode on the colonization patterns of both the intestinal tract and airways during the first year of life, and the other study looked at the relationship between cesarean birth and the risk of asthma in children. Both of these studies show a link between the occurrence of asthma and early colonization patterns in the infant intestine

after cesarean birth. In Sweden, two studies were conducted: one looked at the link between obstetric mode of delivery and autism spectrum disorder (ASD), while the other looked at the link between mode of birth and attention deficit hyperactivity disorder (ADHD). The findings revealed a link between CS birth and an increased risk of autistic spectrum disorder and ADHD. A study in Italy showed how mode of delivery had an impact on the microbiota of colostrum, however more research is needed for further evaluation. In Australia, a study was performed in New Zealand using an untested method of vaginal seeding. These studies found that the CS vaginal seeding approach neither develops nor affects an infant's gut microbiome. However, this method will need to be assessed in the future. Another study in Australia compared the risk of type 1 diabetes in children born by caesarean section vs children born vaginally and determined it was most likely not correlated. In Asia, two studies were conducted in China that shed light on how differences in delivery mode affect an infant's bacterial composition and are linked to the development of asthma and other wheezing diseases. In Japan, two studies revealed that there was a substantial difference in bacterial richness between delivery mode, as well as significant variances between infants born preterm and full term. In India, one study found that infants born via cesarean section had more bacterial species diversity than those born via vaginal birth. In rural Africa, it was seen that a common microbe was present in both rural African and urban European infants of the same age. Overall, the extent to which vaginal births are considered healthier for an infant's microbiome is substantial. Based on the global studies described the data points to less microbial richness in the gut microbiome of an infant born via cesarean section. Developed nations in specific should be targeted to reduce the amount of elective cesarean sections. Future research in this field should explore a longitudinal study on how different delivery modes affect the quality of life as an infant matures.

Country	Author & Year	Vaginal Microbiome	Cesarean Microbiome
China	(Liu et al., 2015)	<i>Escherichia Coli and Bacteroides sp</i> ↑	<i>Staphylococcus sp. and Streptococcus sp.</i> ↑
Japan	(Akagawa et al., 2019)	<i>Bacteroidales and Enterobacteriales</i> ↑	<i>Bacillales and Lactobacillales</i> ↑
India	(Pandey et al., 2012)	<i>Acinetobacter sp and Bifidobacterium sp.</i> ↑	<i>Citrobacter sp.</i> ↑ <i>Clostridium difficile</i> ↑ <i>Bifidobacteria</i> ↓
Venezuela	(Dominguez-Bello et al., 2010).	<i>Lactobacillus, Prevotella, or Sneathia spp</i> ↑	<i>Staphylococcus, Corynebacterium, and Propionibacterium spp.</i> ↑
Brazil	(Mueller et al., 2017).		<i>Bacteroides, Parabacteroides, and Clostridium</i> ↓
Malawi	(Grześkowiak et al., 2012)	<i>Bifidobacteria</i> ↑	
Denmark	(Stokholm et al., 2016).	<i>Escherichia coli</i> ↑	<i>Citrobacter freundii, Enterobacter cloacae, Enterococcus faecalis, Klebsiella oxytoca & pneumoniae, Staphylococcus A.</i> ↑
Italy	(Toscano et al., 2017)	<i>Pseudomonas spp., Staphylococcus spp., Prevotella spp</i> ↓	
New Zealand	(Wilson, et al., 2021).		<i>Bacteroides spp.</i> ↓
Canada	(Azad et al., 2013).		<i>Bacteroidetes & Escherichia-Shigella</i> ↓
Mexico	(Murata et al., 2020).	<i>Proteobacteria</i> ↑ <i>Bacteroidetes</i> ↑ <i>Firmicutes</i> ↓	

Table 1: A summary of the literature referenced in this review and the overall increase or decrease of known bacterial groups.

Works Cited:

Akagawa, S., Tsuji, S., Onuma, C., Akagawa, Y., Yamaguchi, T., Yamagishi, M., Yamanouchi, S., Kimata, T., Sekiya, S. I., Ohashi, A., Hashiyada, M., Akane, A., & Kaneko, K. (2019). Effect of Delivery Mode and Nutrition on Gut Microbiota in Neonates. *Annals of nutrition & metabolism*, 74(2), 132–139. <https://doi.org/10.1159/000496427>

Angela Moya-Pérez, Pauline Luczynski, Ingrid B. Renes, Shugui Wang, Yuliya Borre, C.

Anthony Ryan, Jan Knol, Catherine Stanton, Timothy G. Dinan, John F. Cryan, Intervention strategies for cesarean section–induced alterations in the microbiota-gut-brain axis, *Nutrition Reviews*, Volume 75, Issue 4, April 2017, Pages 225–240, <https://doi.org/10.1093/nutrit/nuw069>

Azad, M. B., Konya, T., Maughan, H., Guttman, D. S., Field, C. J., Chari, R. S., Sears, M. R., Becker, A. B., Scott, J. A., Kozyrskyj, A. L., & CHILd Study Investigators (2013). Gut microbiota of healthy Canadian infants: profiles by mode of delivery and infant diet at 4 months. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne*, 185(5), 385–394. <https://doi.org/10.1503/cmaj.121189>

Begum, M., Pilkington, R., Chittleborough, C., Lynch, J., Penno, M., & Smithers, L. (2019). Caesarean section and risk of type 1 diabetes: whole-of-population study. *Diabetic medicine : a journal of the British Diabetic Association*, 36(12), 1686–1693. <https://doi.org/10.1111/dme.14131>

Curran, E. A., Dalman, C., Kearney, P. M., Kenny, L. C., Cryan, J. F., Dinan, T. G., & Khashan, A. S. (2015). Association Between Obstetric Mode of Delivery and Autism Spectrum Disorder: A Population-Based Sibling Design Study. *JAMA psychiatry*, *72*(9), 935–942.

<https://doi.org/10.1001/jamapsychiatry.2015.0846>

Curran, E. A., Khashan, A. S., Dalman, C., Kenny, L. C., Cryan, J. F., Dinan, T. G., & Kearney, P. M. (2016). Obstetric mode of delivery and attention-deficit/hyperactivity disorder: a sibling-matched study. *International journal of epidemiology*, *45*(2), 532–542.

<https://doi.org/10.1093/ije/dyw001>

C-sections: What to expect: AXA - Global Healthcare. AXA. (2019). Retrieved November 22, 2021, from <https://www.axaglobalhealthcare.com/en/wellbeing/pregnancy/caesarean-section/>.

Dominguez-Bello, M. G., Costello, E. K., Contreras, M., Magris, M., Hidalgo, G., Fierer, N., & Knight, R. (2010). Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. *Proceedings of the National Academy of Sciences of the United States of America*, *107*(26), 11971–11975. <https://doi.org/10.1073/pnas.1002601107>

Dominguez-Bello, M. G., De Jesus-Laboy, K. M., Shen, N., Cox, L. M., Amir, A., Gonzalez, A., Bokulich, N. A., Song, S. J., Hoashi, M., Rivera-Vinas, J. I., Mendez, K., Knight, R., & Clemente, J. C. (2016). Partial restoration of the microbiota of cesarean-born infants via vaginal microbial transfer. *Nature medicine*, *22*(3), 250–253. <https://doi.org/10.1038/nm.4039>

Farr, A., Kiss, H., Hagmann, M., Machal, S., Holzer, I., Kueronya, V., Husslein, P. W., & Petricevic, L. (2015). Role of Lactobacillus Species in the Intermediate Vaginal Flora in Early

Pregnancy: A Retrospective Cohort Study. *PloS one*, 10(12), e0144181.

<https://doi.org/10.1371/journal.pone.0144181>

Grześkowiak, Ł., Collado, M. C., Mangani, C., Maleta, K., Laitinen, K., Ashorn, P., Isolauri, E., & Salminen, S. (2012). Distinct gut microbiota in southeastern African and northern European infants. *Journal of pediatric gastroenterology and nutrition*, 54(6), 812–816.

<https://doi.org/10.1097/MPG.0b013e318249039c>

Leung, J. Y., Li, A. M., Leung, G. M., & Schooling, C. M. (2015). Mode of delivery and childhood hospitalizations for asthma and other wheezing disorders. *Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology*, 45(6), 1109–1117.

<https://doi.org/10.1111/cea.12548>

Liu, D., Yu, J., Li, L., Ai, Q., Feng, J., Song, C., & Li, H. (2015). Bacterial community structure associated with elective cesarean section versus vaginal delivery in Chinese newborns. *Journal of pediatric gastroenterology and nutrition*, 60(2), 240–246.

<https://doi.org/10.1097/MPG.0000000000000606>

Morinis, J., Shah, J., Murthy, P., & Fulford, M. (2011). Horizontal transmission of group B streptococcus in a neonatal intensive care unit. *Paediatrics & child health*, 16(6), e48–e50.

<https://doi.org/10.1093/pch/16.6.e48>

Mueller, N. T., Bakacs, E., Combellick, J., Grigoryan, Z., & Dominguez-Bello, M. G. (2015). The infant microbiome development: mom matters. *Trends in molecular medicine*, 21(2), 109–117. <https://doi.org/10.1016/j.molmed.2014.12.002>

Mueller, N. T., Shin, H., Pizoni, A., Werlang, I. C., Matte, U., Goldani, M. Z., Goldani, H., & Dominguez-Bello, M. G. (2017). Delivery Mode and the Transition of Pioneering Gut-Microbiota Structure, Composition and Predicted Metabolic Function. *Genes*, 8(12), 364. <https://doi.org/10.3390/genes8120364>

Murata, C., Gutiérrez-Castrellón, P., Pérez-Villatoro, F., García-Torres, I., Enríquez-Flores, S., de la Mora-de la Mora, I., Fernández-Lainez, C., Werner, J., & López-Velázquez, G. (2020). Delivery mode-associated gut microbiota in the first 3 months of life in a country with high obesity rates: A descriptive study. *Medicine*, 99(40), e22442. <https://doi.org/10.1097/MD.00000000000022442>

Neu, J., & Rushing, J. (2011). Cesarean versus vaginal delivery: long-term infant outcomes and the hygiene hypothesis. *Clinics in perinatology*, 38(2), 321–331. <https://doi.org/10.1016/j.clp.2011.03.008>

Ogunrinola, G. A., Oyewale, J. O., Oshamika, O. O., & Olasehinde, G. I. (2020). The Human Microbiome and Its Impacts on Health. *International journal of microbiology*, 2020, 8045646. <https://doi.org/10.1155/2020/8045646>

Pandey, P. K., Verma, P., Kumar, H., Bavdekar, A., Patole, M. S., & Shouche, Y. S. (2012).

Comparative analysis of fecal microflora of healthy full-term Indian infants born with different methods of delivery (vaginal vs cesarean): *Acinetobacter* sp. prevalence in vaginally born infants. *Journal of biosciences*, 37(6), 989–998. <https://doi.org/10.1007/s12038-012-9268-5>

Rizzatti, G., Lopetuso, L. R., Gibiino, G., Binda, C., & Gasbarrini, A. (2017). Proteobacteria: A Common Factor in Human Diseases. *BioMed research international*, 2017, 9351507.

<https://doi.org/10.1155/2017/9351507>

Rutayisire, E., Huang, K., Liu, Y., & Tao, F. (2016). The mode of delivery affects the diversity and colonization pattern of the gut microbiota during the first year of infants' life: a systematic review. *BMC gastroenterology*, 16(1), 86. <https://doi.org/10.1186/s12876-016-0498-0>

Mother to Offspring. *JAMA pediatrics*, 172(4), 368–377.

<https://doi.org/10.1001/jamapediatrics.2017.5535>

Shi, Y., Tanimura, K., Sasagawa, Y., & Yamada, H. (2020). Vaginal microbiota associated with preterm delivery. *Journal of infection and chemotherapy : official journal of the Japan Society of Chemotherapy*, 26(11), 1134–1138. <https://doi.org/10.1016/j.jiac.2020.06.003>

<https://doi.org/10.1016/j.jiac.2020.06.003>

Stokholm, J., Thorsen, J., Blaser, M. J., Rasmussen, M. A., Hjelmsø, M., Shah, S., Christensen, E. D., Chawes, B. L., Bønnelykke, K., Brix, S., Mortensen, M. S., Brejnrod, A., Vestergaard, G.,

Trivedi, U., Sørensen, S. J., & Bisgaard, H. (2020). Delivery mode and gut microbial changes

correlate with an increased risk of childhood asthma. *Science translational medicine*, 12(569), eaax9929. <https://doi.org/10.1126/scitranslmed.aax9929>

Stokholm, J., Thorsen, J., Chawes, B. L., Schjørring, S., Krogfelt, K. A., Bønnelykke, K., & Bisgaard, H. (2016). Cesarean section changes neonatal gut colonization. *The Journal of allergy and clinical immunology*, 138(3), 881–889.e2. <https://doi.org/10.1016/j.jaci.2016.01.028>

Toscano, M., De Grandi, R., Peroni, D. G., Grossi, E., Facchin, V., Comberiati, P., & Drago, L. (2017). Impact of delivery mode on the colostrum microbiota composition. *BMC microbiology*, 17(1), 205. <https://doi.org/10.1186/s12866-017-1109-0>

Tun, H. M., Bridgman, S. L., Chari, R., Field, C. J., Guttman, D. S., Becker, A. B., Mandhane, P. J., Turvey, S. E., Subbarao, P., Sears, M. R., Scott, J. A., Kozyrskyj, A. L., & Canadian Healthy Infant Longitudinal Development (CHILD) Study Investigators (2018). Roles of Birth Mode and Infant Gut Microbiota in Intergenerational Transmission of Overweight and Obesity From Mother to Offspring. *JAMA pediatrics*, 172(4), 368–377. <https://doi.org/10.1001/jamapediatrics.2017.5535>

Wilson, B. C., Butler, É. M., Grigg, C. P., Derraik, J., Chiavaroli, V., Walker, N., Thampi, S., Creagh, C., Reynolds, A. J., Vatanen, T., O'Sullivan, J. M., & Cutfield, W. S. (2021). Oral administration of maternal vaginal microbes at birth to restore gut microbiome development in infants born by caesarean section: A pilot randomised placebo-controlled trial. *EBioMedicine*, 69, 103443. <https://doi.org/10.1016/j.ebiom.2021.103443>

Yang, I., Corwin, E. J., Brennan, P. A., Jordan, S., Murphy, J. R., & Dunlop, A. (2016). The Infant Microbiome: Implications for Infant Health and Neurocognitive Development. *Nursing research*, 65(1), 76–88. <https://doi.org/10.1097/NNR.000000000000133>